The Effect of Etelcalcetide on Bone-tissue Properties and Calcification Propensity in End Stage Kidney Disease

PI: Thomas Nickolas, MD, MS
AAAR6244
NCT03960437
ICF Version 18March2019

Columbia University Medical Center Consent Form and HIPAA authorization
Attached to Protocol: IRB-AAAR6244

IRB Protocol Title: The effect of Etelcalcetide on bone-tissue properties and calcification propensity in end stage kidney disease

Principal Investigator: Thomas Nickolas (tln2001)
Participation Duration: 9 months.
Anticipated numbers of subjects: 35

Contact

Thomas Nickolas	Assoc. Professor of Medicine	Principal Investigator	Tel. (212) 305-5020
Maria Alejandra Aponte	Clinical Research Coordinator	Study Coordinator	Tel. (212) 342-4678
Joshua Sung	Clinical Research Coordinator	Study Coordinator	Tel. (212) 305-4945

Research Purpose

You are invited to participate in this study because you have been diagnosed with "Secondary hyperparathyroidism" (SHPT), you are on hemodialysis, and your treating physician plans to initiate treatment with Etelcalcetide.

Secondary hyperparathyroidism (SHPT), is a very frequent complication of patients with chronic kidney problems. It is characterized by high blood levels of the hormone that controls the calcium, named parathyroid hormone (PTH). High levels of this hormone increases the risks of bone loss, fractures, soft tissue calcification and heart problems. Treatment with medications known as calcimimetics can help to normalize these levels. Etelcalcetide is a calcimimetic, approved by the Food and Drug Administration (FDA) for treatment of SHPT in adult patients on hemodialysis.

The purpose of this research is to learn about the effects of Etelcalcetide on the bone and blood vessels. Our goal is to find out if treatment with Etelcalcetide improves your bone quality and decreases propensity to calcify soft tissues.

Information on Research

Introduction

The purpose of this form is to give you information to help you decide if you want to take part in a research study. This ***consent and HIPAA authorization form*** includes information about:

- why the study is being done;
- the things that you will be asked to do if you are in the study;
- any known risks involved;
- any potential benefit;

- options, other than taking part in this study, that you have; and
- the way your health information will be used and shared for research purposes.

The principal investigator Dr. Thomas Nickolas or the study coordinator Dr. Maria Aponte will discuss the study with you. If at any time you have questions about the study, please ask a member of the study team. Take all the time you need to decide whether you want to take part in this research study.

The purpose of this research is described above.

Study Design

35 patients are expected to participate in this study. The study will last 9 months and has different phases:

A. Screening: The first step is to determine whether you are eligible for this study. Only patients on hemodialysis whose treating physician plans to initiate Etelcalcetide will be considered.

B. Bone Biopsy (Optional): We will ask you to obtain a bone biopsy to check the effects on bone after 6 months of treatment with Etelcalcetide. In order to see these changes, you will be given antibiotics that stick to the surface of your bone when taken on a specific schedule (**This process is called labeling**). If you do not take all your medications the information obtained from the biopsy will not be as valuable.

☐ **BEFORE STARTING ETELCALCETIDE:** You will be given a 3-day course of a tetracycline antibiotic called Sumycin at a dose of 250 milligrams, 4 times daily, followed by 12- days off, and then you will be asked to take another 3-day course of the same medication at the same dose. During this period, you will not receive Etelcalcetide.

☐ **AFTER 6 MONTHS OF TREATMENT WITH ETELCALCETIDE:** You will complete 3 days of another tetracycline antibiotic called Demeclocycline followed by 12-days off, and then you will take another 3-day course of the same medication. Then 4-6 days after your last dose, the bone biopsy will be performed in either the Operating Room or the Interventional Radiology Suite (both at Columbia University Medical Center).

C. Dose adjustment (titration): Your treating physician is going to put you on Etelcalcetide and follow up your response to the treatment for 3 months. It is possible your dose will need to be increased or decreased during this time to ensure that the hormone that controls the levels of calcium in your blood (PTH) is adequately treated.

D. Treatment: Once your treating physician finds the best dose of Etelcalcetide for you, you will continue receiving the drug for 6 months. After this period, we will complete the final evaluation of our study.

Study Procedures

The study includes the following procedures:

- **Medical history, and vital signs:** You will be asked about your/your family's current and past medical characteristics. Vital signs, limited to measurement of height, weight, heart rate and blood pressure, will be collected. These procedures will be performed during "Day 1" at baseline and "Day 1" at 9-month time points in your hemodialysis unit.

- **Questionnaires:** You will be asked to complete 2 questionnaires, one related to your diet, and another about your physical activity. Both of them will be completed during "Day 2" at baseline and "Day 2" at 9-month time points at Columbia University Medical Center. Time for completion is variable, but we expect it will take about 30 min.

- **Biochemical assessment**: We will ask you for a blood sample of approximately 80 ml (a little less than five and a half tablespoons). Blood will be drawn only by your dialysis nurse at the start of dialysis through your dialysis line. All blood collected will be frozen at minus 80 degrees centigrade (minus 112 degrees Fahrenheit) for analysis at a later date. Because these tests are experimental, the results will not be shared with you or your treating physician, and will have no impact on your clinical care. It will be performed 3 times at your hemodialysis unit over the course of the study. The blood tests will measure levels of PTH and vitamin D, as well as your bone health, your immune system and your kidney function.

- **Muscle and Frailty measures:** These studies will be performed during the "Day 2" at baseline and "Day 2" at 9-month time points at CUMC.

  ☐ **Grip Strength**: We will use a handheld dynamometer to measure strength of your dominant hand. The maximal grip strength will be analyzed.

  ☐ **Short Physical Performance Battery (SPPB)**: The SPPB assesses standing balance, gait speed and chair stands. You will be asked to maintained your feet in side-by-side, semi tandem, and tandem positons for 30 seconds; perform a 4-m walk at usual speed; and rise from a chair and sit down 10 times as quickly as possible without using their arms. You can to stop anytime if you do not feel comfortable.

- **Advanced Glycation End (AGE) Reader:** We will measure the level of Advanced Glycation End products (AGEs) in the skin of your forearm. We are interested in determining if AGE content in skin predicts bone microarchitecture. Therefore, we would like to perform skin AGE measurements to assess correlations between the two. There is no additional risk to the participant. To make this measurement, we will shine a light over your elbow for approximately one minute. We ask you not to

wear sunscreen for two days before the measurement is made as this can interfere with the result. This procedure involves no risks.

- **Bone Imaging:** These studies will be performed during the "Day 2" at baseline and "Day 2" at 9-month time points at Columbia University Bone Density Unit, Harkness Pavilion, 9th floor.

  Bone Density (DXA): This test involves lying down on a table in different positions while pictures are taken of your bones. This is a painless test that takes about 15 to 20 minutes, and it is used to measure your bone mineral density.
  High-resolution peripheral quantitative computed tomography (HR-pQCT)
  This is a CT scan of your wrist and leg which provides detailed information about your 3-dimensional bone structure, in simple words, it measures the quality of your bones. If your dialysis access is located at the non-dominant forearm, we will use the dominant forearm for HR-pQCT imaging.
  Females who are able to become pregnant will also provide a urine specimen for pregnancy testing. (A negative pregnancy test is required prior to bone imaging).

  Bone and Muscle Biopsy (Only for patients who decide to participate in the bone biopsy): You will undergo a bone and muscle biopsy at your hip area performed under conscious sedation and a localized pain numbing medicine (Lidocaine and Marcaine) to minimize discomfort, either in the Biopsy Suite in the Division of Nephrology, the Operating Room or the Interventional Radiology Suite, all located at CUMC. The procedure will be done either by Dr. Nickolas or another of the trained nephrologist. The bone biopsy provides detailed information about the quality of your bone that cannot be obtained through other tests like x-rays or blood tests. The use of Sumycin and Demeclocycline will allow us to evaluate the characteristics of your bone before and after the treatment with Etelcalcetide.
  The muscle biopsy informs about the health of your muscle fibers. When the bone piece is obtained, there is a tiny piece of muscle that is attached to the bone, and the doctor performing the biopsy will snip the piece of muscle off the bone biopsy. Since the piece of muscle is taken from the bone biopsy, no extra incision is needed.

  Bone biopsy is a minimally invasive procedure. A one-quarter inch cut will be made in the skin over your iliac bone (hip area). A special round, hollow bone biopsy needle will be used to remove a small piece of bone that is about the size of a pencil eraser. The skin incision will be closed with three stitches and then bandaged. You will rest approximately 2 hours after the procedure, lying on the side the biopsy was taken from, over an ice pack, until you leave the hospital. The stitch material will dissolve spontaneously over 4 to 6 weeks. You do not need to have them removed.

  You can resume walking one to two hours after the procedure. Limit any activity that causes discomfort. Vigorous exercise should be deferred until one week after

the biopsy. Daily activity can be resumed when you feel comfortable. You can return to work as soon as you feel comfortable, usually one to two days.

It is recommended that you not eat for 6 hours before the biopsy procedure. If you must, you can drink some clear fluids such as water of apple juice.

Within 30 days prior to the bone biopsy procedure, we will ask you to complete at least one of the following procedures to medically clear you for the biopsy: blood tests, and electrocardiogram (EKG), and a chest x-ray. As per hospital policy, subjects over age 50 may need to have an EKG and pre-surgical blood tests prior to the biopsy, while subjects over age of 60 may need to have blood tests, an EKG and a chest x-ray. If these procedures are required, the cost will be covered by the study.

Schedule Visits

The study includes 5 visits at 3 time points (Baseline, 3 months and 9 months) for all subjects, and 1 additional visit (bone biopsy day) for subjects who participate in the optional bone biopsy.

At some points will be necessary you come to Columbia University Medical Center (Presbyterian Hospital, Milstein Hospital and/or Harkness Pavilion).

Baseline and 9-month time points will consist of 2 days each, one at your Hemodialysis Center (Day 1) and another (Day 2) at Columbia University Medical Center (CUMC).

The schedule and the data collection that will be done at each time points are as follows:

Table 1: All subjects

All subjects					
Time points	**Baseline**		**3-month**	**9-month**	
Location: Hemodialysis Unit (Rogosin or Columbia)	**Day 1**			**Day 1**	
Informed consent	**x**				
Medical History	**x**			**x**	
Weight, Height, Heart Rate, Blood Pressure	**x**			**x**	
Hemodialysis parameters (Kt/V)	**x**		**x**	**x**	
Blood tests	**x**		**x**	**x**	
Location: Columbia University Medical Center (CUMC)		**Day 2**			**Day 2**
Imaging: Bone density and HR-pQCT		**x**			**x**
Questionnaires: Diet and Physical activity		**x**			**x**
Muscle strength assessment		**x**			**x**
AGE Reader		**x**			**x**

Table 2: Subjects enrolled in Bone biopsy

Additional procedures for Bone Biopsy			
Time points	Before Etelcalcetide	After Etelcalcetide	
Location: Columbia University Medical Center (CUMC)	Baseline (Day 2)	9-month (Day 2)	Bone Biopsy Day
Antibiotic #1: Sumycin	x		
Antibiotic #2: Demeclocycline		x	
Bone and Muscle Biopsy			x

Storage and Future Use of Biological Samples, and/or Data

We would like to store the biological samples and/or data that you agreed to provide as part of this study, and possibly use them for future research. They will be stored at CUMC with the researchers on this study.

With your permission, your samples, and/or data will be stored at CUMC for as long as it is deemed useful for research purposes in identifiable form. This means that your samples, and/or data will be labeled with a code number that the researchers on this study or the people managing the repository may be able to link to you. Also with your permission, your samples, and/or data may be used by other Columbia researchers or researchers at other institutions, including commercial companies, for research that may or may not be related to this study. If they are given to researchers who are not researchers on this study, they will only be given in deidentified form. This means that your name and other identifying information have been permanently removed from your samples and/or data, or that your samples and/or data are coded and the researchers who use them do not have the key to the code. The procedures in any repository protocol that will store this material for future use will have storage provisions that are consistent with these statements. Any future testing or research using your samples and/or data may lead to the development and use of information, products, tests and treatments having commercial value. You will not receive any compensation that may result from these tests or treatments.

Please initial below to indicate whether or not you give permission for your specimens to be used for future research.

YES_____ NO_____ (initial) I agree to have my data/specimens stored for future research by the investigators who are conducting this study.

YES_____ NO_____ (initial) I agree to have my data/specimens stored and shared with other investigators who are doing research that is related to this study or my condition.

YES_____ NO_____(initial) I agree to have my data/specimens stored and shared with other investigators who are doing different kinds of research that is not related to this study or my condition.

Permission for future contact

We may want to contact you for additional information or to get a new biological sample in order to learn more about the research findings from this study. We may contact you directly or through you doctor. We may ask you provide a new sample or additional medical information, participate in other research studies or allow us to use your samples, and/or data in identifiable form. If a biological sample, your participation in future research or our use of your samples in identifiable form is requested, you will be asked to sign an additional form to agree to this.

Please initial below to show whether or not you give permission for future contact.

YES_____ NO_____(initial) I give permission to be contacted in the future for research purposes.

YES_____ NO_____(initial) I give permission to be contacted in the future for information relating to this study.

Potential Risks

The potential risks of this study are related to the blood draws, radiation exposure from the HRpQCT, DXA, chest X-rays, and the bone biopsy.

- **Blood draw:** All blood will be drawn only by your dialysis nurse at the start of dialysis through your dialysis line in order to minimize discomfort.

- **Radiation Risk of the DXA scan, HR-pQCT scan and Chest X-rays:** The procedures involving radiation in this research study will expose you to a very small amount (0.18 mSv) of radiation in addition to the amount that you might receive from your normal medical care. There may be an increase in the chances of your developing cancer many years after this study. The additional risk from this research study is less than 0.001198%. At this very low level, scientists are uncertain as to the actual risk from research and there may be no risk at all."

  The chest X-rays are only for pre-operative clearance purpose in people older than 60 years old, and represent 0.1 mSV of the amount mentioned above.

  Unexpected Findings from Radiographic Scans. Although the imaging you will have in this study is being undertaken for research purposes only, it is possible that doctors may notice something that could be important to your health. Although not likely, it is possible that the doctors may notice something that may be very serious and could immediately affect your life. If so, we will contact you to explain what was observed. If you so desire, we will also talk with your private physician. If you do not have a private physician, we will refer you to an appropriate clinic for follow-up. It will be your choice whether to proceed with

additional tests and/or treatments to evaluate what we observed, and you or your insurer will be responsible for these costs

- **Psychological risk**: In rare instances, we may find unexpected information about you such as an unknown diagnosis, which you may find upsetting. Please contact Dr. Nickolas if participation in the study leads to distress.

- **Bone biopsy**: There may be some minor temporary discomfort when the intravenous catheter (a hollow tube inserted into the vein) is introduced into your arm to administer the sedative, and when the local anesthetic is initially injected into the skin at your hip. There may be a bruise and some bleeding at the site of the skin incision and insertion of the biopsy needle. There may be some discomfort when the biopsy is taken.

  A sedative, such as Valium, will be given beforehand. (Although safe and effective, the risks associated with the use of a sedative drug include decreased breathing rate and blood pressure). You will be carefully monitored during this time. The site of the biopsy will be numbed to minimize pain and discomfort with a local anesthetic. The risk of infection will be kept to a minimum by using sterile technique. The incision will be sutured and a pressure dressing bandage applied to prevent bleeding. Pain relief medication, such as Tylenol, may be taken for discomfort according to your doctor's instructions after the biopsy. Every precaution will be taken to avoid any complications.

Please initial below to show whether or not you decide to participate in **the optional bone biopsy.**

YES_____ NO_____(initial) I decide to participate in the bone biopsy.

- **Antibiotics**:

  Tetracycline and Demeclocycline: are antibiotics approved for the treatment of infections. In this instance it is being given to label bone-forming sites. Occasionally, this medication may cause gastrointestinal (stomach and intestine) disturbances such as loss of appetite, nausea, vomiting, diarrhea and heartburn. To reduce the risk of heartburn, you should not take the drug just before going to bed. Allergic reactions have also been reported. This medication may also cause a skin rash with exposure to the sun. Therefore, avoid sunbathing and wear clothing and sun block if you have to be outside in the sun. Other less common side effects include liver, blood and kidney abnormalities. Your participation in this study may involve unforeseeable risks to you. You will be told of significant new findings that may change your decision to participate.

- **Privacy risk:** A risk of taking part in this study is the potential for loss of confidentiality. This includes having your personal information shared with

someone who is not on the study team and was not supposed to see or know about your information. It is extremely unlikely this will occur due to procedures already in place to safeguard your privacy as described in the 'Confidentiality' section of this consent form.

Benefits

You may not benefit directly from this study. However, there may be general benefits to society because the knowledge gained from this study may help better understand the effects of Etelcalcetide on the bones and soft tissues. Any important results will be shared with your treating physicians.

Alternative treatment

The alternative is not to participate in this research study. Your decision whether or not to participate in this study will have no effect on your medical care at this hospital.

Confidentiality

Any information collected for this study that can identify you by name will be kept confidential. Every effort will be made to keep your personal information secure. However, we cannot guarantee total privacy. Despite all of our efforts unanticipated problems may occur, although it is highly unlikely.

Access to your health information is required to be part of this study. If you choose to take part in this study, you are giving us the authorization (i.e. your permission) to use the protected health information and information collected during the research that can identify you. The health information that we may collect and use for this research may include medical history that may be considered sensitive.

Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care that is needed for this research purpose,

The data and specimens collected will be given a code number, and separated from your name or any other information that could identify you. The research file that links your name to the code number will be kept in a password protected database. Only the Principal Investigator and the study staff will be able to see this file. If information from this study is published or presented at scientific meetings, your name and other personal information about you will not be used.

The following people and/or agencies will be able to look at and copy your research records:

- The investigator, Columbia University and New York-Presbyterian Hospital staff and other professionals who may be evaluating the study.

- Authorities from Columbia University and New York-Presbyterian Hospital, including the Institutional Review Board ('IRB'). An IRB is a committee organized to protect the rights and welfare of people involved in research.
- The Office of Human Research Protections ('OHRP') and/or the United States Food and Drug Administration ('FDA').
- The sponsor of this study: Amgen, including persons or organizations working with or owned by the sponsor.

The investigator, regulatory authorities, IRB and study sponsor may keep the research records indefinitely. If the results of the study are published or presented at a medical or scientific meeting, you will not be identified.

Your authorization to use and share your health information does not have an expiration (ending) date.

Once your health information has been disclosed to a third party (for example, a pharmaceutical company participating in a study), federal privacy laws may no longer protect it from further disclosure.

You may change your mind and revoke (take back) this consent and authorization at any time and for any reason. To revoke this consent and authorization, you must contact the Principal Investigator

Thomas Nickolas, MD
Associate Professor of Medicine
Columbia University Medical Center Division of Nephrology
622 West 168th Street, PH4, Rm 124 New York, NY 10032

However, if you revoke your consent and authorization, you will not be allowed to continue taking part in the Research. Also, even if you revoke this consent and authorization, the Researchers and the Sponsor (if applicable) may continue to use and disclose the information they have already collected.

Research Related Injuries

Taking part in this research study may result in injury or harm to you. In the event of an injury resulting from your participation in this study, you should seek appropriate medical care and inform the study doctor. In the event of an emergency you should go to an emergency room. If you are injured or harmed as a result of participating in the study and receive medical care through the New York-Presbyterian Hospital (NYPH), a Columbia doctor, or any other health provider, you will be sent a bill for whatever medical care you receive. All or part of your bill may be paid by your health insurance. Columbia University, New York-Presbyterian Hospital (NYPH) and Amgen are not offering to pay you for pain, worry, lost income, the cost of your medical care or non-medical care costs that might occur as a result of your taking part in this study. However, you do not waive any of your legal rights in signing this form.

Compensation

You will receive $50 cash upon completion of all imaging scans at baseline time point (Day 2), and $50 cash upon completion of the same imaging scans after treatment with Etelcalcetide at 9-month time point (Day 2). These visits are at Columbia University Medical Center (CUMC). Additionally, you will be given a $400 gift card upon completion of the bone biopsy.

Additional Cost

There will be no additional costs to you for any research procedure. You or your insurance will remain responsible for the cost of your regular medical care.

Voluntary participation

Taking part in this study is your choice. You can decide not to take part in or stop being in the study at any time. Your choice will not change the treatment you receive from doctors and staff at Columbia University Medical Center and New York-Presbyterian Hospital.

Additional Information

You may call Dr. Thomas Nickolas at (212)-305-5020 if you have any questions or concerns about this research study. If you have any questions about your rights as a research participant, or if you have a concern about this study, you may contact the Institutional Review Board listed below: Institutional Review Board Columbia University Medical Center 154 Haven Avenue, 1st Floor New York, NY 10032 Telephone: (212) 305-5883 irboffice@columbia.edu.

Statement of Consent

I have read the consent form and talked about this research study, including the purpose, procedures, risks, benefits and alternatives with the researcher. Any questions I had were answered to my satisfaction. I am aware that by signing below, I am agreeing to take part in this research study and that I can stop being in the study at any time. I am not waiving (giving up) any of my legal rights by signing this consent form. I will be given a copy of this consent form to keep for my records.

Signature

Study subject

Print Name	Signature	Date

Person obtaining consent

Print Name	Signature	Date