

**Title of the study:Phenylbutyrate Therapy in maple Syrup Urine Disease**

**NCT01529060**

**Date document submitted : October 16, 2017**

## Section C: Background Information

Maple syrup urine disease (MSUD; OMIM 248600) is a severe inborn error of amino acid metabolism caused by deficiency of the mitochondrial branched-chain alpha-ketoacid dehydrogenase complex (BCKDC) resulting in the accumulation of branched-chain amino acids (BCAA) (isoleucine, leucine, and valine) and their corresponding branched-chain alpha-ketoacids (BCKA) [alpha-keto-beta-methylvalerate (KMV), alpha-ketoisocaproate (KIC), and alpha-ketoisovalerate(KIV)] in tissues and plasma. The relative prevalence of the condition in the general population in the US is 1 in 150,000. However, in some isolated populations like the Mennonites, the prevalence is much higher (1:386). The disorder typically manifests with potentially lethal episodes of intoxication presenting with acute neurological deterioration, feeding problems, weight loss, and a maple syrup odor to the urine. These episodes usually occur during states of catabolism induced by fasting or intercurrent illnesses and result primarily from the increases in plasma concentrations of leucine and its alpha-ketoacid. Based on its severity, MSUD has been classified into five clinical subtypes: 1) "classic" neonatal severe form, 2) "intermediate" form, 3) "intermittent" form, 4) "thiamine-responsive" form, and 5) "E3-deficient with lactic acidosis" form. Although the correlation between clinical severity and degree of residual BCKDC activity is often inconsistent, the later onset intermediate and intermittent forms are usually associated with some degree of residual activity, while the classic form usually exhibits very low or no BCKDC activity. Current treatment is based on dietary manipulations with protein restriction and a synthetic formula with reduced BCAA content. However, mental and social impairment are still present in the majority of these patients in spite of dietary management.

The block in BCAA metabolism that results in MSUD occurs at the second step, the rate limiting step catalyzed by the enzyme complex BCKDC. The complex consists of three catalytic components: a decarboxylase (E1) composed of two E1alpha and two E1beta subunits, a transacylase (E2) core of 24 identical lipoate bearing subunits, and a dehydrogenase (E3) existing as a homodimer. The subunits of the complex are encoded by four nuclear genes, synthesized in the cytosol, and imported in the mitochondria where assembly occurs. Mutations in the genes encoding the E1alpha, E1beta, and E2 subunits result in an MSUD phenotype while mutations in the E3 subunit cause a different phenotype. Regulation of enzymatic activity depends on the phosphorylation status of the E1alpha subunit that is specified by a kinase (BDK) which inactivates BCKDC and by a mitochondrial matrix resident type 2C phosphatase gene, PP2Cm, that activates it. There appears to be no correlation between the molecular defects and the severity of the clinical presentation.

In theory residual activity in this complex could be enhanced by altering the phosphorylation status of the E1alpha subunit. While this approach would not be effective in "null" activity patients, patients with even low residual activity may benefit with potential decrease in frequency of decompensation, improved rescue therapy during periods of decompensation and/or improved protein tolerance. Moreover, as BCKDC is located in almost all body tissues, even small increases in BCKDC activity may be effective. In general, it has been recognized that enzyme activity in vitro and DNA mutation do not generally predict clinical severity or level of residual activity in vivo.

Our study seeks to investigate the potential small molecule inhibition of the kinase that regulates BCKDC by applying a novel activity of an FDA-approved compound, sodium phenylbutyrate (NaPBA), in MSUD. Sodium phenylbutyrate is an FDA-approved drug that has been used to treat patients with urea cycle disorders (UCDs). In our extensive studies with UCDs, we noted that patients on therapy with NaPBA had decreased plasma levels of BCAA. This was subsequently confirmed in the ongoing Rare Diseases Clinical Research Network study "Longitudinal Study of Urea Cycle Disorders". This lead us to hypothesize that NaPBA has effects on BCAA metabolism.

Previously in H- 9281, Branched Chain Amino Acids and Regulation of Body Protein Turnover, we performed a pilot open-label study of sodium phenylbutyrate in three healthy volunteers and five MSUD subjects with clinical history of late onset disease to test whether PB might have effects on BCAA and the downstream BCKA. The design of the pilot study was a fixed-sequence, cross-over study with three days of steady state protein intake without drug followed by one day washout and then three days of PB treatment. BCAA and BCKA were determined at three time points on the last day of each study period. Upon treatment with phenylbutyrate, a reduction in both BCAA and BCKA was detected in all three control subjects ( $p < 0.05$ ) and three (patients 3, 4 and 5) out of the five MSUD patients ( $p < 0.05$ ). In these three MSUD responders, the leucine reduction ranged from 24% to 34% of the baseline levels. There was no clear correlation between the levels of residual enzymatic activity with the response of plasma BCAA and their BCKA to phenylbutyrate. Additionally, two of the responders (patients 4 and 5)

carried E2 mutations whereas the third (patient 3) responder carried an E1alpha mutation. These data suggest that irrespective of the subunit affected, MSUD patients have the potential to respond to sodium phenylbutyrate.

## **Section D: Purpose and Objectives**

The purpose of this protocol is to investigate the efficacy of sodium phenylbutyrate in the treatment of patients with maple syrup urine disease. The primary outcome measurements will be Cmax and Area Under the Curve (AUC) for BCAA and BCKA on the last study day of each intervention period.

## **Section E: Protocol Risks/Subjects**

### **E1. Risk Category**

Category 2: Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects.

### **E2. Subjects**

Gender:

Both

Age:

Adolescent (13-17 yrs), Adult (18-64 yrs), Child (3-12 yrs), Geriatric (65+ yrs)

Ethnicity:

All Ethnicities

Primary Language:

English, Spanish

Groups to be recruited will include:

Asymptomatic patients with chronic conditions, healthy; Patients

Which if any of the following vulnerable populations will be recruited as subjects?

Children, Cognitively impaired

Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?

Anytime consent is obtained, it is incumbent on the individual obtaining the consent to ascertain whether the potential participant and his/her legal representative understand all aspects of the study. Obtaining informed consent is an interactive process with questions asked of both the Investigator and potential participant. A participating investigator or his designee will obtain informed consent and sign the consent form along with the parent/legal representative.

Some subjects may be cognitively impaired, a common sequela of hyperammonemia. In the case of cognitively impaired adults (chronologically over 18 years of age) whose mental age is younger than 18 years of age, informed consent will be obtained from the subject's legal representative after study rationale, risks, benefits and procedures have been discussed. Assent for these adult subjects whose mental age is less than 18 years of age will be documented in the subject's medical record. If the cognitively impaired participant is chronologically between the ages of 7 and 17, the parent or legal guardian will consent and assent will be waived. See the Waiver of Adult and Child Assent forms attached in Section S.

Information from three sources will assist investigators in assessing whether a cognitively impaired subject has the capacity to give assent: the medical records available, the subject's legal representative and the subject himself. Medical records may contain developmental testing results stating mental age, and parents and guardians often know this information. Finally, it will be the subject's responses during the consent process itself which will disclose whether he/she understands the study and is therefore able to give his/her assent. The subject should be able to accurately state study purpose, procedures and risks in his/her own words, and verbally agree to participation in order for assent to be granted. Mere failure to object will not be taken as subject assent. See assurance documents attached in Section S.

Subjects may also include affected children between 3 and 17 years of age who are capable of completing study procedures. If the participant's mental age is the same as their actual age, we will follow the usual consent procedures with those 7-17 years old giving assent. Assent will be obtained if it is determined that the subject understands all aspects of the study. Assent will be documented by the subject's signature on the "Subject" line on the consent form. We will waive the requirement for assent of subjects less than 7 years of age. See assurance documents attached in Section S.

For Spanish-speaking subjects, a translator will be available to aid in the translation and explanation of the entire protocol and to answer questions. In these cases, short form Spanish consent will be used in addition to the full English consent form.

All tests except those performed within Texas Children's Hospital will be coded. The database linking coded samples to subject identity will be password-protected, access to which will be limited to essential study staff. Personal identifying information will be recorded in a secure database and consents or other pertinent clinical information stored in a secure file at TCH. Identifiable subject-specific data will not be reported in any public format, nor will it be reported to any third party to which Baylor may contract

### **E3. Pregnant woman/fetus**

Will pregnant women and/or fetuses (as described in 45 CFR 46 Subpart B) be enrolled in the research?

No

### **E4. Neonates**

Will neonates of uncertain viability or nonviable neonates (as described in 45 CFR 46 Subpart B) be enrolled in the research?

No

### **E5. Children**

Will children be enrolled in the research?

Yes

## **Section F: Design/Procedure**

### **F1. Design**

Select one category that most adequately describes your research:

z.z) ARCHIVED DO NOT USE - Other: Drug Phase 2/3

Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.

This will be a single-site, randomized, active-controlled, double-blind, cross-over study designed to enroll subjects with MSUD. Subjects will be randomly assigned to receive either sodium phenylbutyrate (PB) or placebo for 2 weeks, and then crossed over to receive the other treatment for 2 weeks. Randomization and initial treatment group assignment will be performed by the Investigational Pharmacy Services at Texas Children's Hospital in a 1:1 ratio using established randomization procedures.

No unaffected control subjects will be studied. The "active-control" design of the study through which each MSUD patient/subject receives sodium phenylbutyrate (PB) or placebo for 2 weeks, then crosses over to receive the other treatment for 2 weeks, enables each subject's response to sodium phenylbutyrate to be evaluated by comparing data obtained while on NaPBA to data obtained while he/she was receiving a placebo.

**Inclusion Criteria:**

Patients must be 3 years or older at enrollment with a diagnosis of maple syrup urine disease (MSUD) confirmed by the presence of plasma alloisoleucine (>5 micromol/L) and/or genetic testing showing mutations in both alleles of any subunit of BCKDHA (E1alpha subunit gene, MSUD type 1A), BCKDHB (E1beta subunit gene, MSUD type 1B), or DBT (E2 subunit gene, MSUD type 2). Subjects must be capable of completing study procedures, including taking oral or G-tube medication, and have a history of compliance to diet and treatment.

**Exclusion Criteria:**

Subjects may not have used sodium phenylbutyrate within 30 days of Visit 1. They may not have an active infection (viral or bacterial) or any condition which may exacerbate their MSUD causing metabolic decompensation. Enrollees cannot have any clinical or laboratory abnormality of Grade 3 or greater according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) (or for conditions not covered by the CTCAE, a severe or life-threatening toxicity). Within the 24 hours prior to Visit 1, subjects may not have taken any medications known to significantly affect renal clearance or to increase protein catabolism. Subjects may not participate if they have a known hypersensitivity to phenylacetate or phenylbutyrate or creatinine levels 1.5 times or more ULN.

Since a total of 53 mL will be drawn over Days 14 and 15 of both treatment periods, subjects weighing less than 13.6 kg or 30 pounds will not be enrolled.

## **F2. Procedure**

Subjects with confirmed MSUD will be studied in the General Clinical Research Center at Texas Children's Hospital using a cross-over design with two 14-day treatment periods. In order to confirm subject's diagnosis, a review of pertinent medical records will be performed prior to study enrollment.

Data collection occurs during three or four study visits, depending on the scheduling of the treatment periods. (Subjects will have two visits per treatment period if the periods are not contiguous, and three visits if the treatment periods are back-to-back.)

Day 1 of Treatment Period 1 is an outpatient visit to the GCRC Outpatient Clinic. After informed consent is granted, randomization will be performed. Study staff will then:

- Perform a physical examination
- Record medical history, concomitant medications and a 24-hour diet recall to plan future inpatient meals.
- Measure vital signs, height and weight.
- Collect blood for safety laboratory assessments (complete blood count (CBC), Chem 7, and urinalysis).
- Perform urine pregnancy test, if applicable.
- Collect single blood sample for plasma amino acids and branched chain alpha ketoacids.
- Collect single blood sample for pharmacokinetics (4-phenylbutyric acid/phenylbutyrate, phenylacetylglutamine and phenylacetic acid/phenylacetate) and for storage. This sample for storage will be saved so that, if necessary, analysis can be repeated and /or findings verified.
- Calculate NaPBA Dose .
- Dispense Treatment Period 1 study drug/placebo.
- Administer Initial Treatment Period 1 study drug/placebo.
- Monitor subject for anaphylactic reaction for one hour prior to discharge.

Study drug/placebo will be administered orally three times daily. Sodium phenylbutyrate dosage will be 500 mg/kg/day in patients weighing less than 20kg and 10 g/m<sup>2</sup>/day in larger patients in three divided doses per day, the standard UCD dose studied in our preliminary studies. The maximum allowed adult dose of phenylbutyrate is 2 grams per day. The Investigational Pharmacy Service at Texas Children's Hospital will dispense the sodium phenylbutyrate/placebo powder. Subjects will be sent home with a scales on which to weigh the study drug/placebo. It is then mixed with food and/or water or flavored syrup and administered orally or through nasogastric or gastrostomy tube. Subjects will receive the same amount of study drug/placebo for each arm of the study, and only the Investigational Pharmacy will know when the subject is receiving study drug and when they are taking placebo.

Other medications as well as the subject's therapeutic diet will be continued as prescribed throughout

the study. Because Buphenyl-TM can sometimes cause stomach upset, you will be started on ranitidine (Zantac-TM).

This initial visit will take about 4 hours.

Subjects will be requested to perform a 3-day diet record for Days 11, 12 and 13 of both treatment periods.

On Day 14 of Treatment Period 1, subjects will return for a one-night inpatient stay on the GCRC. After an AM admission, study staff will: • Perform a physical examination. • Document concomitant medications, intercurrent illness and adverse events. • Measure vital signs, weight and height. • Collect blood for safety laboratory assessments (complete blood count (CBC), comprehensive metabolic panel and urinalysis). • Perform urine pregnancy test, if applicable. • Begin 24-hour blood sampling (8 samples over 24 hours) to measure plasma amino acids and branched chain alpha ketoacids as primary endpoints. • Begin 24-hour blood sampling (8 samples over 24 hours) to measure pharmacokinetics(4-phenylbutyric acid/phenylbutyrate, phenylacetylglutamine and phenylacetic acid/phenylacetate and for storage. These samples for storage will be saved so that, if necessary, analyses can be repeated and /or findings verified. • Begin 24-hour urine collection to be tested to measure amino acid and branched chain keto acid levels.

During the morning of Day 15/Treatment Period 1, 24-hour blood sampling and urine collection are completed and subject's vital signs are taken. Subjects may be discharged home to return at a later time to begin Treatment Period 2 or may begin Treatment Period 2 with the first dose of study drug/placebo with lunch.

Procedures on Day 1 of Treatment Period 2 include: • Documentation of adverse events and concomitant medications. • Measurement of vital signs, height and weight. • Collection of single blood sample for plasma amino acids and branched chain alpha ketoacids. • Collection of single blood sample for pharmacokinetics (4-phenylbutyric acid/phenylbutyrate, phenylacetylglutamine and phenylacetic acid/phenylacetate) and for storage. This sample for storage will be saved so that, if necessary, analyses can be repeated and /or findings verified. • Initiation of Treatment Period 2 study drug/placebo. • Monitoring of subject for anaphylactic reaction for one hour prior to discharge.

If treatment periods are not contiguous, the following procedures will also be performed: • Collection of blood for safety laboratory assessments (complete blood count (CBC), Chem 7, and urinalysis). • Performance of urine pregnancy test, if applicable.

Subjects return to the GCRC on Day 14 of Treatment Period 2 for another overnight inpatient admission to the GCRC. Study staff will: • Perform a physical examination. • Document concomitant medications, intercurrent illness and adverse events. • Measure vital signs, height and weight. • Collect blood for safety laboratory assessments (complete blood count, comprehensive metabolic panel and urinalysis). • Perform urine pregnancy test, if applicable. • Begin 24-hour blood sampling (8 samples over 24 hours) to measure plasma amino acids and branched chain alpha ketoacids as primary endpoints. • Begin 24-hour blood sampling (8 samples over 24 hours) to measure pharmacokinetics(4-phenylbutyric acid/phenylbutyrate, phenylacetylglutamine and phenylacetic acid/phenylacetate and for storage. These samples for storage will be saved so that, if necessary, analyses can be repeated and /or findings verified. • Begin 24-hour urine collection to be tested to measure amino acid and branched chain keto acid levels.

On the morning of Day 15/Treatment Period 2, subject is discharged after 24-hour blood sampling and urine collection are completed and vital signs are taken.

## **Section G: Sample Size/Data Analysis**

See Separate document attached

## **Section H: Potential Risks/Discomforts**

## H1. Potential Risks/Discomforts

Describe and assess any potential risks/discomforts; (physical, psychological, social, legal, or other) and assess the likelihood and seriousness of such risks:

The risks associated with venipuncture are minimal. Adverse events in clinical trials of sodium phenylbutyrate include the following; amenorrhea/irregular menstrual cycles (23%), decreased appetite (4%), body odor, taste aversion (3%), abdominal pain, gastritis, nausea, vomiting, constipation, rectal bleeding, peptic ulcer disease, pancreatitis (one patient), aplastic anemia (one patient), arrhythmia (one patient), edema, renal tubular acidosis, depression, rash, headache, syncope, weight gain (2%). Neurotoxicity has been reported in cancer patients taking 250-300 mg/kg/day of intravenous phenylacetate but was reversed upon discontinuance of the drug. Laboratory abnormalities have included; acidosis (14%), alkalosis or hyperchloremia (7%), hypophosphatemia or hyperuricemia (2%), hypernatremia or hypokalemia (1%), hypoalbuminemia (11%), decreased total protein (3%), anemia (9%), leukopenia or leukocytosis (4%), and thrombocytopenia (1%).

According to accepted guidelines, the maximum amount of blood to be drawn over a 24-hour period is 3% of total blood volume if the subject is an outpatient, and 5% of total blood volume if the subject is an inpatient. The maximum amount of blood which can be safely drawn from research participants in any one-month period should not exceed 10% of the total blood volume.

Since a total of 53 mL will be drawn over Days 14 and 15 of both treatment periods, only subjects weighing more than 13.6 kg and 30 pounds can be enrolled. Since a total of 124 mL will be drawn over the entire study, only subjects weighing 18.2 kg or 40 pounds may be studied with admissions occurring within one month's time. A record of total blood volume withdrawn during each admission will be maintained in the subject's medical record.

## H2. Data and safety monitoring plan

Do the study activities impart greater than minimal risk to subjects?

Yes

NOTE: The answer to the questions in H2 requires the completion of the form: 'Section H – Data and Safety Monitoring Plan' as an attachment in Section S.

## H3. Coordination of information among sites for multi-site research

Is the BCM Principal Investigator acting as the SPONSOR-INVESTIGATOR for this multi-site research?

No or Not Applicable

Is BCM the COORDINATING CENTER for this multi-site research?

No or Not Applicable

## Section I: Potential Benefits

Describe potential benefit(s) to be gained by the individual subject as a result of participating in the planned work.

One potential benefit to the individual subject participating in this research is the possible introduction an efficacious adjunct treatment for their maple syrup urine disease. Since sodium phenylbutyrate is already an FDA-approved drug, the implementation of positive findings in the clinical arena could be fast. Participants may benefit directly from this project if findings indicate NaPBA is effective in reducing BCAA and BCKA levels and should be included in their treatment regimen.

Describe potential benefit(s) to society of the planned work.

Maple syrup urine disease is a severe inborn error of amino acid metabolism which results in the accumulation of BCAA and BCKA in tissues and plasma. This accumulation leads to neurological deterioration, feeding problems, weight loss and a maple syrup odor to the urine. In the most severe form, MSUD can damage the brain during times of physical stress (such as infection, fever, or not eating

for a long time). Even in the mildest form, repeated periods of physical stress can cause mental retardation and high levels of leucine. Current treatment is based on dietary manipulations with protein restriction and a synthetic formula with reduced BCAA content. However, mental and social impairment are still present in the majority of these patients in spite of dietary management.

If study findings show sodium phenylbutyrate lowers BCAA and BCKA levels in these patients, it may prove to be an effective adjunct treatment for these patients. A treatment option that could prevent or decrease the accumulation of BCAA and BCKA during states of catabolism induced by fasting or intercurrent illnesses, and thereby minimize or prevent the neurologic sequelae and loss of human potential that result, would greatly benefit society.

Do anticipated benefits outweigh potential risks? Discuss the risk-to-benefit ratio.

In weighing the potential risks of this research against the possible benefits of applying a novel activity of the FDA-approved compound sodium phenylbutyrate (NaPBA) in MSUD, we believe that the benefits outweigh the associated risks.

## **Section J: Consent Procedures**

### **J1. Waiver of Consent**

Will any portion of this research require a waiver of consent and authorization?

No

### **J1a. Waiver of requirement for written documentation of Consent**

Will this research require a waiver of the requirement for written documentation of informed consent?

No

### **J2. Consent Procedures**

Who will recruit subjects for this study?

PI

PI's staff

Describe how research population will be identified, recruitment procedures, any waiting period between informing the prospective participant and obtaining consent, steps taken to minimize the possibility of coercion or undue influence and consent procedures in detail.

Patients may hear about the study through the MSUD Family Support Group (the primary patient advocacy organization for this diagnosis), from their physicians in Baylor's Metabolic Clinic at TCH or from physicians at other metabolic treatment centers across the country. Past and current patients of Dr. Lee may be contacted directly by study staff for possible recruitment. Subjects referred by other physicians will be approached by study staff only after the treating physician receives permission from the patient/parents for them to do so. Subject/Parental permission will be documented by the referring physician on the Authorization for Study Staff to Contact form attached in Section S. This form must be received by study staff before they will contact the potential subject. All prospective participants will be asked to sign a medical records release form along with the study consent form prior to screening. Medical records may be obtained to confirm MSUD diagnosis and affirm that none of the exclusionary conditions are present.

A one-page synopsis of the study using verbiage from the IFC has been prepared to hand out to potential participants at the MSUD Family Support Group meeting during the summer of 2014. This synopsis is attached in section S.

Consent forms will be given/mailed to potential participants prior to enrollment so that they have ample time to review the information and ask questions about the study. Investigators will ensure that the

participant or their legally authorized representative understand the information provided and obtain informed consent. One parent may sign the consent as this study involves greater than minimal risk, but presents the prospect of direct benefit to the individual subjects. We may obtain consent from subjects up to three weeks prior to admission in order to register and randomize the subject so that the Investigational Pharmacy Service at Texas Children's Hospital can prepare the assigned treatment drug/placebo ahead of time.

For subjects who live outside of the Houston area or are unable to come to the Medical Center to complete this consent process in person, telephone consent is obtained. When obtaining consent over the telephone, study staff will follow 21CFR50.27 instructions for obtaining verbal consent. The "screening script" will be the text of the approved consent form. With a witness listening, the entire consent form will be reviewed with the potential enrollee. After informed consent is given, this consent will be documented by the presenter and the witness on a consent form. In these cases, the informed consent process is always repeated in person prior to admission when the subject is actually in Houston. The subject/parent signs the consent form at that time, and this signed consent is saved in the study file along with the phone consent copy signed by the presenter and the witness.

Are foreign language consent forms required for this protocol?

Yes

Which of the following ways will you document informed consent in languages other than English?

Short-Form consent documents

### **J3. Privacy and Intrusiveness**

Will the research involve observation or intrusion in situations where the subjects would normally have an expectation of privacy?

Yes

### **J4. Children**

Will children be enrolled in the research?

Yes

### **J5. Neonates**

Will non-viable neonates or neonates of uncertain viability be involved in research?

No

### **J6. Consent Capacity - Adults who lack capacity**

Will Adult subjects who lack the capacity to give informed consent be enrolled in the research?

Yes

### **J7. Prisoners**

Will Prisoners be enrolled in the research?

No

## **Section K: Research Related Health Information and Confidentiality**

Will research data include identifiable subject information?

Yes

Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.

Yes

Specific information concerning alcohol abuse:

No

Specific information concerning drug abuse:

No

Specific information concerning sickle cell anemia:

No

Specific information concerning HIV:

No

Specific information concerning psychiatry notes:

Yes

Demographic information (name, D.O.B., age, gender, race, etc.):

Yes

Full Social Security #:

No

Partial Social Security # (Last four digits):

No

Billing or financial records:

No

Photographs, videotapes, and/or audiotapes of you:

No

Other:

No

At what institution will the physical research data be kept?

Each subject will have a hardcopy research file/chart which will be stored in a locked file cabinet in the Study Coordinator's office on the 15th floor of the Clinical Care Center. These records will not be de-identified or coded. This is a single-site study, and no case report forms or reporting of patient demographics or personal health information to a central coordinating center will occur. Proof of diagnosis and eligibility, along with paper copies of safety lab and plasma amino acid results and other research-related documents will be kept in these secure files.

How will such physical research data be secured?

Each subject will have a hardcopy research file/chart which will be stored in a locked file cabinet in the Study Coordinator's office on the 15th floor of the Clinical Care Center.

At what institution will the electronic research data be kept?

The electronic research data will be kept at Texas Children's Hospital in a password-protected electronic medical record system.

Such electronic research data will be secured via BCM IT Services- provided secured network storage of electronic research data (Non-Portable devices only):

Yes

Such electronic research data will be secured via Other:

Yes, (describe below):

The electronic research data will be kept at Texas Children's Hospital in a password-protected electronic medical record system.

Will there be anyone besides the PI, the study staff, the IRB and the sponsor, who will have access to identifiable research data?

No

Please describe the methods of transmission of any research data (including PHI, sensitive, and non-sensitive data) to sponsors and/or collaborators.

Blood samples sent to Virginia Tech will be coded. The key for these samples will be kept in Research Assistant's password-protected computer in the Genetics Office on the 15th floor of the Clinical Care Center at TCH. Safety labs and plasma amino acids will be sent to TCH Pathology and labeled with PHI. These results will be in the password-protected TCH medical record system as well as the research chart locked in the file cabinet in the Study Coordinator's office.

Will you obtain a Certificate of Confidentiality for this study?

No

Please further discuss any potential confidentiality issues related to this study.

N/A

## Section L: Cost/Payment

Delineate clinical procedures from research procedures. Will subject's insurance (or subject) be responsible for research related costs? If so state for which items subject's insurance (or subject) will be responsible (surgery, device, drugs, etc). If appropriate, discuss the availability of financial counseling.

Costs of outpatient care and laboratory analyses at TCH and study medication will be encumbered by the study. For out-of-town families, the study will pay shipping costs, but will not reimburse for any expenses related to sample collection.

Distribution Plan: Participants will be compensated \$200 following completion of each arm of the study. Total compensation for the study will be \$400. The costs of parking in a Texas Medical Center parking lot will be paid by the study through validation stickers and parking tokens distributed at the time of subject visit. Meals can be provided for the subject by the GCRC when he/she is actually on the GCRC and the cost of other meals for the subject and accompanying family member can be reimbursed within a month of receipt submission. (Continued below.)

If subjects will be paid (money, gift certificates, coupons, etc.) to participate in this research project, please note the total dollar amount (or dollar value amount) and distribution plan (one payment, pro-rated payment, paid upon completion, etc) of the payment.

Dollar Amount:

400

Distribution Plan:

If subject is unable to pay for meals, food vouchers for the Food Court at the Clinical Care Center may be given. Travel to and from BCM for study visits will also be covered. This includes reimbursement for fuel and food purchased during the trips. The study will pay for one family member to travel with the subject, and any air travel and hotel stays will be arranged by study staff and paid by the study. There are no caps or limits to travel reimbursements, and when possible Mercy Medical Airlift which provides charitable medical air transportation will be used. A check for study compensation and reimburse for expenses incurred will be mailed to the subject after each two-week study treatment period is completed. The check is usually issued and mailed to the subject within one month of submission of the receipts.

## Section M: Genetics

How would you classify your genetic study?

Discuss the potential for psychological, social, and/or physical harm subsequent to participation in this research. Please discuss, considering the following areas: risks to privacy, confidentiality, insurability, employability, immigration status, paternity status, educational opportunities, or social stigma.

Will subjects be offered any type of genetic education or counseling, and if so, who will provide the education or counseling and under what conditions will it be provided? If there is the possibility that a family's pedigree will be presented or published, please describe how you will protect family member's confidentiality?

## Section N: Sample Collection

### SAMPLE: Blood

What is the purpose of the sample collection?

Blood will be collected for safety labs (complete blood count and comprehensive metabolic panel or Chem 7). These will be processed at Texas Children's Hospital Pathology. Plasma amino acids, branched chain alpha-ketoacids, and NaPBA metabolites (4-phenylbutyric acid/phenylbutyrate, phenylacetylglutamine and phenylacetic acid/phenylacetate) will also be obtained. The plasma amino acids will be processed at Baylor, and the branched chain keto acids and NaPBA metabolites will be transferred to outside labs for processing. With each blood draw for plasma amino acids, branched chain alpha-ketoacids and NaPBA metabolites, a sample will be collected for storage. These samples for storage will be saved so that, if necessary, analyses can be repeated and /or findings verified.

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.

On Day 1/Treatment Period 1 lab analysis will include: complete blood count with differential and platelets, chem 7, plasma amino acids, branched chain alpha-ketoacids and NAPBA metabolites (4-phenylbutyric acid/phenylbutyrate, phenylacetylglutamine and phenylacetic acid/phenylacetate). In addition, a 1-mL sample will be drawn for storage. A total of 11 mL (just over 2 teaspoons) of blood will be drawn during this study visit.

On Days 14-15/Treatment Period 1 baseline lab analysis will include: complete blood count with differential and platelets, chem 7, plasma amino acids (baseline or pre-dose, 2-hr, 4-hr, 8-hr, 12-hr, 16-hr, 20-hr and 24-hr samples), branched chain alpha-ketoacids (baseline or pre-dose, 2-hr, 4-hr, 8-hr, 12-hr, 16-hr, 20-hr and 24-hr samples), and NAPBA metabolites (baseline or pre-dose, 2-hr, 4-hr, 8-hr, 12-hr, 16-hr, 20-hr and 24-hr samples). In addition, a 1-mL sample will be drawn for storage at baseline or pre-dose, 2-hrs, 4-hrs, 8-hrs, 12-hrs, 16-hrs, 20-hrs and 24-hrs. A total of 53 mL (10 and a half teaspoons) of blood will be drawn during this study visit.

If the treatment periods are contiguous, Day 1/Treatment Period 2 lab analysis will be: plasma amino acids, branched chain alpha-ketoacids and NAPBA metabolites (4-phenylbutyric acid/phenylbutyrate, phenylacetylglutamine and phenylacetic acid/phenylacetate). In addition, a 1-mL sample will be drawn for storage. These tests can be performed on 7 mL (1 and a half teaspoons) of blood. But, if the treatment periods are not contiguous, the safety labs (complete blood count with differential and platelets and Chem 7) will need to be repeated, bringing the total amount of blood to be drawn for the visit to 11 mL (just over 2 teaspoons).

On Day 14-15/Treatment Period 2 lab analysis will include: complete blood count with differential and

platelets, comprehensive metabolic panel, plasma amino acids (pre-dose, 2-hr, 4-hr, 8-hr, 12-hr, 16-hr, 20-hr and 24-hr samples), branched chain alpha-ketoacids (pre-dose, 2-hr, 4-hr, 8-hr, 12-hr, 16-hr, 20-hr and 24-hr samples), and NAPBA metabolites (pre-dose, 2-hr, 4-hr, 8-hr, 12-hr, 16-hr, 20-hr and 24-hr samples). In addition, a 1-mL sample will be drawn for storage at pre-dose, 2-hrs, 4-hrs, 8-hrs, 12-hrs, 16-hrs, 20-hrs and 24-hrs. A total of 53 mL (10 and a half teaspoons) of blood will be drawn during this study visit.

The total amount of blood to be drawn during the entire study will be 124 mL (about 25 teaspoons) if treatment periods are contiguous, and 128 mL (about 26 teaspoons) if they are not.

The maximum amount of blood that can safely be drawn over a 24-hour period is 5% of total blood volume. Since we will be drawing 53 mL over a 24-hour period (Days 14 and 15 of both treatment periods), and 5% of the estimated blood volume of patients weighing 13.6 kg (30 pounds) is 54 mL, we will limit study enrollment to those weighing more than 13.6 kg or 30 pounds.

There are also guidelines about the maximum amount of blood which can safely be drawn from research participants in any one-month period. Current standards indicate that the maximum amount of blood which can be safely drawn from research participants in any one-month period should not exceed 10% of the total blood volume. If participants complete both 14-day treatment periods contiguously, a total of 124 mL blood would be drawn over a month's time. Since 10% of the estimated blood volume of patients weighing 18.2 kg (40 pounds) is 130 mL, it would be unsafe for subjects weighing less than 18.2 kg to complete the treatment periods within a one-month period. Subjects who fall within the 13.6 kg to 18.2 kg weight range will not be allowed to complete both treatment periods contiguously. They must have a wash-out period of more than 2 weeks between treatment cycles so that the amount of blood drawn within any one-month period is less than 124 mL.

Is there the possibility that cell lines will be developed with this sample? No

Sample will be obtained from:

Research Labs

Will the sample be stripped of identifiers?

No

**If sample will be released outside the hospital:**

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?

Yes. Samples will be coded.

Will sample material be sold or transferred to any third parties? Will the information be de-identified?

BCKA samples will be sent to Susan Hutson, Department of Human Nutrition, Foods and Exercise, Virginia Polytechnic and State University, for processing. If the sample for storage is used, part of that sample will be sent to Dr. Hutson for measurement of branched chain alpha-ketoacids. Samples for NAPBA metabolites will be sent to Children's National Medical Center for processing.

**If sample will be banked for future use:**

Where will the sample be banked and for how long?

The blood samples drawn for storage may be stored in locked freezers as long as the study is still in progress. All frozen samples will be labeled with initials and subject study number only.

Does the banking institution have an approved policy for the distribution of samples?

Yes.

**If the entire sample will NOT be used during the course of this research study:**

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?

Any samples not used during the course of this study will be discarded at the time of study completion.

Will samples be made available to the research subject (or his/her medical doctor) for other testing?

No

**If a subject withdraws from the study:**

Will subject have the option to get the remaining portion of their sample back?

No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?

If the subject revokes authorization prior to sample processing, all samples including the sample for storage will be destroyed.

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?

If the safety labs have been processed, the results will remain in the subject's electronic medical record. Data from other samples including the sample for storage will be deleted. Only data from safety labs will be recorded in the subject's medical record.

Will study data or test results be recorded in the subject's medical records?

Yes

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?

Results of safety labs can be revealed to the subject as the study is conducted. The results of the branched chain alpha-ketoacids, and NaPBA metabolites (4-phenylbutyric acid/phenylbutyrate, phenylacetylglutamine and phenylacetic acid/phenylacetate) will be revealed to the subject at study completion. The subject may reveal these results to his/her doctor.

Please identify all third parties, including the subject's physician, to receive the test results.

No third parties will receive the test results.

**SAMPLE: Urine**

What is the purpose of the sample collection?

Urine for urinalysis and, if applicable, pregnancy. A 24-hour collection will be performed. This urine will be tested to measure amino acids and branched chain keto acids.

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.

N/A

Is there the possibility that cell lines will be developed with this sample?No

Sample will be obtained from:

Research Labs

Will the sample be stripped of identifiers?

No

**If sample will be released outside the hospital:**

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?

The 24-hour collections will be coded and released to Dr. Susan Hutson.

Will sample material be sold or transferred to any third parties? Will the information be de-identified?

No

**If sample will be banked for future use:**

Where will the sample be banked and for how long?

The urine samples may be stored in locked freezers until shipped to Dr. Hutson. All samples will be labeled with initials and subject study number only. Only BCM study staff will be able to link labeled samples to individual subjects.

Does the banking institution have an approved policy for the distribution of samples?

Yes

**If the entire sample will NOT be used during the course of this research study:**

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?

Pregnancy and urinalysis testing will be performed by Department of Pathology at TCH, and remaining sample discarded. All urine sent to Dr. Hutson will be used during the course of this study.

Will samples be made available to the research subject (or his/her medical doctor) for other testing?

No

**If a subject withdraws from the study:**

Will subject have the option to get the remaining portion of their sample back?

No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?

If subject revokes authorization before sample is processed, it will be destroyed.

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?

Results of pregnancy testing and urinalysis will not be deleted, and will remain in subject's medical record. Results obtained by Dr. Hutson will be deleted.

Will study data or test results be recorded in the subject's medical records?

Yes

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?

Results of pregnancy test and urinalysis will be revealed to the research subject. Subject may forward them on to his/her doctor. Results of testing performed by Dr. Hutson can be revealed to the subject at study completion.

Please identify all third parties, including the subject's physician, to receive the test results.

No third parties will receive the results.

## Section O: Drug Studies

Does the research involve the use of ANY drug\* or biologic? (\*A drug is defined as any substance that is used to elicit a pharmacologic or physiologic response whether it is for treatment or diagnostic purposes)

Yes

Does the research involve the use of ANY gene transfer agent for human gene transfer research?

No

### O1. Current Drugs

[Drug : Buphenyl](#)

Is this study placebo-controlled?

Yes

If yes, be sure that you justify the use of the placebo for this research in the space below.

The "active-control" design of the study through which each MSUD patient/subject receives sodium phenylbutyrate (PB) or placebo for 2 weeks, then crosses over to receive the other treatment for 2 weeks, enables each subject's response to sodium phenylbutyrate to be evaluated by comparing data obtained while on NaPBA to data obtained while he/she was receiving a placebo.

Will the research involve a radioactive drug that is not approved by the FDA?

No

## Section P: Device Studies

Does this research study involve the use of ANY device?

No

## Section Q. Consent Form(s)

None

## Section R: Advertisements

**Mode of Advertising: Other: flyers for metabolic dietitians and physicians and patients**

Exact language of Advertisement:

A flyer outlining the study may be sent to metabolic dietitians and physicians at other metabolic centers. This flyer is attached to the protocol in section S. A patient flyer for metabolic physicians and dietitians to hand out to potential subjects has also been attached in section S.