"HEXT: The Hypoparathyroidism Studies, Extended: the Effect of PTH on the Skeleton in Hypoparathyroidism"
IRB# AAAE0544
Principal Investigator: John P Bilezikian MD
Date: April 22, 2016

PROTOCOL

STUDY PURPOSE AND RATIONALE:

Hypoparathyroidism is a rare disorder in which parathyroid hormone (PTH) is markedly decreased or absent from the circulation. Without PTH, calcium homeostasis is markedly abnormal, leading to reduced serum calcium concentrations. Hypocalcaemia is often associated with other important abnormalities such as increased urinary calcium excretion and markedly reduced parameters of bone turnover.

PTH(1-84) is an attractive therapeutic approach for hypoparathyroidism. The current mainstay of therapy, calcium and vitamin D, has important clinical limitations. Large doses of calcium and vitamin D are required and often associated with hypercalciuria and vitamin D toxicity. Moreover, this approach does not correct the skeletal deficiencies that might develop due to lack of PTH. In contrast, PTH(1-84) replaces precisely what is missing in this disorder.

STUDY DESIGN AND STATISTICAL PROCEDURES:

Design: Open-label study of PTH(1-84) treatment
Specific Aim:
1. To determine the actions of PTH(1-84) to provide long term control of serum calcium and urinary calcium excretion with use of standard amounts of calcium and vitamin D supplementation.
2. To determine the extent to which PTH(1-84) improves quality-of-life on long-term basis.
3. To establish the safety of PTH(1-84) when administered for up to 12 years.
4. To attempt to quantify improvements in the typical signs/symptoms of hypoparathyroidism post PTH administration.

STATISTICAL ANALYSES:

Statistical goal: calcium and calcitriol supplementation to be maintained at 50% below initial levels prior to commencement of PTH(1-84).
Sample size and power: 75 subjects will allow for detection of a difference in calcium supplementation of 50% with a power of 80%, using a t-test and two-tailed alpha of 0.05.
Outcome objective: Maintenance of serum calcium at traditional doses of calcium and vitamin D

STUDY PROCEDURES:

There will be one visit conducted every six months in the study offices of the principal investigator, Dr. John Bilezikian. In addition to these visits, there will be, for new patients who have not used PTH(1-84) before, a Screening Visit four weeks prior to the baseline visit for the purpose of performing screening labs as well as a Pre-Baseline Local Quest Lab performed to ensure stability prior to Baseline.

A note on blood testing: all research blood tests will be conducted prior to the performance of daily injection of the study drug and fasting from midnight the night before (water consumption in the morning will be encouraged). Fasting only affects the C-terminal telopeptide (CTX) level, a measure of bone turnover; if a subject is not able to be fasting for the visit, CTX will not be measured at this timepoint.

Screening Visit (-4 Weeks): THIS VISIT APPLIES ONLY TO NAIVE PATIENTS [Study is closed to new enrollment]
At this visit, consent will be obtained and all necessary laboratory testing will be performed to ensure meeting inclusion and exclusion criteria. The four weeks between consent and baseline should allow sufficient time for participants to obtain previous medical records if needed and for all test results to be available.
Events:

- Consent
- HIPPA
- Blood test: basic metabolic panel, hepatic function panel, TSH, magnesium, phosphorus, vitamin D25, Vitamin D125, Intact PTH
- Pregnancy testing for females of child bearing potential
- DXA & HR-pQCT (can be performed at Baseline instead as long as it is pre-PTH use)
- SF-36 QOL questionnaire
- Physical Exam
- Medical history
- Vital Signs: height, weight, blood pressure, heart rate, respiratory rate, temperature
- Recording of concomitant medications/drugs used from the last three months through time of visit
- Given materials and lab requisitions to perform 24-hour urine calcium/creatinine at a Quest Diagnostics lab local to the patient's home (henceforth, "Local Quest Lab")

Pre-Baseline Local Quest Labs (-2 Weeks): THIS VISIT APPLIES ONLY TO NAIVE PATIENTS [Study is closed to new enrollment]
This event is to be conducted 2 weeks (14 days +/- 3 days) prior to the Baseline Visit. It is to be conducted at the participant's Local Quest Lab.
Events:

- Blood test: basic metabolic panel, hepatic function panel, magnesium, phosphorus
- 24-hour urine calcium/creatinine

Baseline Visit: [Study is closed to new enrollment]
At this visit inclusion and exclusion criteria will be verified after which the participant will have baseline bloods drawn and then receive their first dose of PTH(1-84) (see How to Determine Dose of PTH(1-84)).
Events:
[If not already performed as part of screening visits]

- Consent
- HIPPA
- Blood test: basic metabolic panel, hepatic function panel, TSH, magnesium, phosphorus, vitamin D25, Vitamin D125, Intact PTH

- Pregnancy testing for females of child bearing potential
- DXA & HR-pQCT
- SF-36 QOL questionnaire
- Physical Exam
- Medical history
- Vital Signs: height, weight, blood pressure, heart rate, respiratory rate, temperature
- Recording of concomitant medications/drugs used from the last three months through time of visit
- Given materials and lab requisitions to perform 24-hour urine calcium/creatinine at a Quest Diagnostics lab local to the patient's home (henceforth, "Local Quest Lab")
- Pregnancy testing for women of child bearing potential
- Injection Training (includes performing injection, proper drug storage, needle disposal)
- First injection of PTH(1-84)

Initiation of PTH injections:
Before beginning PTH(1-84) injections, investigators must determine the dose that will best suit the participant. If there is a history of PTH(1-84) use by a participant, the dose determination is made easier. However, if there is no history of prior PTH(1-84) use, dose will be determined by the clinicians using a combination of their medical judgment, existing lab values, reliance on supplementation, and the participant's chronic symptoms.
Likewise, to capture evidence of physiological changes in the participant upon initial administration of PTH(1-84) and at any instance of titration of PTH(1-84) dose, a series of labs will be performed (see Interim Local Quest Labs). This will help us capture valuable safety and efficacy data and help guide clinical decision making for individual participants.

Determining the Starting Dose of PTH(1-84):
Varied sensitivity and multiple factors including reliance on supplementation and diet make it very difficult to establish one rule to apply to all hypoparathyroidism patients. Therefore, the following guidelines, while helpful, are merely guidelines.

If a participant has never used PTH(1-84) ("naïve") they will be started on a dose of 50mcg as it is the dose that has, in previous studies, shown itself to be the best starting dose based on its high rate of efficacy combined with its low risk (compared to higher doses) of causing hypercalcemia in a patient of unknown sensitivity to PTH(1-84). If a participant has come from another study using PTH(1-84) and the dose was known and considered effective, that dose may be selected by the clinicians as the starting dose.

However, as has been stated, dose will be determined by the clinicians using a combination of their medical judgment, existing lab values, reliance on supplementation, and the participant's chronic symptoms.

Interim Local Labs:
To assess ongoing safety and efficacy of the PTH/Supplement regimen the following local labs will be performed at the following frequencies upon the start of PTH injections and at any titration of PTH dose:
1 week post PTH: Basic Metabolic Panel and 24-hour urine calcium/creatinine

1 month post PTH: Basic Metabolic Panel
2 months post PTH: Basic Metabolic Panel
3 months post PTH: Basic Metabolic Panel and 24-hour urine calcium/creatinine

6-Month follow-up visits:

- In a verbal interview, capture participant's type and amounts of calcium, calcitriol, magnesium, vitamin D supplements and hydrochlorothiazide
- Perform fasting blood tests including basic metabolic panel, hepatic function panel, phosphorus, and magnesium and urinary calcium from 24 hour urine collection.

NOTE: the fasting blood tests may be performed 7-10 days PRIOR to the scheduled visit at the participant's local laboratory so that results may be reviewed at the office visit. 24-hour urine collection may be performed 7-10 days before or after the scheduled visit. Local Quest Laboratories are preferred but other CLIA-certified laboratory facilities are compliant per protocol. Fasting only affects the C-terminal telopeptide (CTX) level, a measure of bone turnover; if a subject is not able to be fasting for the visit, CTX will not be measured at this time point.

- Collect biochemical markers (from blood test).
- Collection of 2-hour urine, if subject is unable to perform 24-hour urine collection
- Perform bone density testing by DXA (Dual X-ray Absorptiometry) and HR-pQCT (High Resolution peripheral Quantitative Central Tomography).
- Pregnancy testing for women of child bearing potential
- Capture quality of life via the SF36 questionnaire.
- Review of Prior/Concomitant medications
- AE/SAE Monitoring (including clinical episodes of hypocalcemia/hypercalcemia)
- Review of compliance
- Provide study materials as needed (study drug, injection pens, needles, and alcohol swabs.

VISIT WINDOWS: Study visits are scheduled for once every six months. However because our participant population travels from all over the country we must build significant flexibility into the timing of visits. Thus visit windows will be once every six month +/- three months. Additionally, the timing of visits will always be calculated off of a participants baseline date, so if a patient is at the outside of the three month window for a visit it is conceivable that they will need to return within three months for their next visit.

Patients off PTH treatment:
Patients off treatment can remain part of the study protocol for as long as they desire to do so.

Supplementation of calcium, vitamin D, calcitriol:
Participants will be instructed to always take their calcium with a serving of food. The purpose of this is to ensure optimal absorption of calcium. Calcium carbonate may not absorb efficiently on an empty stomach in subjects with reduced gastric acid.

Criteria for increasing PTH(1-84) after initiation of therapy:
There are scenarios in which participants might benefit from an increase to the dose of PTH(1-84), namely, if calcium, vitamin D or calcitriol supplementation needs to be increased

significantly in order to obtain calcium homeostasis or if increases in calcium, vitamin D or calcitriol show a clinically significant impact on other health aspects, such as gastrointestinal health or urinary calcium levels.

Since the number of different clinical scenarios where an increase to the PTH(1-84) dose are many and difficult to forecast we make no attempt to list them all here. Rather, we state that increases to PTH(1-84) will be made using the clinicians best judgment.

However, if PTH(1-84) dose is altered up or down the following safety mechanisms will be carried out:

Safety Algorithms:
The following SAFETY algorithm for serum calcium levels are general rules to follow. It must be noted that participant-specific needs and investigator discretion may override these algorithms. Note: Some subjects with hypoparathyroidism feel most comfortable outside the conventional normal ranges for serum calcium. Some participants therefore may be exceptions to this algorithm. Such exceptions will be determined by the Investigators.

Potential Outcome #1: If serum calcium falls below 7.5 mg/dL, or if the participant is experiencing symptomatic hypocalcaemia worse than baseline, the serum calcium will be re-measured within 2 weeks, based on severity. If the serum calcium remains below 7.5 mg/dL, changes to the subject's calcium, calcitriol or PTH regimen will be made. Serum calcium will be re-measured within 2 weeks.

Potential Outcome #2: If serum calcium increases to 9.5 mg/dL or greater and/or if the participant is experiencing symptomatic hypercalcemia, changes to the subject's calcium, calcitriol or PTH regimen will be made. Serum calcium will be re-measured within 2 weeks.

Potential Outcome #3: If urinary calcium increases from baseline by 50% or more AND ALSO EXCEEDS the normal range upper limit of 250 mg/24h for females or 300 mg/24h for males, changes to the subject's calcium, calcitriol or PTH regimen will be made. Urine calcium will be re-measured within 2 weeks. Note: If there is a conflict between following the serum calcium and urine calcium algorithms the course of action to be followed will be determined by the clinical judgment of the study physicians with algorithms for serum calcium or symptomatic states taking precedence.

Restarting PTH(1-84) Treatment:
If bone density has been stable for one year off PTH(1-84) treatment, the team will discuss whether the study participant may restart PTH(1-84) treatment, perhaps at a lower dose. The stability of bone density and the appropriate dose of PTH(1-84) will be determined by the study physicians using study results and their best clinical judgment. Subjects will be instructed to obtain laboratory testing after reinitiation of PTH as described above under "Interim Local Labs."

STUDY DRUG:

Study drug is PTH(1-84), also called recombinant human parathyroid hormone (1-84), and also called NPSP558, provided by NPS Pharmaceuticals. Study drug will be available in 25mcg, 50mcg, 75mcg, and 100mcg doses because individual participant doses will vary.

STUDY QUESTIONNAIRE:
Participants will be asked to fill out the Standard Form 36 ("SF36") Quality of Life Questionnaire at every study visit (2 visits a year).

STUDY SUBJECTS [Study is closed to new enrollment]:
Subjects who have fully concluded their participation in the AAAA5457 or in AAAD7261, AAAI1061 or AAAI1649 are eligible to participate in this study and are considered to have fully met all inclusion/exclusion criteria.
New study participants however, will need to satisfy the following criteria:

INCLUSION CRITERIA:
1. Signed and dated informed consent form (ICF) before any study-related procedures are performed.
2. Adult males or females 18 to 85 years of age.
3. History of hypoparathyroidism for 18+ months, including evidence of hypocalcemia and concomitant serum intact PTH concentrations below the lower limit of normal within 12 months prior to Baseline.
4. Requirement for calcitriol 0.25+ mcg per day per day prior to Baseline.
5. Requirement for supplemental oral calcium 1500+ mg per day between supplemental and dietary sources.
6. Serum thyroid function tests within normal laboratory limits at screening for all subjects not receiving thyroid hormone replacement therapy. For patients on thyroid hormone replacement therapy, the dose must have been stable for at least 3 months prior to screening
7. Serum creatinine < 1.5 mg/dL on a single measurement prior to use of study drug
8. Physically capable of performing daily subcutaneous (SQ) self-injections, preferably in the thigh, of study medication (or have designee perform injection).
9. Willingness and ability to comply with the protocol (prior to screening).
10. With regard to female patients: Women of childbearing potential must have a negative pregnancy test at Screening and agree to use two medically acceptable methods of contraception for the duration of the study with pregnancy testing at every scheduled visit.

Clarification to Contraception [Study is closed to new enrollment]:
With regard to female patients: Women who are postmenopausal (absence of menses for at least one year) and women who are surgically sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy) have been enrolled. Women of childbearing potential have also been enrolled and must agree to use medically acceptable methods of contraception for the duration of the study with pregnancy testing at every scheduled visit. Medically acceptable methods of contraception include: true sexual abstinence (not having any type of intercourse); hormonal methods of contraception (oral, injected, vaginal rings, patch, implanted, etc.); placement of an intrauterine device or intrauterine system; barrier methods of contraception (condom or occlusive diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

Premenopausal women whose partner is a woman or whose partner is a man with a history of vasectomy are exempt from requiring the use of a method of birth control.

EXCLUSION CRITERIA:
Patients who have any of the following during the screening visit are not eligible for enrollment in this study:

1. Known history of hypoparathyroidism resulting from an activating mutation in the CaSR gene or impaired responsiveness to PTH (pseudohypoparathyroidism). If unknown, it shall be assumed to be not-present.
2. Any disease that might affect calcium metabolism or calcium-phosphate homeostasis other than hypoparathyroidism, such as active hyperthyroidism, Paget's disease, insulin-dependent diabetes mellitus (IDDM) or poorly controlled Type II diabetes mellitus (HbA1C 9+%), severe *and* chronic cardiac, liver or renal disease, Cushing's syndrome, neuromuscular disease such as rheumatoid arthritis, myeloma, pancreatitis, malnutrition, rickets, recent prolonged immobility, active malignancy, primary or secondary hyperparathyroidism, a history of parathyroid carcinoma, hypopituitarism, acromegaly, or multiple endocrine neoplasia types I and II.
3. To be eligible, patients with a history of thyroid cancer must be documented to be disease-free for a period of at least 5 years (or 2 years with evidence of follow up and a doctor's note of clearance).
4. Patients dependent on regular parenteral calcium infusions (e.g. calcium gluconate) to maintain calcium homeostasis.
5. Patients that have undergone gastric resection or have active peptic ulcer disease requiring medical therapy.
6. Use of prohibited medications such as, raloxifene hydrochloride, lithium, methotrexate, or systemic corticosteroids within the last 6 months.
7. Treatment with PTH-like drugs, including PTH(1-84), PTH(1-34) or other N terminal fragments or analogs of PTH or PTH-related protein within the last 6 months.
8. Other drugs known to influence calcium and bone metabolism, such as calcitonin, sodium fluoride, or cinacalcet hydrochloride within the last 6 months.
9. Use of oral bisphosphonates within the previous 6 months or IV bisphosphonate preparations within the previous 12 months prior to screening.
10. Seizure disorder/epilepsy and a history of a documented seizure within the previous 6 months.
11. In regard to participants between 18 and 21 years of age: Presence of open epiphyses as determined by x-ray.
12. Radiotherapy to the skeleton within 5 years.
13. Serum 25-hydroxyvitamin D levels greater than 1.5-fold the laboratory upper limit of normal. (i.e., 151+ ng/mL)
14. Any disease or condition in the opinion of the Investigator that has a high probability of precluding the patient from completing the study or where the patient cannot or will not appropriately comply with study requirements.
15. Participation in any other investigational trial in which receipt of investigational drug or device occurred within 6 months prior to screening for this study.
16. Pregnant or lactating women.
17. History of diagnosed drug or alcohol dependence within the previous 3 years.

18. Clinical history of renal calculi within the past 6 months.
19. Any condition that negatively affects gastrointestinal absorption, including but not limited to short bowel syndrome, bowel resection, tropical sprue, celiac disease, ulcerative colitis, and Crohn's disease.
20. Chronic/severe cardiac disease including but not limited to cardiac insufficiency, arrhythmias, bradycardia (resting heart rate < 60 beats/minute), or hypotension (systolic and diastolic blood pressures < 100 and 60 mmHg, respectively).
21. History of cerebrovascular accident (CVA) in the past 5 years or earlier, if there is residual impairment that would affect participation in the study.

RECRUITMENT [Study is closed to new enrollment]:
Study subjects will be enrolled from the RACE Study (IRB AAAI1649) being conducted at Columbia University Medical Center (Metabolic Bone Diseases Program). Participants from other sites in the multicenter RACE Study, from within the Unites States, will also be eligible for enrollment.

All participants will sign the HEXT Consent Form.

Subjects will be recruited by the study physicians, Dr. Bilezikian, Dr. Rubin, Dr. Cusano or by study coordinators. We expect that the Hypoparathyroidism Association (HPTH.org) and study site investigators from the earlier multisite studies will be involved in referring potential study subjects.

The HEXT Study intends to have a total enrollment of 75 participants. Of the 10 new "slots" available we anticipate the some of these will be participants who complete the REPLACE, RELAY, or RACE Studies, and that some will be new participants who have hypoparathryoidism but haven't been on PTH(1-84) yet. The reason for adding 10 new "slots" is to ensure that we can reach our overall recruitment goals.

CONFIDENTIALITY OF STUDY DATA:
Study data will be collected into computer files, which will be kept on a password protected computer ("End User Device") with an encrypted hard drive. All files that contain any PHI or PII will be individually password-protected on those encrypted and password protected systems. We also utilize a "Multi-User Server" to store study data and that server is certified with the Columbia University Medical Center Information Technology Department as System ID 34.

Study participants will be given a study number and an acrostic, the key to which will be kept on a password protected file on the encrypted and password protected computer. Study specimens for storage will be marked only with dates and the participants study number and/or acrostic. Therefore, the only place where the study codes can be linked to the participants is in the key file protected as previously stated.

Likewise, any specimens that are ever shipped to another lab for processing will be unidentifiable to non-study staff.

All participants will sign a study specific HIPAA form upon enrollment.

POTENTIAL RISKS:
The potential risks to participation include, blood draw risks, radiation exposure from DXA and HR-pQCT, changes in blood and urine calcium levels, and PTH injection site reactions.

Blood Draw:
Having blood drawn might be painful. One can potentially bleed excessively or have a bruise at the site of the needle-stick. Rarely, people could have inflammation or infection at the site of the needle-stick.

Radiation Exposure:
In a DXA exam (bone density test) and HR-pQCT exam participants are exposed to radiation. However, the amount of radiation exposure in this study is within the limits allowed by the FDA for research of this kind and is also consistent with the guidelines of the Columbia University Joint Radiation Safety Committee. However, because radiation exposure is cumulative throughout one's lifetime, additional exposure should always be carefully considered.

This study performs DXA and HR-pQCT at 6-month time intervals and never more frequently.

PTH injection site reactions:
These reactions can include pain, bruising, redness, itching, bleeding or infection.

Osteosarcoma risk:
When rats are exposed to teriparatide [PTH(1-34)] at very high doses (3 to 58 times higher than the human dose) for what is equivalent to 75 years of human life, a rare cancer known as osteosarcoma can develop. The risk to human subjects appears to be much less if not a risk at all. Over 1.5 million patients have been exposed to teriparatide or to PTH(1-84) over the past 9 years. At most, only 6 cases of osteosarcoma have been reported, of which only 3 have been published. Even if these 6 cases were documented to have been osteosarcoma (and there is reasonable doubt on this point), one would expect this number based upon epidemiological expectations alone. The incidence of osteosarcoma in adult human subjects is 1 per 250,000. These six cases, then, if indeed are validated, would be consistent with epidemiological expectations with inferring causality to the PTH molecule. Among the millions of other individuals who have a disorder characterized by higher than normal levels of PTH for long periods of time (hyperparathyroid disorders) osteosarcoma, is exceedingly rare. The predominance of evidence, therefore, is against PTH as a cause of osteosarcoma in human subjects. PTH(1-34) (Forteo®) was approved for the treatment of osteoporosis in 2002, however, the labeling as instructed by the FDA carries with it a "black box" warning. PTH(1-84) (Natpara®) is FDA-approved for the treatment of hypoparathyroidism and will also carry a “black box” warning.

The design of this research study does not affect the care received by the primary care physicians (PCPs) of the participants. Specifically, if during the study, the PCP wishes to start a participant on a medication, they may do so. Thus, participating in this study should not put participants at any risk for diminishing care by their PCP. Likewise, no drugs other than calcium and vitamin D

have been approved as a therapy for hypoparathyroidism and therefore, our study is not keeping participants from taking any approved therapy during the study.

POTENTIAL BENEFITS:
Participants may learn about the nature of how minerals are processed in their bones, and about their bone density and bone quality. Information about how PTH affects the metabolism of the bones is likely to become clearer as a result of studying all the test results.

On a greater scale, the information that our participants help us gather from this study may help not only other people with hypoparathyroidism, but also people with osteoporosis who might use teriparatide or PTH(1-84).