Study Title:
Phase 2 Study of Theophylline Treatment for Pseudohypoparathyroidism

NCT number:
NCT03029429

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Institutional Review Board
Informed Consent Document for Research

Principal Investigator: Ashley Shoemaker, MD, MSCI **Revision Date: 05JUL2022**
Study Title: Phase 2 Study of Theophylline for the Treatment of Pseudohypoparathyroidism IND 133103 (11/1/2016)
Institution/Hospital: Vanderbilt University Medical Center

This informed consent applies to ADULTS

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study. Anyone you authorize to receive your medical record will also get this note.

1. What is the purpose of this study?

You are being asked to take part in this research study because you have the genetic disorder pseudohypoparathyroidism (PHP). People with PHP may have multiple medical problems, including resistance to multiple hormones and obesity. This study will test whether an investigational drug (theophylline) is a safe and effective treatment for the symptoms of PHP. Theophylline is approved by the Food and Drug Administration (FDA), but is not approved as a treatment for pseudohypoparathyroidism.

2. What will happen and how long will you be in the study?

This study is a 52 week randomized clinical trial.

If you join the study, we would randomly assign you to one of 2 study groups. This means the group you are in would be decided by chance, like "flipping a coin."

People in one group will get an inactive medication called a placebo. A placebo looks exactly like the experimental drug but it has no drug in it. People in the other group will get the experimental medication, theophylline. We would not tell you which group you would be in and the research team would not know which group you would be in. But, we could find out which group you were in if we ever needed to know for safety reasons. For every 2 patients assigned to the experimental group, 1 patient will be assigned to the placebo group.

You should not participate in strenuous exercise or drink caffeine or alcohol in the 3 days prior to study visits. An overview of the study is provided in table 1.

<u>SCREENING VISIT</u>
You will arrive at the Vanderbilt Clinical Research Center before 3pm. We will review your medical history. You will have a physical exam and vital signs will be measured, like at a doctor's visit for a "check-up".

If you are female and able to have children, a blood pregnancy test will be performed. A blood sample will be taken to test hormone levels, blood counts, chemistries, kidney and liver function. These tests are done to determine if it is safe for you to participate in the study. If the study doctor determines that the lab levels are significantly abnormal, the study visit will end.

You and your parents will complete several surveys. These surveys will ask questions about what kind of foods you like, how hungry you are, your mood and your development as a child. If the study doctor is worried that you may be depressed or suicidal, we will refer you to a mental health provider and the study visit will end.

You will have an electrocardiogram (ECG). This will tell us about the electrical activity in your heart. We will place sticky electrodes on your chest but the ECG will not hurt.

If you are found eligible to participate, you will continue on to VISIT 1. We will provide a standard dinner meal and bedtime snack. You will spend the night in the Clinical Research Center.

Table 1: Summary of Study Procedures

	Screening	Visit 1	Visit 2	Visit 3	Lab only	Visit 4
Overnight stay	X					X
Physical exam	X		X	X		X
Vital Signs	X	X	X	X		X
Blood draw	X	X	X	X		X
OGTT		X		X		X
Fasting		X		X		X
Metabolism test		X				X
Bone age x-ray		X				X
DXA		X				X
6-minute walk		X		X		X
Questionnaires		X	X	X		X
ECG	X		X			X
Drug dispensing		X	X	X	X	
Local blood draw		X (3-5 days and 4 weeks after the visit)	X (week prior to the visit)	X (week prior to the visit)		
Phone call		X (3-5 days and 4 weeks after the visit)				

VISIT 1 (DAY 1)

In the morning, we will measure your metabolism. You will wear a nose clip and breathe through a special mouthpiece or wear a special hood for 30 minutes. This allows us to measure the oxygen and carbon dioxide in the air you breathe in and out. We will measure your heart rate and blood pressure.

You will next have an oral glucose tolerance test (OGTT). An intravenous catheter (IV) will be placed in a vein in your arm so that we can take blood samples. You will drink a sugar drink. We will take blood samples from the IV over the next 2 hours. The blood samples will be used to test hormone levels and blood sugar levels. After two hours, the test is finished and the IV will be removed. After the test, you will be allowed to eat breakfast.

You will then be allowed to eat breakfast.

We will also provide lunch during the visit.

A whole body dual-energy x-ray absorptiometry (DXA) scan will be done. This is an x-ray that measures how strong your bones are and your body composition. You will lie on a table while the x-ray is done. The test takes about 10 minutes.

You will have a bone age x-ray of your left hand, fingers and wrist to determine the approximate age of your skeletal system.

You will do an exercise test where you are asked to walk up and down a hallway as many times as you can in 6 minutes. If you become too tired, you are allowed to rest during the test. This walking test will be repeated 2 more times during the visit.

You will be sent home with a supply of the study drug or placebo. The capsule will be taken by mouth once a day with your evening meal. If you are unable to swallow a capsule, a liquid medication will be provided. This medication is taken by mouth every 6 hours.

PHONE CALL and LOCAL LABS

Three to five days after your visit we will call you over the phone to learn about any illnesses or new symptoms. You will also have a blood sample taken at a local lab. If you take the capsule, the blood sample will be drawn 12 hours after the last medication dose. If you take the liquid medication, the blood sample will be drawn 2 hours after the last medication dose. We will mail you a new supply of study drug or placebo after this lab draw.

We will call you again after 4 weeks to again ask about any illnesses or new symptoms. You will also have a blood sample taken at a local lab. If you take the capsule, the blood sample will be drawn 12 hours after the last medication dose. If you take the liquid medication, the blood sample will be drawn 2 hours after the last medication dose. We may adjust your medication dose based on the lab results.

One week prior to visit 2 (week 11) you will have a blood sample taken at a local lab. If you take the capsule, the blood sample will be drawn 12 hours after the last medication dose. If you take the liquid medication, the blood sample will be drawn 2 hours after the last medication dose. We may adjust your medication dose based on the lab results.

At week 40 (between visit 3 and 4) you will have a blood sample taken at a local lab to check your hormone levels. We may adjust your medication dose based on the lab results.

If you require medication dose adjustments, you will need another blood sample drawn at your local lab between 3-5 days after starting the new dose. If you take the capsule, the blood sample will be drawn 12 hours after the last medication dose. If you take the liquid medication, the blood sample will be drawn 2 hours after the last medication dose.

VISIT 2 (WEEK 12)

The week before the visit you will be asked to have a blood draw done at your local lab. If you take the capsule, the blood sample will be drawn 12 hours after the last medication dose. If you take the liquid medication, the blood sample will be drawn 2 hours after the last medication dose. We may adjust your medication dose based on the lab results.

You will have a physical exam and vital signs will be measured, like at a doctor's visit for a "check-up".

A blood sample will be taken to test hormone levels and liver function. If you are female and able to have children, a blood pregnancy test will be performed.

We will ask you to report any illnesses or symptoms since your last phone call. During the visit, you and your parents will complete several surveys as above.

We will provide you with a new supply of study drug or placebo. You will be asked to return your old medication containers and any leftover medication.

VISIT 3 (WEEK 26)
The week before the visit you will be asked to have a blood draw done at your local lab. If you take the capsule, the blood sample will be drawn 12 hours after the last medication dose. If you take the liquid medication, the blood sample will be drawn 2 hours after the last medication dose. We may adjust your medication dose based on the lab results.

You will arrive to the CRC by 9am. You should not have anything to eat or drink, other than water for 8 hours before the visit.

You will have a physical exam and vital signs will be measured, like at a doctor's visit for a "check-up".

You will next have an oral glucose tolerance test (OGTT) as described above. If you are female and able to have children, a blood pregnancy test will be performed. After the test, you will be allowed to eat breakfast.

You will then be allowed to eat breakfast.

You will receive lunch during the visit.

We will ask you to report any illnesses or symptoms since your last visit. During the visit, you and your parents will complete several surveys as above.

You will do an exercise test where you are asked to walk up and down a hallway as many times as you can in 6 minutes. If you become too tired, you are allowed to rest during the test. This walking test will be repeated 2 more times during the visit.

We will provide you with a new supply of study drug or placebo. You will be asked to return your old medication containers and any leftover medication.

VISIT 4 (WEEK 52)
You will arrive at the Clinical Research Center before 5pm the night before the visit. We will provide a standardized dinner and snack. We will ask you to report any illnesses or symptoms since your last visit.

In the morning, we will repeat the study procedures from VISIT 1.

You will be asked to return your old medication containers and any leftover medication. This is the end of the study.

3. Costs to you if you take part in this study:

There is no cost to you for taking part in this study.

4. Side effects and risks that you can expect if you take part in this study:

Blood tests
Pain, redness, soreness, bruising, or infection may occur at the needle stick site. Rarely some people faint. The study doctor may put some cream (called EMLA) on your skin to numb the area so they will not feel the needle stick as much. The numbing cream may make your skin or the area have a change in skin color, but this is rare.

ECG
You may not like the sticky pads placed on your chest; they might irritate your skin. It might pull your skin when we take the pads off, similar to a Band-Aid being removed.

OGTT
You may not like the sugar drink.

Questionnaires
You may find it a bother to answer these questions. It is possible some information about you may be found out by others.

Metabolism
To measure energy expenditure, you will have to lie quietly in bed for 30 minutes while breathing through a special mouthpiece or hood. You may find the nose clip or mouthpiece uncomfortable.

DXA and bone age radiation risks
This research study involves exposure to radiation from two DXA whole body scans and three bone age x-rays. This radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation that you will receive by participating in this study is equal to your body receiving 18 days of radiation from your natural surroundings, or less than 1% of the amount allowed in a year for people who are exposed to radiation as part of their work.

Theophylline
Common side effects
Caffeine-like effects such as nausea, vomiting, headache and insomnia are common with theophylline. Anti-nausea medications will be provided as needed.

Adverse reactions from an overdose
If the theophylline levels get too high, symptoms commonly include vomiting, nervousness, rapid heart rate and tremors. Rarely, patients can have electrolyte abnormalities, cardiac arrhythmias, seizures or low blood pressure. Death has been reported from an acute overdose of theophylline.

Side effects of theophylline are related to blood theophylline levels. It is very important that you take the prescribed dose of medication at the same time each day. It is also important that you have your blood levels checked as directed by the study staff. Other things that can change your theophylline levels include changes in your medications, fever, untreated hypothyroidism and interactions with food or alcohol. Should there be any concerns for problems with the liver (liver toxicity), additional blood will be drawn.

Please avoid alcohol while in this study. Contact the study staff if you have a fever for more than 2 days or if you have vomiting more than once in a day, a rapid heartbeat or shaking hands.

These medications may hurt an unborn child. If you are a female and are able to become pregnant, you will have a test to make sure that you are not pregnant before they receive treatment in this study.

Medication interactions
Other medications you take may interact with theophylline. It is very important that you tell the study doctor before you take any new medications or over-the-counter supplements. We will provide a letter for your regular doctors informing them about this study. The medicines in table 2 are most-likely to interact with theophylline. You may NOT take these medications while in the study.

Table 2: Drugs with clinically significant drug interactions with theophylline				
Adenosine	Diazepam	Halothane	Midazolam	Rifampin
Allopurinol	Disulfiram	Interferon alpha	Moricizine	St. Johns Wort
Aminoglutethimide	Enoxacin	Isoproterenol (IV)	Pancuronium	Sulfinpyrazone
Carbamazepine	Ephedrine	Ketamine	Pentoxifylline	Tacrine
Cimetidine	Erythromycin	Lithium	Phenobarbitol	Thiabendazole
Ciprofloxacin	Flurazepam	Lorazepam	Phenytoin	Ticlopidine
Clarithromycin	Fluvoxamine	Methotrexate	Propafone	Troleandomycin
		Mexiletine	Propranolol	Verapamil

Estrogen may increase the risk of a theophylline overdose. If you are a female taking estrogen or oral contraceptive pills ("birth control pills"), we will start with a lower dose of theophylline. If you need to stop OR start taking estrogen during this study, please contact the study doctor immediately.

5. Risks that are not known:

Because this treatment is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time.

6. Payment in case you are injured because of this research study:

If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury.

There are no plans for Vanderbilt to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

7. Good effects that might result from this study:

a) The benefits to science and humankind that might result from this study. We may find a new treatment for PHP.

b) The benefits you might get from being in this study. You will receive information on your metabolism and body composition. If any hormone lab results are abnormal, you will be referred to your primary care doctor or endocrinologist for treatment.

8. Other treatments you could get if you decide not to be in this study:

You can continue to receive routine medical care from your physician and endocrinologist.

9. Payments for your time spent taking part in this study or expenses:

We may ask you for your Social Security number and address before they are compensated for taking part in this study. You will receive $50 for completing the screening visit. You will receive an additional $150 for completing visits 1, 3 and 4 and $100 for completing visit 2. Checks will be mailed to your home address 2-4 weeks after the study. If you live more than 50 miles from Vanderbilt University, we will provide travel assistance. Eligible expenses include plane tickets for the patient and one parent or car mileage (50 cents per mile). If you live more than 100 miles from Vanderbilt, we will provide a hotel room the night before study visit 3.

10. Reasons why the study doctor may take you out of this study:

You will be taken out of the study if you are found not to meet the inclusion/exclusion criteria.

11. What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

12. Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Dr. Ashley Shoemaker at 615-343-8116. If you cannot reach the research staff, please page the study doctor at (615) 831-6167.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

13. Clinical Trials Registry.

A description of this clinical trial is available on www.clinicaltrials.gov, as required by U.S. Law (NCT03029429). This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

14. Confidentiality:

Study results will be kept in a password protected research database. Only Dr. Shoemaker and her study staff will have access to the information that identifies you as being in this study. Paper records will be kept in a locked office. The results of some tests run on your samples may not be recorded in your medical records and you and your regular doctor may not be told of the results.

Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Shoemaker and her staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

This study may have some support from the National Institutes of Health (NIH). If so, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

15. Authorization to Use/Disclose Protected Health Information

All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been gathered or kept by Vanderbilt as a result of your healthcare. This includes data gathered for research studies that can be traced back to you. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, you are agreeing ("authorization") to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Dr. Ashley Shoemaker and her study team may share the results of your study and/or non-study linked laboratory results, x-rays and DEXA scan, as well as parts of your medical record, to the groups named below. These groups may include people from the Federal Government Office for Human Research Protections, the Vanderbilt University Institutional Review Board and the Food and Drug Administration. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Ashley Shoemaker in writing and let her know that you withdraw your consent. Her mailing address is – Village at Vanderbilt, 1500 21st Ave South, Suite 1514, Nashville, TN 37212. At that time, we will stop getting any more data about you. But, the health data we stored before you withdrew your consent may still be used for reporting and research quality.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

Date	Signature of patient/volunteer

Consent obtained by:

Date	Signature
	Printed Name and Title

Time

Date of IRB Approval: 09/18/2025
Date of Expiration: 09/17/2026