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Principal Investigator

Name, Degree	Branch/Institute	Bldg/Rm	Phone	E-mail
Rachel I. Gafni, MD	CSDB, NIDCR	30/228	301-594-9924	gafnir@mail.nih.gov

Associate Investigators

Name, Degree	Branch/Institute	Bldg/Rm	Phone	E-mail
Beth Brillante, RN, MBA	NIDCR	10/9C403	301-451-2260	bbrillante@mail.cc.nih.gov
Lori Guthrie, RN	NIDCR	10/8N118A	301-594-0844	guthriel@mail.nih.gov
James Reynolds, MD	CC	10/1C461	301-496-5675	jreynolds@mail.cc.nih.gov
Alison Boyce, MD	NIDCR	30/228	301-443-2700	alison.boyce@nih.gov
Michael T. Collins, MD	NIDCR	30/228	301-496-4913	Mc247k@nih.gov
Laura L. Tosi, MD	NHGRI	10/3C710	301-453-2832	ltosi@childrensnational.org
Andrea Burke, MD, DMD	NIDCR	30/228	301-443-2704	Andrea.burke@nih.gov
Mary Scott Ramnitz, MD	NICHD	30/228	301-408-6988	Maryscott.ramnitz@nih.gov

Non-NIH Collaborators

Name, Degree	Institution/Location	E-mail
Hua Zhou, MD	Helen Hayes Hospital	zhouh@helenhayeshosp.org
David Dempster, PhD	Helen Hayes Hospital	dempster@helenhayeshosp.org
Klaus Klaushofer, MD	Ludwig Boltzmann Institute of Osteology, Vienna, Austria	Klaus.Klaushofer@osteologie.at
Paul Roschger, PhD	Ludwig Boltzmann Institute of Osteology, Vienna, Austria	paul.roschger@osteologie.at
Craig Langman, MD	Northwestern University, CMH	c-langman@northwestern.edu

Research Contact

Name, Degree	Branch/Institute	Bldg/Rm	Phone	E-mail
Lori Guthrie, RN	CSDB/NIDCR	10/8N11	301-594-0844	guthriel@mail.nih.gov

Medical Advisory Investigator

Name, Degree	Branch/Institute	Bldg/Rm	Phone	E-mail
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Total requested accrual:

Subjects – maximum accrual 69 (36 new subjects to start PTH, up to 10 screened but not started on PTH, 23 previously enrolled)
Volunteers (0)

Project Uses Ionizing Radiation:

- ☐ No ☒ Yes
☐ Medically-indicated only
☐ Research-related only
☒ Both

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Drug/Device/#: PTH 1-34/#102,394
Sponsor: Rachel I. Gafni, MD

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David Dempster (via Helen Hayes Hospital)
Klaus Klaushofer (via Ludwig Boltzmann Institute of Osteology)

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Samples are being stored: ☐ No ☒ Yes

Flesch-Kincaid reading level of consent form: 9.1 (7.9 excluding the term "hypoparathyroidism")

Précis

Objectives

The primary objective of this study is to evaluate the skeletal effects of hormone replacement therapy with HPTH in hypoparathyroidism.

Study Population

This study will enroll up to 69 subjects with physician-diagnosed hypoparathyroidism.

Design

This study will treat hypoparathyroid individuals with synthetic human PTH 1-34 (HPTH) for up to 5 years, periodically assessing skeletal changes through biochemical markers and iliac-crest bone biopsies, which will allow for ultrastructural, cellular, and molecular analyses.

With respect to HPTH treatment, this study is a single group, within-subjects, repeated measures treatment trial. With respect to all bone biopsy analyses, the design is a parallel group design with each subject allocated to one of the 3 biopsy follow-up times: 1, 2 or 4 years after initiation of HPTH therapy. Post-baseline biopsy timing will be randomly assigned (1:1.2:1.4, respectively) to each subject, stratified by gender and by menopausal status, when relevant. Changes from baseline (time 0) to 1, 2 and 4-years will be compared. Subjects who were on conventional therapy in the former version of the protocol will also be randomized into the new study design. In contrast to new subjects, whose biopsy is performed at the end of the conventional care run-in period, the pre-conventional care biopsy will be used as the baseline for the those subjects entering the new design after having been on conventional care in the older protocol. Because it is not known with certainty what effects duration of time on conventional therapy will have on biopsy results, randomization will also be stratified on status of prior study participation. The subjects who were on HPTH therapy at the time of the protocol redesign are followed as a separate group under this protocol.

Outcome Measures

Primary:

Changes in static and dynamic bone histomorphometry after 1 year, 2 years, and 4 years of HPTH therapy. Primary outcome measurements include:

- Mineralized perimeter
- Bone formation rate

- Cortical width
- Cortical area
- Osteoid width
- Osteoid perimeter
- Mineral apposition rate

Secondary:

1. Changes in bone mineralization density distribution at 1, 2 and 4 years of HPTH therapy. The specific outcomes that will be measured include:
 - Spectral calcium-mean
 - Calcium-peak
 - Calcium-width
2. Changes from baseline will be assessed in the following outcomes:
 - Biochemical markers of bone metabolism: osteocalcin, bone-specific alkaline phosphatase, collagen cross-linked N-telopeptide.
 - Serum and urine calcium; 1,25-OH₂-Vitamin D
 - Bone density assessed by DXA and quantitative CT
 - Nephrocalcinosis by ultrasound and CT
 - Fatigue Symptom Inventory
 - 6-Minute Walk Test
 - SF-36 Health Survey

Tertiary:

Changes in blood chemistries and FGF23, renal mineral handling, and PTH sensitivity with the initiation of HPTH, which include:

- Serum albumin, calcium, phosphorus, magnesium, sodium, potassium, chloride, Total CO₂, creatinine, glucose, urea nitrogen, and FGF23
- Urine cAMP, creatinine, phosphorus, calcium, and pH

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List of Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BMD	Bone mineral density
CaSR	Calcium-sensing Receptor
CBC	Complete Blood Count
CRF	Case Report Form
CT	Computed Tomography
DCC	Data Coordinating Center
DNA	Deoxyribonucleic Acid
DSMC	Data and Safety Monitoring Committee
DXA	Dual-energy X-ray Absorptiometry
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
HPTH	Synthetic Human PTH 1-34
IND	Investigational New Drug Application
IRB	Institutional Review Board
MCV	Mean Corpuscular Volume
NIDCR	National Institute of Dental and Craniofacial Research
NIH	National Institutes of Health
PDS	Pharmaceutical Development Service
PRPL	Patient Recruitment and Public Liaison
PTH	Parathyroid Hormone
rhPTH	Recombinant human PTH 1-34
RBC	Red Blood Cells
RDW	Red Cell Distribution Width
RSC	Radiation Safety Committee
SAE	Serious Adverse Event
UP	Unanticipated Problem

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WBC White Blood Cells

1 INTRODUCTION

Parathyroid hormone (PTH) is an 84-amino acid peptide produced by the parathyroid glands; its primary function is the maintenance of serum calcium levels by enhancing calcium release from the bone, increasing calcium reabsorption by the kidney, and stimulating the formation of 1,25-OH₂-Vitamin D, which allows for increased intestinal calcium absorption. Hypoparathyroidism is a rare condition caused by inadequate production or secretion of PTH. It may be due to a variety of genetic disorders, autoimmune conditions and infiltrative diseases, or as a result of parathyroid gland injury or removal during neck surgery. PTH deficiency leads to hypocalcemia, hyperphosphatemia, and, frequently, hypercalciuria. The hypercalciuria can be particularly severe in patients with hypoparathyroidism due to activating mutations in the calcium-sensing receptor; their altered responsiveness to ambient calcium levels leads to urinary calcium wasting, even in the face of hypocalcemia. The manifestations of hypocalcemia can be significant, including neuromuscular irritability causing tetany, cramping, carpopedal spasms, and seizures. The only readily available and FDA-approved treatments are vitamin D analogs such as calcitriol (1,25-OH₂ Vitamin D) given in conjunction with calcium supplementation. Calcitriol increases intestinal calcium absorption, leading to increased serum calcium levels, however it does not correct the impaired renal calcium reabsorption that is typical of this disorder. Thus, while conventional therapy may normalize serum calcium levels, management is often complicated by further increases in urine calcium excretion. Chronic hypercalciuria may lead to nephrocalcinosis, renal insufficiency or failure.¹

Hypoparathyroidism is one of the few remaining hormone deficiencies for which hormone replacement therapy is not approved. Replacement therapy using synthetic human parathyroid hormone 1-34 (HPTH) in hypoparathyroidism has been studied in several clinical trials at the NIH. The initial crossover pilot study of 10 subjects demonstrated that HPTH maintained both serum and urinary calcium in the normal range over a 24-hour period when given as a single daily subcutaneous injection for 10 weeks.² HPTH resulted in a lower urinary calcium level than calcitriol for a given level of serum calcium. Subsequently, results of a randomized controlled-dose study showed that twice-daily, compared to once daily, HPTH given for 14 weeks provides effective short-term treatment for hypoparathyroidism with a markedly reduced total daily dose, an apparent reduction in bone turnover, and a decreased incidence of bone pain compared to a once-daily regimen. Twice daily HPTH produced higher levels of serum calcium, with fewer fluctuations into the hypocalcemic range. Markers of bone turnover were elevated above the normal range in response to both treatment regimens, however, twice daily produced significantly lower serum marker levels suggesting that this dose regimen increased bone turnover to a lesser extent than once daily HPTH.³ A similar study in children also showed better metabolic control with twice daily HPTH versus a

single daily injection, however, there were no significant differences in bone markers between the 2 groups.⁴ In a long-term study, 27 adults with hypoparathyroidism were randomized to either calcitriol or HPTH. The findings demonstrated that twice-daily HPTH administration maintains serum calcium in the low normal or just below the normal range over a 3-year period; there were no statistically significant difference in urine and serum calcium between the two groups. In the HPTH treated group, however, markers of bone turnover (osteocalcin, alkaline phosphatase) were significantly elevated during the 3-year study, at levels at least 2-fold greater than normal. Despite this increase in bone turnover, there was no change in the bone mineral density (BMD) as measured with dual energy x-ray absorptiometry (DXA). This contrasts with the calcitriol-treated group that experienced a rise in spinal bone mineral density over time with no rise in bone markers.⁵

PTH deficiency is associated with decreased skeletal turnover. Adults with chronic hypoparathyroidism develop hypermineralized, dense, bones that are abnormal in their geometric, histomorphometric, and microarchitectural features, presumably due to chronic lack of bone turnover.⁶⁻⁸ Cortical width and cancellous bone volume are increased, while dynamic indices of bone turnover such as bone formation rate and mineral apposition rate are decreased.⁸ The cellular mechanisms underlying the evolution and maintenance of the high bone mass in hypoparathyroidism have not been well explored. Remodeling activities of bone cells (osteoclasts and osteoblasts) involve sequential breakdown of old bone and formation of newly formed bone matrix. Normal bone remodeling involves the excavation of microscopic areas of bone followed by the production of new bone to fill in these areas. Patients with hypoparathyroidism have decreased remodeling activity with low bone turnover⁸ that leads to the accumulation of bone that, under normal circumstances, would be replaced by newly formed bone matrix. With replacement PTH therapy, the rise in bone turnover as evidenced by the rise in bone markers should restore this physiologic state. The concern, however, is that in the 3-year NIH study,⁵ these biochemical markers remain above the normal range, suggesting a chronically high bone turnover state. Recently, NIH reported a case of a 20 year-old hypoparathyroid woman with a calcium sensing receptor (CaSR) mutation treated with HPTH for 14 years; HPTH treatment did not ameliorate her hypercalciuria nor did it prevent the development of nephrocalcinosis and bone biopsies revealed dramatic increases in cancellous bone volume.⁹ However, her young age at the time of PTH initiation makes these finding not generalizable to adults with hypoparathyroidism. An interim analysis of 5 subjects in this particular protocol study has demonstrated that, after 1 year of PTH therapy, bone volume and bone remodeling as assessed by bone biopsy and biochemical markers are markedly increased compared to baseline (unpublished data); however, it is not known if these changes will persist or return to baseline over time. Preliminary unpublished data presented by investigators also treating hypoparathyroid subjects with PTH

1-84 suggest that the increases in bone turnover may return to normal by 2 years on PTH therapy.^{10,11} Given this conflicting data, additional data is necessary, as there remains the possibility of compromised bone quality and strength with long-term PTH therapy.

Although HPTH is not approved or marketed for use in hypoparathyroidism, a structurally identical drug, recombinant human PTH (rhPTH, teriparatide, Forteo®, Eli Lilly and Co.) has been shown to restore skeletal integrity and increase bone mass in the elderly population and was approved for treatment of osteoporosis in 2002.^{12,13} Daily rhPTH treatment in the patients with osteoporosis has an anabolic effect on cortical bone and improves cancellous bone microarchitecture.¹⁴ Whereas much information is currently known about the effects of rhPTH on osteoporosis in the elderly and the NIH studies have examined HPTH's effects on calcium metabolism in hypoparathyroidism, very little is known about the effects of HPTH on hypoparathyroid bone. This study is uniquely designed to address these questions. Exploration of this area is important to elucidate the role of PTH in maintaining skeletal integrity, especially in the setting of the recent availability of PTH for the off-label use of the treatment of hypoparathyroidism.

This study was originally designed to evaluate the effects of twice versus three times daily HPTH replacement on the skeleton of children and adults with hypoparathyroidism. However, preliminary data from this study suggested that the effects of the two dosing regimens are similar, and new questions about the long-term effects of HPTH therapy on bone have emerged. In addition, the previous version of this protocol called for 3 to 4 iliac crest biopsies per subject, and concerns had been raised about subject burden and the integrity of data from multiple biopsies on the same side of the iliac crest. Therefore, we originally revised the protocol to allow for an examination of effects of HPTH over a 5-year period, exclude children, and to reduce the number of biopsies to 2 per subject.

This document describes a revision to the original protocol (October 27, 2006 – April 28, 2009); this current protocol (initially approved April 9, 2010) examines the effects of HPTH over a 5-year period, reduces the number of biopsies to two per subject, and eliminates the comparison between twice-a-day and three-times-a-day dosing of HPTH. This protocol uses twice-daily dosing only and will recruit a total of 36 new subjects with hypoparathyroidism. This protocol has also re-enrolled qualified subjects that were on either conventional therapy (calcium and calcitriol) or HPTH therapy under the original protocol.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess changes in static and dynamic bone histomorphometry after 1 year, 2 years, and 4 years of HPTH therapy.

2.2 Secondary Objectives

The secondary objectives are:

1. To explore changes in bone mineralization density distribution as assessed by quantitative back-scattered electron imaging after 1 year, 2 years, and 4 years of HPTH therapy.
2. To assess changes in serum and urine calcium, bone density, nephrocalcinosis, and biochemical markers of bone metabolism over the course of HPTH therapy.
3. To explore whether the effects of HPTH on the microarchitectural characteristics of bone and biochemical markers of bone and calcium metabolism differ by the presence or absence of the calcium-sensing receptor mutation and other subject characteristics.

2.3 Tertiary Objective

The tertiary objective is to assess early changes in blood chemistries and FGF23, renal mineral handling, and PTH sensitivity with the initiation of HPTH in patients with hypoparathyroidism.

3 SUBJECTS

3.1 Description of Study Populations

Under the current protocol, 36 new subjects (i.e., not previously enrolled) with physician-diagnosed hypoparathyroidism who meet the revised eligibility criteria listed below will be enrolled. Previously enrolled subjects who were on conventional therapy for hypoparathyroidism were re-evaluated under the revised eligibility criteria and re-consented and re-enrolled if they were eligible and interested.

Previously enrolled subjects who were on HPTH therapy were re-consented and allowed to continue on HPTH therapy in the current protocol as a separate group that would not enter the randomization nor have any additional biopsies performed. However, they will return to the NIH for 6-month follow-up visits and assessments. Those subjects on HPTH at the time of re-consent were not re-assessed using the revised criteria, and their study data will be analyzed separately from the other subjects' data.

3.2 Inclusion Criteria

1. Age eligibility at screening:
 - a. Premenopausal women: aged 18 to 45 years,
 - b. Postmenopausal women: aged ≥ 53 years to 70 years and 5 years since last menses. For women without a uterus, subjects must have a clinical history of menopause for at least 5 years and an FSH > 30 U/L.
 - c. Men: aged 18 to 70 years
2. Physician-diagnosed hypoparathyroidism of at least 1-year duration, confirmed by medical record review. The investigators will confirm the diagnosis during the screening visit at which time the subject must have an intact PTH < 30 pg/mL.

3.3 Exclusion Criteria

1. Moderate to severe hepatic disease defined as hepatic transaminases (ALT and AST) > 2 times the upper limit of normal
2. Severe renal insufficiency defined as a calculated GFR < 25 mL/min/1.73 m², using the CKD-EPI equation¹⁵.
3. Allergy or intolerance to tetracycline antibiotics
4. Pregnant or lactating or planning to become pregnant during the course of the study. (Women who are able to get pregnant must agree to use an effective form of birth control while in this study.)
5. Perimenopausal defined by no menses for 6 months to 5 years and an FSH > 20 U/L at the screening and/or baseline visits.
6. Chronic diseases that might affect mineral metabolism such as diabetes, celiac disease, Crohn's disease, Cushing's syndrome, or adrenal insufficiency
7. Concurrent treatment with doses of thyroid hormone intended to suppress thyroid stimulating hormone below the assay's detection limit or persistent thyroid cancer
8. History of a skeletal disease unrelated to hypoparathyroidism, such as osteoporosis or low bone density (defined as a DXA Z-Score < -2 in all subjects or T-score < -2 in subjects ≥ 20 year old), osteosarcoma, Paget's disease, alkaline phosphatase > 1.5 times the upper limit of normal, or metastatic bone disease

9. History of retinoblastoma or Li-Fraumeni syndrome
10. History of treatment with bisphosphonates, calcitonin, tamoxifen, selective-estrogen receptor modulators, or directed skeletal irradiation
11. Use of oral or intravenous corticosteroids or estrogen replacement therapy for more than 3 weeks within the last 6 months
12. Use of depot medroxyprogesterone for contraception within the past 12 months
13. Chronic inadequate biochemical control with conventional therapy and/or calcium infusion dependent
14. Seizure disorder requiring antiepileptic medications
15. Treatment with PTH for more than 2 weeks continuously at any time, prior to study entry
16. Any cognitive impairment that limits the subject's ability to comply, independently or through the assistance of a legally authorized representative, with protocol procedures
17. Open epiphyses as determined by an X-ray of the hand and wrist in subjects < 21 years of age.

4 STUDY DESIGN AND METHODS

4.1 Study Overview

As revised in April 2010, the current protocol involves the recruitment of 36 new subjects (not previously enrolled) with hypoparathyroidism and the re-enrollment of qualifying subjects from the original protocol who were either on conventional therapy (calcium and calcitriol) or on HPTH therapy. All newly enrolled subjects will be placed on conventional therapy for 2 to 6 months (\pm 1 month), have a baseline bone biopsy performed at the start of HPTH therapy, and have their second biopsy performed after 1, 2, or 4 years of HPTH therapy, with the timing of the second biopsy determined by random assignment. The subjects on conventional therapy under the previous version of the protocol were randomized to a second biopsy at year 1, 2, or 4; however, their pre-conventional therapy biopsy will be used as their baseline biopsy. Subjects who were receiving HPTH under the previous version of the protocol are being maintained on HPTH in a separate group as a means to continue their care and to describe the effects of HPTH therapy on bone and markers of bone metabolism over time. Those subjects will not have another biopsy performed. All new and re-enrolled subjects will receive HPTH therapy for a maximum of 5 years. Subjects will be initiated on HPTH at a starting dose of 0.2 μ g/kg/dose subcutaneously twice a day. Because HPTH will not be administered to subjects with open epiphyses, a bone x-ray will be conducted on all subjects less than 21 years of age to confirm epiphyseal fusion. Subjects currently on HPTH

therapy 3 times per day under the previous version of the protocol will be placed on HPTH 2 times per day, initially keeping the total daily dose the same. Over the 5-year course of HPTH therapy, the subjects will have their blood and urine measured repeatedly and evaluated by the study investigators, who will adjust subjects' HPTH dosing according to a standardized algorithm. During HPTH therapy, subjects will visit the NIH Clinical Center every 6 months for outcome assessments. At the conclusion of the 5-year treatment period, subjects will be transitioned back to conventional care and followed for a minimum of 3 months before returning them to care under their own physicians. All subjects, including those who discontinue HPTH prior to 5 years, will be asked to return for a final, follow-up visit approximately 6 months after the start of the post-HPTH stabilization phase (i.e., the initiation of transition to conventional care).

With a study period of approximately 6 years, the duration of the active phase of the study will be 9 years. New subjects will have 13 NIH visits, subjects currently on conventional care will have 12 NIH visits, and subjects currently on HPTH therapy will have up to 9 visits, depending on the amount of time they have been treated with HPTH under the previous version of the protocol. Additional visits may occur in order to evaluate adverse events.

The study design diagram and the schedule of events may be found in Appendix 24.3 and Appendix 24.4.

4.2 Recruitment

It is estimated that new patient accrual will take approximately 8 years. Recruitment strategies will include IRB-approved advertising and direct contact with healthcare providers. Printed advertisements may be sent to health care providers and patient support groups, such as the Hypoparathyroidism Association. Interested individuals will contact the NIH Patient Recruitment and Public Liaison (PRPL) via a toll free telephone number (800-411-1222) or email (prpl@mail.cc.nih.gov) to be prescreened for the protocol using questions provided by the research team (Appendix 24.2). Individuals who are deemed eligible by the PRPL staff will have their contact information forwarded to the study staff. In addition, the current Clinicaltrials.gov listing for the study has been updated to reflect the current design of the protocol, and a recruitment website (<http://www.hypoparathyroidstudy.org>) containing IRB-approved content is available on the internet.

4.3 Screening

4.3.1 Pre-Screening

Potential subjects who have contacted the study team and indicated interest in the study will be pre-screened by telephone. During this phone pre-screen, study staff will briefly describe the study and

administer a pre-screening questionnaire (Appendix 24.2) to those who are interested in participating. Patients who are eligible after completing the telephone pre-screen interview will be asked to arrange for a copy of their medical records to be sent to the clinical site. Based on a review of their medical records, further qualified subjects will be scheduled for an inpatient screening visit at the NIH Clinical Center to obtain informed consent and then to further establish eligibility.

4.3.2 Inpatient Screening Visit

Newly recruited subjects (subjects not previously enrolled in this protocol) will attend a 2 to 3 day inpatient screening visit at the NIH Clinical Center in order to obtain informed consent, to discuss protocol procedures and expectations, to establish eligibility, and to optimize conventional therapy. Procedures and tests during this inpatient screening visit will include:

1. History

- a. Detailed history of disease
- b. Current medications
- c. Dietician consultation
- d. Short Calcium Questionnaire (Appendix 24.5)

2. Physical Exam

- a. Height and weight measurement
- b. Vital signs (pulse, blood pressure, temperature, and respiratory rate)
- c. Physical examination

3. Blood tests

- a. Blood chemistries: sodium, potassium, chloride, bicarbonate, creatinine, glucose, urea nitrogen, albumin, calcium, magnesium, phosphorous, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, LD, total protein, total CK, and uric acid
- b. TSH and Free T4
- c. 25-OH vitamin D, 1,25 (OH)₂ vitamin D, intact PTH

- d. Complete blood count (CBC): white blood cells (WBC), red blood cells (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), red cell distribution width (RDW), and platelets
 - e. Mineral panel or calcium level (repeated as needed during the visit): albumin, calcium, magnesium, and phosphorous
 - f. Ionized calcium
 - g. DNA testing for genetic forms of hypoparathyroidism, if indicated (separate consent form, Appendix 24.6)
4. Urine testing
- a. Urine pregnancy test in females with childbearing potential
 - b. Urinalysis: glucose, protein, urobilinogen, pH, hemoglobin, ketones, nitrite, leukocyte esterase, appearance, specific gravity, color, RBC, WBC, and squamous cells
 - c. 24-hour urine for calcium, phosphorus, creatinine, magnesium, sodium, citrate, pH, and potassium
5. Imaging
- a. Renal Ultrasound to assess the presence of nephrocalcinosis
 - b. Radiograph of hand and wrist to confirm epiphyseal fusion in subjects < 21 years of age
 - c. DXA scan of the spine, femur, radius and total body to assess bone density

4.4 Study Design

With respect to HPTH treatment, this study is a single group, within-subjects, repeated measures treatment trial. With respect to all bone biopsy analyses, the design is a parallel group design with each subject allocated to one of the 3 biopsy follow-up times: 1, 2 or 4 years after initiation of HPTH therapy. Post-baseline biopsy timing will be randomly assigned (1:1.2:1.4, respectively) to each subject, stratified by gender and by menopausal status, when relevant. Changes from baseline (time 0) to 1, 2 and 4-years will be compared. Subjects who were on conventional therapy in the former version of the protocol will also be randomized into the new study design. In contrast to new subjects, whose biopsy is performed at the end of the conventional care run-in period, the pre-conventional care biopsy will be used as the baseline for the those subjects entering the new design after having been on conventional care in the older protocol. Because it is not known with certainty what effects duration of time on conventional therapy will have on biopsy results, randomization will also be stratified on status of prior study participation. The

subjects who were on HPTH therapy at the time of the protocol redesign are followed as a separate group under this protocol.

4.5 Study Procedures

4.5.1 Conventional Therapy Prior to Start of HPTH

After the screening visit, newly enrolled subjects will complete a run-in period on conventional therapy of calcium and calcitriol. The run-in period will last 2 to 6 months (\pm 1 month), depending on disease status at enrollment and clinical response to optimized conventional therapy. During the run-in period, the clinical investigators will provide conventional care for hypoparathyroidism, which includes periodic blood and urine testing and adjustments in calcium and calcitriol dosing. If necessary, thyroid hormone replacement will be optimized. Subjects may also receive vitamin D supplementation to ensure 25-OH-Vitamin D levels \geq 25 ng/mL.

4.5.2 Inpatient Baseline Visit and Start of HPTH Therapy

This visit occurs at the end of the conventional therapy run-in period. The purpose of this 7 to 10 day inpatient visit is to obtain baseline clinical and research measurements, to perform a baseline biopsy, to initiate the 5-year HPTH therapy, and to randomize subjects to the timing of their second biopsy. This visit is only required for newly enrolled subjects and subjects currently on conventional care under the previous version of the protocol. Both groups of subjects will complete the same procedures at this visit, except for the consent process and the iliac crest biopsy. Subjects on conventional care from the previous version of the protocol will be re-consented at this visit after a review of their eligibility; however, they will not undergo a biopsy at this visit. Their pre-conventional therapy biopsy will be substituted for their baseline biopsy. The newly enrolled subjects will undergo a baseline iliac crest biopsy at this visit. At the baseline visit, the following procedures will be conducted:

1. History
 - a. Detailed history of current disease and adverse events
 - b. Current medications
 - c. Dietician consultation
 - d. Short Calcium Questionnaire (Appendix 24.5)
 - e. SF-36 Health Survey (Appendix 24.7)
2. Physical Exam

- 298 a. Height and weight measurement
- 299 b. Vital signs (pulse, blood pressure, temperature, and respiratory rate)
- 300 c. Physical examination
- 301 3. Fitness measures
- 302 a. Fatigue Symptom Inventory (Appendix 24.8)
- 303 b. 6-Minute Walk Test (Appendix 24.9)
- 304 4. Blood tests (IV catheter may be placed for convenience of drawing blood during this inpatient
- 305 visit)
- 306 a. Blood chemistries: sodium, potassium, chloride, bicarbonate, creatinine, glucose, urea
- 307 nitrogen, albumin, calcium, magnesium, phosphorous, alkaline phosphatase, ALT, AST,
- 308 total bilirubin, direct bilirubin, LD, total protein, total CK, and uric acid
- 309 b. TSH and Free T4
- 310 c. 25-OH vitamin D, 1,25 (OH)₂ vitamin D*, intact PTH
- 311 d. CBC: WBC, RBC, hemoglobin, hematocrit, MCV, RDW, and platelets
- 312 e. Research bloods for storage and potential future use (as yet undetermined)
- 313 f. Mineral panel or calcium level (performed and repeated as needed): albumin, calcium,
- 314 magnesium, phosphorous*
- 315 g. Bone-specific alkaline phosphatase
- 316 h. Osteocalcin
- 317 i. Ionized calcium
- 318 j. FGF23*
- 319 k. Acute care panel*
- 320 **Blood draws for an acute care panel, mineral panel, 1,25 (OH)₂ vitamin D, and FGF23 will be*
- 321 *completed at 8AM, 12PM, 4PM, and 8PM on the first day of HPTH therapy (Day 0). Blood*
- 322 *draws for an acute care panel, mineral panel, 1, 25 (OH)₂ vitamin D, and FGF23 will also be*
- 323 *collected at 8AM on the second day of HPTH therapy (Day 1). A morning blood draw will be*
- 324 *completed on subsequent in-patient days for an acute care panel.*
- 325 5. Urine testing
- 326 a. Urine pregnancy test in females with childbearing potential

- b. Urinalysis: glucose, protein, urobilinogen, pH, hemoglobin, ketones, nitrite, leukocyte esterase, appearance, specific gravity, color, RBC, WBC, and squamous cells
 - c. Two 24-hour urine collections for testing of calcium, phosphorus, creatinine, magnesium, sodium, citrate, N-telopeptide, pH, and potassium
 - d. Spot urine for cAMP, creatinine, phosphorous, calcium, and pH
6. Imaging
- a. Renal ultrasound to assess the presence of nephrocalcinosis
 - b. CT of the kidney without contrast to assess the presence of nephrocalcinosis
 - c. DXA scan of the spine, femur, radius and total body to assess bone density
 - d. Quantitative CT of the L1 and L2 spine to assess bone density
7. Baseline bone biopsy for newly enrolled subjects (see Section 4.5.6)
8. Randomization of newly enrolled subjects and previously enrolled conventional care subjects to a second biopsy after 1, 2, or 4 years of HPTH therapy. A dynamic allocation scheme will be used to ensure balance across biopsy arms by gender, menopausal status, and prior participation in the protocol (see Section 10.3). The principal investigator or designee will perform the randomization procedure using a secure, web-based randomization system.

All subjects will receive HPTH at a starting dose of 0.2 µg/kg/dose subcutaneously twice a day. After the initial dosing, HPTH will be titrated based on serum calcium levels, according to the dosing algorithm in Appendix 24.10. Each subject will receive education and written materials about HPTH administration and dosing adjustment prior to discharge (Appendix 24.11). The drug will be provided to all subjects free of charge. The NIH Clinical Center Pharmaceutical Development Service (PDS) will be responsible for labeling, storing, preparing, dispensing, and maintaining accountability records for HPTH.

4.5.3 Follow-up Visits During HPTH Therapy

Subjects will be seen at the NIH every 6 months (± 2 weeks) until they have completed up to 5 years of HPTH therapy. The second biopsy will occur at one of these visits, with the timing of that biopsy determined by random assignment. Subjects currently on HPTH therapy under the previous version of the protocol will be re-consented at the first follow-up visit they attend. Follow-up visits may be conducted on an inpatient or outpatient basis at the discretion of the investigator, except for biopsy visits which must be inpatient. Follow-up visits will last 1-3 days if a biopsy is not being performed and 5-7 days if a biopsy is being performed. Additional visits may be scheduled at the discretion of the investigator in order to

assess adverse events or other problems that may arise. All subjects will undergo the procedures and tests described below at each follow-up visit, unless otherwise noted:

1. History

- a. Detailed history of current disease and adverse events
- b. Current medications
- c. Dietician consultation
- d. Short Calcium Questionnaire (Appendix 24.5)
- e. SF-36 Health Survey (Appendix 24.7).

2. Fitness measures

- a. Fatigue Symptom Inventory (Appendix 24.8)
- b. 6-Minute Walk Test (Appendix 24.9)

3. Physical Exam

- a. Height and weight measurement
- b. Vital signs (pulse, blood pressure, temperature, and respiratory rate)
- c. Physical examination

4. Blood tests

- a. Blood chemistries: sodium, potassium, chloride, bicarbonate, creatinine, glucose, urea nitrogen, albumin, calcium, magnesium, phosphorous, alkaline phosphatase, ALT, AST, total bilirubin, direct bilirubin, LD, total protein, total CK, and uric acid
- b. TSH and Free T4
- c. 25-OH vitamin D, 1,25 (OH)₂ vitamin D, intact PTH
- d. CBC: WBC, RBC, hemoglobin, hematocrit, MCV, RDW, and platelets
- e. Research bloods for storage and potential future use (as yet undetermined)
- f. Mineral panel or calcium level (performed and repeated as needed): albumin, calcium, magnesium, phosphorous
- g. Bone-specific alkaline phosphatase
- h. Osteocalcin

- i. Ionized calcium
- j. Twenty-four hour blood sampling: Every 2-hour \pm 15 min sampling (for 24 hours) for calcium, magnesium, phosphorus, and albumin will be done after 1 year on PTH. An IV catheter or PICC line may be placed for convenience of drawing blood during this inpatient visit.
- 5. Urine testing
 - a. Urine pregnancy test in females with childbearing potential
 - b. Urinalysis: glucose, protein, urobilinogen, pH, hemoglobin, ketones, nitrite, leukocyte esterase, appearance, specific gravity, color, RBC, WBC, and squamous cells
 - c. Two 24-hour urine collections for testing of calcium, phosphorus, creatinine, magnesium, sodium, citrate, N-telopeptide, pH, and potassium
- 6. Imaging - to be done at the start of PTH therapy and then annually (with the exception of the DXA)
 - a. Renal ultrasound to assess the presence of nephrocalcinosis
 - b. CT of the kidney without contrast to assess the presence of nephrocalcinosis
 - c. DXA scan of the spine, femur, radius and total body – every visit to assess bone density
 - d. Quantitative CT of the L1 and L2 spine to assess bone density
- 7. Second and final bone biopsy at one of the visits (see Section 4.5.6)

4.5.4 Outpatient Blood and Urine Collections

All subjects will be given a laboratory slip to be used at their local laboratory for measurement of serum calcium and 24-hour urine calcium, sodium, and creatinine. Subjects will be instructed to obtain blood tests at least once a week (\pm 2 days) immediately after starting PTH therapy. After 4 consecutive serum calcium levels within the target range, subjects will be instructed to obtain blood work a minimum of once a month (\pm 1 week). Urine collections should be obtained approximately every 3 months (\pm 2 weeks). Additional outpatient blood or urine tests may be ordered as clinically indicated. Participants will be instructed to have lab results sent to the research team. The principal investigator or designee will review the results of these tests, adjust medication doses, and order additional testing according to the HPTH dosing algorithm (Appendix 24.10). Prior to making any dose adjustment decision, the investigator will assess the subject's adherence to medication instructions. The investigator will record all dosing decisions, along with the laboratory values associated with those decisions.

4.5.5 Monitoring of Calcium-Citrate Ratio and Concomitant Potassium Citrate

All subjects will be monitored for hypocitraturia during the inpatient visits. As hypocitraturia may increase the risk of renal calcifications, subjects with a urinary calcium/citrate ratio greater than 0.7 will receive potassium citrate supplementation, in attempt to lower this ratio. It should be noted that complete normalization of the urinary citrate excretion and reduction of the calcium/citrate may be impossible in these subjects, due to chronic renal tubular dysfunction associated with this disease. Urinary citrate and pH will be monitored on the outpatient collection, as well as during the NIH visits, in subjects treated with potassium citrate. If the urinary pH rises above 7, adjustments to potassium citrate dosing may be made after consultation with the nephrologist on the study team.

4.5.6 Bone Biopsy Procedures

Two percutaneous transiliac crest biopsies will be performed after antibiotic labeling, with one biopsy performed prior to HPTH therapy and the second during HPTH therapy. The biopsy will be performed by a licensed practitioner credentialed in this procedure in the operating room of the NIH Clinical Center under local anesthesia with sedation. The baseline and second biopsy will be obtained from opposite sides. Subjects will be pre-treated with either tetracycline or demeclocycline. Tetracycline will be delivered according to the following schedule: 3 days of tetracycline (250 mg 4 times per day), 12 days off drug, 3 days of tetracycline (250 mg 4 times per day), 4 days off drug and biopsy on the fifth day (+ 7 days). Demeclocycline will be delivered according to the following schedule: 3 days of demeclocycline (150 mg 4 times per day), 12 days off drug, 3 days of demeclocycline (150 mg 4 times per day), 4 days off drug and biopsy on the fifth day (+ 7 days). Refer to Appendix 24.12 for details. The biopsy is performed through a small skin incision (approximately 4 cm), which is closed with stitches that will dissolve within 2 to 3 weeks. The skin over the area of the hip will be cleaned and a numbing medication will be injected with a small needle into the skin, through the underlying tissues, and onto the surface of the bone. A trephine with a 7.5 mm diameter is used to remove the bone specimen. Subjects will undergo a routine pre-anesthesia consult and be asked to sign a separate surgical consent form prior to the procedure.

4.6 End of Participation

4.6.1 Post HPTH Therapy Stabilization and Follow-up

For subjects completing 5 years of HPTH therapy and for subjects who meet withdrawal or treatment failure criteria during the study (see Section 8), the study team will provide care for a minimum of 3 months (\pm 2 weeks) and until the investigator deems them to be stable and ready for transition to local

physicians. During this stabilization phase, subjects will be restarted on calcitriol and calcium supplements and HPTH will be gradually weaned as tolerated to keep calcium levels within the target range. Subjects will undergo periodic blood testing via their local lab (at minimum bi-weekly during the stabilization phase). These lab values will be used to guide adjustments in calcium and calcitriol dosing.

All subjects who receive HPTH therapy for more than 6 months will be asked to return to the clinic to complete a follow-up visit 6 months (\pm 2 weeks) after the start of the post-HPTH stabilization phase. All subjects will undergo the procedures and tests described below during the follow-up visit:

1. History

- a. Detailed history of current disease and adverse events
- b. Current medications
- c. Dietician consultation
- d. Short Calcium Questionnaire (Appendix 24.5)
- e. SF-36 Health Survey (Appendix 24.7).

2. Fitness measures

- a. Fatigue Symptom Inventory (Appendix 24.8)
- b. 6-Minute Walk Test (Appendix 24.9)

3. Physical Exam

- a. Height and weight measurement
- b. Vital signs
- c. Physical examination

4. Blood tests

- a. Chemistry 20 panel
- b. Thyroid panel
- c. 25-OH vitamin D, 1,25 (OH)₂ vitamin D, intact PTH
- d. CBC
- e. Research bloods for storage and potential future use (as yet undetermined)
- f. Mineral panel or calcium level (performed and repeated as needed)

- g. Bone-specific alkaline phosphatase
 - h. Osteocalcin
 - i. Ionized calcium
5. Urine testing
- a. Urine pregnancy test in females with childbearing potential
 - b. Urinalysis
 - c. Two 24-hour urine collections for testing of calcium, phosphorus, creatinine, magnesium, sodium, citrate, N-telopeptide, pH, and potassium
6. Imaging
- a. DXA scan of the spine, femur, radius and total body
 - b. Renal Ultrasound

See Section 4.7 for details of post-study transition to primary care physician.

4.7 Communication with Referring Physicians

With written consent of the subjects, referring physicians will receive clinical information about the health status of subjects during the trial on an as-needed basis. At the conclusion of the post-HPTH stabilization phase, local physicians will be provided with clinical summaries of the current health status of the subjects, as well as information about any medically relevant, untoward events that occurred during the trial.

5 STORAGE OF DATA AND SAMPLES

5.1 Data

Study staff will complete electronic case report forms (eCRFs) via a web-based electronic data capture (EDC) system that is compliant with Part 11 Title 21 of the Code of Federal Regulations. The EDC is housed on a secure server at Rho, Inc. in North Carolina. The Principal Investigator is responsible for management of study related records at the completion of the protocol. The investigators will retain all study-related records for at least 2 years after discontinuation of the study and as required by regulation.

5.2 Samples

Research samples collected from subjects consented to this protocol will be stored in locked freezers belonging to the Craniofacial and Skeletal Diseases Branch located in Building 30 on the NIH Bethesda

campus. A section of the bone specimen will be shipped to non-NIH investigators at the Helen Hayes Hospital and the Ludwig Boltzmann Institute of Osteology for analysis (see Section 9.1 for outcome measures derived from these analyses). The non-NIH investigators may return portions of these bone specimens to NIH where they will be maintained in a secure location that is only accessible to the study team. A label will be applied to each research sample containing the subject ID, collection date, and specimen type. Study staff will use a computer-based specimen tracking system, accessed via secure NIH servers. The system will be used to document sample collection, notify laboratories of shipments, track shipments, and provide details on the disposition of all samples.

5.2.1 Samples and Data Management after Completion of the Protocol

The principal investigator is responsible for management of samples and data at the completion of the protocol. Samples will be destroyed at the end of the protocol unless there has been IRB approval to retain them.

5.2.2 Research Collaborations Involving Stored Specimens or Data

The Principal Investigator will seek NIH IRB review and approval for research collaborations in which coded samples are sent to non-NIH investigator(s). She will identify the names of the collaborating researchers and their affiliated institutions, as well as intended plans for use.

6 ADDITIONAL CONSIDERATIONS

6.1 Research with Investigational Drugs or Devices

6.1.1 Synthetic Human Parathyroid Hormone (HPTH)

Synthetic human parathyroid hormone 1-34 (HPTH) is the first 34 amino acids of the intact 84-amino acid parathyroid hormone. This peptide fragment, which contains all of the hormone's biological activity, was first synthesized in the early 1970's.¹⁶ HPTH acts by binding to the PTH receptors in the bone to mobilize calcium. It also acts on the kidney to increase calcium reabsorption, increase phosphate excretion, and stimulate the enzyme 1- α -hydroxylase to convert 25-OH-Vitamin D to its active form, 1,25-OH₂-Vitamin D. The main goal of hormone replacement therapy with HPTH is the simultaneous normalization of serum and urine calcium, phosphorus, magnesium and markers of bone turnover. This drug has not been approved by the FDA for the treatment of hypoparathyroidism. An Investigational New Drug Application has been obtained for the investigational use of HPTH in this study.

6.1.2 Pharmacokinetics

Detailed pharmacokinetics are known about HPTH as well as rhPTH 1-34, which is structurally identical to HPTH.¹⁷⁻¹⁹ It is well absorbed after subcutaneous injection with 95% becoming bioavailable. Peak concentrations are reached at approximately 30 minutes after subcutaneous injection and gradually decline to non-quantifiable levels within 3 hours. The half-life of HPTH injected subcutaneously is approximately 60-75 minutes. HPTH is metabolized by the liver and excreted by the kidneys. While the drug has not been studied in patients with chronic renal failure or on dialysis, the pharmacokinetics do not appear to be altered in patients with mild to moderate renal insufficiency (creatinine clearance: 30 – 72 mL/min). The drug has not been studied in patients with hepatic insufficiency.

6.1.3 Pharmacodynamics

In euparathyroid adults with osteoporosis, subcutaneous HPTH induces a rapid decrease in serum phosphate followed by a later rise in serum calcium occurring between 90 and 120 minutes after injection, associated with an increase in 1,25-OH₂ Vitamin D levels.¹⁹ Urine calcium excretion also increases in patients with osteoporosis, particularly with higher doses of HPTH, which were also associated with more prolonged increases in urinary calcium.²⁰ However, frank hypercalciuria was not noted with rhPTH in more recent randomized-placebo controlled trial of post-menopausal women.¹² In the NIH experience, serum calcium peaked 3-4 hours and 1,25-OH₂ Vitamin D peaked 8 hours after a subcutaneous injection.^{2,3}

6.1.4 Formulation and Preparation

HPTH is formulated from GMP grade raw material obtained from Bachem Americas Inc, in Torrance, California. In the NIH Pharmacy, the formulation is made in a 5% D-mannitol solution, sterilized and packaged in 2 mL Type I glass vials with Teflon stoppers. The vials are tested for sterility, pyrogenicity, peptide content and other factors before being released for patient use. The vials contain 1.0 mL of HPTH in frozen, sterile solution to be used for injection only. In the past, subjects have been supplied with either 50 µg/mL or 200 µg/mL concentrations of HPTH, depending on their dosing level. Under the revised protocol, all enrolled subjects will be supplied with HPTH in a 100 µg/mL concentration, including those subjects who are already receiving HPTH.

6.1.5 Storage, Stability, and Handling

Intact vials of HPTH, 100 mcg, are projected to be stable for at least 24 months when stored in the freezer (at or below -70°C) and for at least 6 months when stored in the freezer (-25°C to -10°C).

Since HPTH contains no antibacterial preservatives, it should be used within 24 hours of initial entry to the vial. Patients may remove 3 doses from 1 vial of HPTH if the vial is kept refrigerated and it is used within a 24-hour period.

HPTH vials are stable through a freeze-thaw-freeze cycle. Vials that have been left at controlled room temperature (15°C to 30°C) for up to 48 hours may be returned to the freezer for long-term storage.

6.1.6 Packaging and Labeling

HPTH is packaged and labeled by the PDS in 100 µg/mL vials, using a lot of HPTH that is designated for use in the study. Subjects are provided with a 6-month supply of study drug at each visit. The vials are dispensed in a sealed plastic bag.

The vial label contains the following elements:

- Name and address of the PDS
- Name and strength of the drug
- Lot number
- Statement that the drug is for investigational use only

The packaging label contains the following elements:

- Name of the prescribing physician
- Instructions for use
- Subject name and medical record number
- Date dispensed
- Storage requirements

6.1.7 Receipt, Dispensation, and Return of Clinical Supplies

HPTH will be received and dispensed by designated PDS staff according to PDS Standard Operating Procedures. The PDS staff will document receipt and dispensation of investigational product on drug accountability logs. The records of receipt will identify the name, lot number, and expiration date of the product, the amount received, and the date and time of receipt. The dispensation records will identify the name, lot number, and expiration date of the product, as well as the identification number of subjects and

the quantity of drug dispensed to each subject. Accidental or intentional destruction of the investigational product will also be documented. All records will be available for inspection by the clinical trial monitor.

The investigational product will be dispensed to the subjects at each visit, beginning with the baseline visit. Each subject will receive a 6-month supply of HPTH. The drug supply will be enclosed in a container with cold packs to maintain stability. Subjects will not be asked to return used and unused vials at each visit or at the conclusion of the study.

6.1.8 Investigational Product Administration

All subjects will receive educational and written materials about the use of the investigational product. The principal investigator and research nurses will provide training at the baseline visit and as needed at subsequent visits. Subjects will also receive ongoing education about the appropriate methods for storing, handling, and disposing of the investigational product in the home setting. All subjects will be provided with the appropriate syringes and needles necessary to administer the investigational product.

6.2 Gene Therapy

Not applicable.

7 RISKS / DISCOMFORTS

7.1 Assessment/Procedures with no Risks or Noteworthy Discomfort

The following assessments/procedures are deemed to have no risks and to cause no noteworthy discomfort: collection of medical history, including concomitant medications, dietician consultation, and short calcium questionnaire; physical examination (including vital signs); SF-36, and the fatigue symptom inventory

7.2 6-Minute Walk Test

The 6-minute walk test may result in tiredness. A rehabilitation specialist will be present throughout the test.

7.3 Blood Draws

The total amount of blood drawn throughout the study will be 604 ml over a 6 year period; per the protocol blood draw schedule (Appendix 24.14). The maximum amount of blood drawn during one study visit will be 91 mL and the maximum amount drawn over an 8-week period will be 123 mL. This amount is less than the NIH guidelines of 10.5 ml/kg/8 weeks (< 550 mL) for adults. Drawing blood for the tests and placement of IV catheters may cause discomfort or a bruise at the injection site, and rarely, an

infection may occur. Blood drawing by experienced personnel limits the risk of excessive pain, bruising and infection. Twenty-four hour blood sampling is inconvenient to the subject and will cause sleep disruption. Sampling will be done through an indwelling catheter, PICC line, or repeated venipuncture. Indwelling catheterization is associated with a very small risk of infection.

7.4 DNA Testing

Patients may be asked to undergo DNA testing to evaluate for possible genetic causes of hypoparathyroidism, if not done previously. There is the possibility that DNA testing may lead to unexpected discoveries, such as non-paternity. In addition, information gained by genetic analysis could possibly lead to yet unknown discrimination, for example, difficulty in obtaining life insurance. Any information gained in this analysis is confidential and will not be disclosed to any person or institution not collaborating in this research effort, unless consent is provided by the patient. Results of genetic tests may be placed in the medical record.

7.5 Urine Collection

Urine collections may be an inconvenience to the patient, but collections are not associated with any discomfort or risks.

7.6 Renal Ultrasound

Renal ultrasounds are not associated with any risks; however, lying on a hard table may be uncomfortable.

7.7 Radiation

Renal and spinal CT and DXA scan contribute to total radiation of the study. The "Effective Dose Equivalent" is the sum of the absorbed radiation dose to the 5 organs, other than the skin, which receive the highest doses: testes, ovaries, red bone marrow, lungs, and kidneys. The total effective radiation dose in this study is 1.1 rem, which is below the 5.0 rem per year NIH Radiation Safety Committee (RSC) guideline for adults.

7.8 Tetracycline Antibiotics for Bone Biopsy Labeling

Some patients experience side effects such as nausea, vomiting, diarrhea, and hypersensitivity reactions in response to tetracycline antibiotics. Exposure to sunlight while taking tetracycline antibiotics can cause skin eruptions and should be avoided. Subjects are informed of the cautions to be exercised in taking tetracycline antibiotics and are instructed not to take these medications if they may be pregnant.

7.9 Trans-iliac Crest Bone Biopsy

Subjects may experience discomfort and pain at the biopsy site for several days and can be treated safely with acetaminophen or more potent analgesics as needed. Bleeding and infection at the site of biopsy are possible but rare. Subjects may experience some transient anesthesia-related symptoms such as nausea, vomiting, decreased appetite, fatigue, and decreased blood pressure. Subjects will undergo a routine pre-anesthesia consult and be asked to sign a separate surgical consent form prior to the procedure.

7.10 HPTH

7.10.1 FDA-Approval

There are no PTH preparations that are FDA-approved for the treatment of hypoparathyroidism. Recombinant human PTH 1-34 (rhPTH) (teriparatide, Forteo®) is FDA-approved for the treatment of osteoporosis. rhPTH and HPTH are structurally identical, with rhPTH being manufactured by recombinant DNA technology and HPTH being manufactured by direct synthesis. An Investigational New Drug Application has been obtained for the investigational use of HPTH in this study.

7.10.2 Carcinogenesis, Mutagenesis, and Reproductive Toxicology

Administration of high-dose teriparatide (rhPTH) for 2 years to euparathyroid Fischer 344 rats demonstrated a dose and duration-related increase in osteosarcomas, osteoblastomas, and osteomas associated with a large increase in bone mass and focal osteoblast hypoplasia.²¹ Similar studies in macaques did not replicate this finding,²² and the relevance of these rat studies to humans is unclear. There have been 2 reports of humans treated with rhPTH developing osteosarcoma; however, causality has not been established.^{23,24} The package labeling for rhPTH includes a black box warning stating that teriparatide should not be used in individuals with an increased baseline risk of osteosarcoma including those with a Paget's disease, children or young adults with open epiphyses, or history of radiation therapy to the skeleton. To eliminate the confounding effects of the pubertal growth spurt, we have excluded pediatric enrollment. All subjects less than 21 years of age will undergo a bone x-ray to ensure epiphyseal fusion. Additionally, they recommend that individuals with a history of skeletal malignancies or metabolic bone diseases other than osteoporosis not receive teriparatide treatment beyond 2 years.¹⁸

In vivo and *in vitro* mutagenesis studies were negative. There was no effect on male or female fertility in rats given up to 160 times the equivalent human dose. In pregnant rats, teriparatide induced mild growth retardation and reduced motor activity in the offspring. Affect on human fetal development and presence in breast milk have not been studied; therefore rhPTH is not indicated for use in pregnant or lactating women.¹⁸

7.10.3 Drug Interactions

There are no known drug interactions with HPTH. However, hypercalcemia from overdosage with teriparatide may predispose patients to digitalis toxicity.¹⁸

7.10.4 Adverse Events

The safety of parathyroid hormone replacement therapy has been demonstrated in clinical trials involving the treatment of hypoparathyroidism and osteoporosis. In a long-term NIH study comparing HPTH to conventional care for the treatment of hypoparathyroidism, there were no significant differences between treatment groups in the incidence of most adverse events, such as neuromuscular irritability, fatigue, or arthralgias.⁵ Mild intermittent bone pain in the lower extremities occurred in 7 subjects receiving HPTH and in 3 subjects receiving conventional care. The most common adverse events (>10% of subjects) observed in clinical trials of rhPTH for osteoporosis included arthralgia, pain, and nausea. Another common adverse event in these trials was the development of hypercalcemia. In this study, an increase in serum calcium is a desired pharmacologic effect and would not be considered an AE, unless serum calcium > 11 mg/dL persisted for more than 4 weeks. Transient orthostatic hypotension has been infrequently observed in subjects treated with rhPTH for osteoporosis. This event typically occurred within 4 hours of dosing and resolved spontaneously.¹⁸ Additional information about other adverse events is available in the Forteo® package insert (Appendix 24.13).

Resistance to PTH and anti-PTH antibodies have been reported in 3% of women treated with rhPTH.¹⁸ In patients with hypoparathyroidism, PTH resistance would manifest by diminishing responsiveness to the therapy that will require increasingly greater doses of PTH to maintain normal serum calcium. Among the subjects who develop resistance, many will be able to continue therapy if the resistance is small or partial. Others may develop substantial resistance with unstable serum calcium and phosphate levels. PTH therapy will be discontinued in those subjects, and those subjects will be withdrawn from the study after returning them to conventional therapy (see Section 4.6).

Decreases in BMD of the radius, as measured by DXA, have been noted in preliminary data from this protocol²⁵ and other studies treating hypoparathyroid subjects with HPTH⁵ and PTH 1-84¹⁰. Histomorphometric analysis has also shown an increase in cortical porosity^{11,25,26}. Decreases in radial BMD have been reported in euparathyroid postmenopausal women treated with rhPTH 1-34 without an apparent increase in wrist fractures¹² or change in cortical porosity¹⁴. The clinical relevance of these changes in radial BMD in hypoparathyroid treated with HPTH is unknown. Thus, this protocol excludes and withdraws subjects with DXA BMD T-scores or Z-scores < -2.

Since this study has started, hypocitraturia (defined as a urine calcium to citrate ratio > 0.7 mg/mg) has been observed in many subjects initiation of HPTH therapy. Of note, some subjects also had elevated urine calcium/citrate ratios prior to the initiation of HPTH. Hypocitraturia has not been previously reported in hypoparathyroidism and, to our knowledge, urine citrate has not been assessed in other studies using PTH 1-34 or PTH 1-84 in the treatment of hypoparathyroidism. Thus, the risk of hypocitraturia-associated nephrocalcinosis or nephrolithiasis in this patient population, on conventional or PTH therapy, is not known. The urine calcium/citrate ratio will be monitored throughout the study and subjects will be treated with potassium citrate, as tolerated, as described in section 4.5.5.

There is a risk of unforeseen adverse effects with every new drug treatment. The risks of participation are reasonable relative to the significant health benefits and medical knowledge that may be achieved.

8 SUBJECT SAFETY MONITORING

Subjects will be informed that they may choose to withdraw or the investigator may remove them if it is in the subjects' best interest or if the subjects are unable to complete the required assessments. Voluntary withdrawal from the protocol is always an option for the research participants. As described throughout Section 4.5, subjects will have blood and urine measured and evaluated by the study investigators on an ongoing basis, and HPTH dosing will be adjusted according to a standardized dosing algorithm. The principal investigator or designee will evaluate all clinical laboratory results for clinically significant abnormalities and document the evaluation on a CRF. Clinically significant laboratory findings will be recorded and reported as AEs (see Appendix 24.1) regardless of their association with the use of the investigational product.

At each study visit, the study investigator will inquire about the occurrence of any AEs since the last visit. The principal investigator will also review all source documentation related to inpatient study procedures for evidence of AEs. Events will be followed until they return to baseline, until follow-up is no longer medically necessary, or until the end of the AE surveillance period.

The following conditions will require the withdrawal of a subject from the HPTH therapy:

- Pregnancy
- New-onset illness requiring chronic use (> 3 weeks) of a medication that affects the bone such as oral glucocorticoids, growth hormone, suppressive doses of thyroid hormone, estrogen or testosterone. Inhaled, topical, and intranasal glucocorticoids are permitted.

- Women who enter menopause after initiation of HPTH therapy will not be withdrawn from the study unless they require hormone replacement therapy for > 3 weeks.
- Use of depot medroxyprogesterone for contraception. Subjects wishing to use oral, transdermal, intravaginal, or intrauterine hormonal contraceptives may remain in the study.
- Significant deterioration in metabolic control on PTH as defined by repeated measurements of serum calcium < 7 mg/dL for more than 4 weeks.
- Severe chronic bone pain or other unexpected new-onset chronic medical condition that cannot be explained and may be related to PTH therapy
- Development of DXA or QCT Z-Score or T-score < -2. As peak bone mass is not achieved until the third decade of life, subjects beginning PTH before age 20 will only have Z-score assessed for withdrawal determination.
- Decline in calculated GFR of < 25 mL/min/1.73 m² or decline in calculated GFR by 25 mL/min/1.73m² without clear etiology that persists on three monthly measurements (measured at the NIH or the subject's local laboratory).
- Increase in hepatic transaminases (ALT and AST) > 2x the upper limit of normal
- Treatment failure as defined by significant metabolic deterioration
- Recurrence of thyroid cancer in subjects with history of thyroid cancer
- Subject noncompliance with study procedures.
- Investigator judgment based on subject's best medical interest

Subjects who require discontinuation of HPTH therapy will be gradually weaned off HPTH while therapeutic doses of calcitriol and calcium are established as described in Section 4.5.5.

9 OUTCOME MEASURES

9.1 Primary Outcome Measures

The primary outcomes are changes in static and dynamic bone histomorphometry after 1 year, 2 years, and 4 years of HPTH therapy. Those changes will be determined from antibiotic-labeled biopsies taken before and during HPTH therapy. The static and dynamic bone histomorphometry variables that will be assessed as primary outcomes are listed in the following:

1. Mineralized perimeter

2. Bone formation rate
3. Cortical width
4. Cortical area
5. Osteoid width
6. Osteoid perimeter
7. Mineral apposition rate

9.2 Secondary Outcome Measures

The secondary outcome measures are listed below:

1. Changes in bone mineralization density distribution will be assessed in bone biopsies by back-scattered electron imaging at 1, 2 and 4 years of HPTH therapy. The specific outcomes that will be measured include:
 - a. spectral calcium-mean
 - b. calcium-peak
 - c. calcium-width
2. Non-biopsy outcomes are being measured every 6 months (annually for some outcomes) over the 5 years of HPTH therapy. Changes from baseline in the following outcomes will be assessed:
 - a. Biochemical markers of bone metabolism: osteocalcin, bone-specific alkaline phosphatase, collagen cross-linked N-telopeptide.
 - b. Serum and urine calcium; 1,25-OH₂-Vitamin D
 - c. Bone density assessed by DXA and quantitative CT
 - d. Nephrocalcinosis by ultrasound and CT
 - e. Fatigue Symptom Inventory
 - f. 6-Minute Walk Test
 - g. SF-36 Health Survey

Where appropriate, biochemical and biopsy data will be compared to age, sex, and ethnicity-matched controls.

9.3 Tertiary Outcome Measures

The tertiary outcomes are early changes in blood chemistries and FGF23, renal mineral handling, and PTH sensitivity with the initiation of HPTH. Tertiary outcome measures include:

- a. Serum albumin, calcium, phosphorus, magnesium, sodium, potassium, chloride, Total CO₂, creatinine, glucose, urea nitrogen, and FGF23
- b. Urine cAMP, creatinine, phosphorus, calcium, and pH

10 STATISTICAL ANALYSIS

10.1 Analysis of Data/Study Outcomes

The overall analysis objective is to utilize exploratory and hypothesis testing methods to characterize the response profile over time to HPTH therapy in the primary and secondary endpoints. The bone biopsy measures are assessed at baseline and at 1, 2, and 4 years in 3 separate arms, while most other endpoints are assessed every 6 months from baseline to 5 years of therapy. Thus, analyses of bone biopsy endpoints involve both within-arm and between-arm comparisons at the 3 times, while all other analyses will utilize standard repeated measures methods for longitudinal data.

These analyses will initially include all randomized subjects who remain evaluable for the endpoints, including those eligible out of the subjects currently on conventional therapy plus the 36 newly enrolled subjects. However, if covariate adjustment in analyses described below indicates that there are differences between these strata, then the 3 strata will be analyzed separately. The subjects who were on HPTH under the previous version of the protocol will be analyzed separately using similar analysis methods, recognizing the limitations of the small sample size (≤ 8). Any subject who enters menopause prior to the second bone biopsy will remain in the study and will undergo the second biopsy; however, the results will be reported separately and not included in the data analyses of the randomized groups. It is felt that reviewing the results from a menopausal woman anecdotally may give insight into possible treatment effects in a menopausal sub-population. Data will be summarized graphically and in tabular form using standard descriptive statistics for categorical and continuous measures, with appropriate consideration of underlying distributional assumptions. All tests of significance will be two-tailed at the 0.05 level.

For the bone biopsy endpoints, paired t-tests will be used to test the hypotheses that the 1, 2, and 4-year changes from baseline are significantly different from zero. One-way analysis of variance (ANOVA) will be used to compare these differences to each other, with protected individual linear contrasts performed if

the overall F-test is significant. The effects of selected baseline covariates, including gender and menopausal status, will be assessed using analysis of covariance (ANCOVA) in a sensitivity analysis. Exploratory graphical methods will also be used to assess distributional assumptions and potential differences in responses between the strata. Log-transformation of raw data or non-parametric test alternatives may be considered if indicated by these exploratory analyses.

In the event that the 1, 2, and 4-year changes from baseline are not significantly different from each other by ANOVA, we will consider pooling them using a paired t-test to test for significance of the pooled changes from baseline, ignoring the follow-up time. This may be indicated if either the observed standard deviation of the differences is larger than expected or if greater power is desired to test for an overall smaller effect size. For example, with 24 subjects, there is 80% power to detect a change from baseline in mineralizing perimeter of 4% if the standard deviation is 7%, as expected, but it is 9%, if the standard deviation is as large as 15%, using a 0.05 level paired t-test.

Since there are a number of pre-specified reasons for discontinuing subjects from study (see Section 8) and the dropout rate could be relatively high (33%), secondary sensitivity analyses may be performed on the bone biopsy data if a large number of those discontinuations or dropouts occurs before the subject's second biopsy. For each such missing follow-up bone biopsy, the second biopsy endpoint value will be imputed using different rules (e.g. baseline biopsy value, and mean, minimum or maximum of those present) and the results of analyses of those data will be compared to the primary analysis on only evaluable subjects to determine if there is evidence that dropouts may have biased the primary analysis results.

All other endpoints are assessed repeatedly over the 5-year study period, and most are assessed every 6 months. This longitudinal multivariate data set will be analyzed using standard mixed models or generalized estimating equations techniques to characterize the therapy response profile for each endpoint. Patterns of missing data will be assessed and appropriate accommodations will be made in the methods depending on the apparent mechanism for generating the missing data. Dimensional reduction techniques may be employed with sets of related endpoints that are highly correlated. The objective will be to produce a graphical and analytical profile of each physiological and behavioral response to therapy over time. In addition, mixed model methods will be used to determine if patterns in selected secondary endpoints over time are predictive of primary biopsy endpoints, in order to evaluate their potential use as either surrogate biomarkers for bone histomorphometric measures or as classifiers that could be used to identify subjects more responsive to HPTH treatment.

Subjects and their data will be monitored closely throughout the study for safety; data will be submitted regularly for DSMC review as described in Section 15. In addition, preliminary analyses using methods described above may be performed when all evaluable subjects meet certain early milestones, for example, after all subjects have completed their one year biopsy. These analyses will be designed to evaluate early changes from baseline in primary and secondary measures after one year of HPTH treatment and to assess the predictive values of selected secondary measures in relation to the primary endpoints.

10.2 Power Analysis

Sample size calculations were based on 2 of the primary bone biopsy outcome measures, cancellous bone mineralizing perimeter and bone formation rate, using preliminary data from the 5 previously enrolled subjects who had biopsies at baseline and at 1 year of HPTH therapy. For mineralizing perimeter, the mean (standard deviation) of the 1-year changes from baseline was 22 (7) %, and for bone formation rate it was 0.23 (0.07) $\mu\text{m}^2/\text{mm}/\text{d}$. For design purposes, we assumed that a clinically meaningful change in mineralizing perimeter from baseline to either 1, 2 or 4 years of therapy is 10% and will establish the sample size required to detect a difference at least that large with adequate power. Using a two-tailed 0.05 level paired t-test, we found that 8 new subjects in each follow-up arm yielded 93% power to detect a difference of 10% at any of the follow-up times. For bone formation rate, we assumed that a clinically meaningful change from baseline is 0.10 $\mu\text{m}^2/\text{mm}/\text{d}$, which corresponds to an identical standardized minimum detectable effect size of $0.10/0.07=1.4$ compared to $10/7=1.4$ for mineralizing perimeter. As a result, 8 new subjects per arm will also yield 93% power to detect significant paired differences in bone formation rate of 0.10 $\mu\text{m}^2/\text{mm}/\text{d}$.

A secondary analysis objective of the primary bone biopsy endpoints is to determine if there are differences between the changes from baseline over time, using analysis of variance (ANOVA) for these between-biopsy-arm comparisons. With 8 new subjects per arm, there is 75% power to detect a significant difference in mineralizing perimeter with a two-tailed 0.05 level overall F-test if the 3 differences from baseline are, for example, 10%, 15% and 21%, assuming a within-group standard deviation of 7%. Similar results were obtained for bone formation rate.

Finally, based on current experience, the dropout rate of subjects on HPTH therapy for 5 years could be as high as 1 in 3 (33%). To account for that, 36 new eligible subjects will be randomized to the 3 biopsy follow-up time arms, which should result in at least 24 new subjects being evaluable for the primary analyses of the bone biopsy endpoints at years 1, 2 and 4. Up to 10 additional subjects may be screened but not enter the treatment or randomization phase.

10.3 Randomization and Stratification

While there is only one treatment group, subjects will be randomized 1:1.2:1.4 at baseline to the 3 bone biopsy follow-up times of 1, 2, or 4 years, respectively. Heavier weighting is given to the arms with longer follow-up times as these arms are anticipated to have more dropouts. In addition, the randomization will be stratified on 3 factors, gender (Male/Female), menopausal status (pre / post menopausal), and prior participation in this trial (Yes/No). Stratification on gender is indicated because of known gender-based differences in bone formation. Stratification on menopausal status is indicated because of known hormonal changes that may influence bone mineralization. Stratification on prior participation is indicated because the subjects enrolled under the previous version of the protocol will have their pre-conventional therapy biopsy used as their baseline biopsy (new subjects will have their baseline biopsy at the end of conventional therapy) and the effects of conventional therapy on the biopsies is not known with certainty. In order to avoid potential loss of power in the primary analyses if these 3 strata are found to be different, 36 new subjects will be enrolled in one stratum and those eligible to continue from among the 10 currently enrolled subjects will be enrolled in the other stratum.

Since the target subject sample size is relatively small and there are 3 binary stratification variables, a dynamic allocation algorithm based on the Pocock-Simon method²⁷ will be used. This algorithm weights the probabilities of assignment to the 3 arms for each subject so as to increase the probability the subject will be assigned to the arm which will result in the least overall imbalance between the 3 groups with respect to the distributions of the 3 stratification factors. Given dropouts during the enrollment period, the algorithm will also consider any imbalances resulting from those dropouts occurring before their second biopsy and will adaptively rebalance the 3 arms across the two stratification variables with prospectively randomized subjects. The algorithm is transparently implemented within the web-based randomization system when subjects are randomized at baseline.

11 HUMAN SUBJECTS PROTECTION

11.1 Subject Selection

Selection of subjects will not be limited by gender, race, or ethnicity. However, as hypoparathyroidism in adults most frequently occurs as a surgical complication of thyroid surgery for autoimmune thyroid disease and/or thyroid cancer, conditions which occur more commonly in Caucasian women, a disproportionate number of Caucasian women are expected to be enrolled in this protocol. Men and women over age 70 have been excluded to avoid the onset of senile osteoporosis as a confounding factor. Because bone metabolism is altered during menopause and because this would confound the results of the

study, women who are likely to enter menopause during the study (those ages 46 – 52) will not be enrolled.

11.2 Justification for Exclusion of Children

Children have been excluded from this trial because their rapid changes in growth and bone mineralization would affect interpretation of the data and rhPTH is not recommended for use in children.

11.3 Justification for Exclusion of Other Vulnerable Subjects

PTH has not been studied for use in pregnancy, and bone metabolism is altered during pregnancy, lactation. Therefore, pregnant and lactating women have been excluded.

11.4 Justification of Sensitive Procedures

Not applicable.

11.5 Safeguards for Vulnerable Populations

Verbal confirmation of contraception use will be obtained from women of child-bearing potential during the history and a pregnancy test will be performed during screening and each inpatient NIH visit.

11.6 Qualifications of Investigators

The following investigators are licensed physicians who are board certified or board eligible in the specialty of endocrinology and have expertise in treating patients with hypoparathyroidism. They are qualified to recruit and screen subjects, perform assessments, assess adverse events, order and interpret tests, prescribe treatments including HPTH handle specimens, perform regulatory reporting/paperwork, evaluate and interpret data.

- Rachel I. Gafni, MD (will obtain informed consent)
- Alison M. Boyce, MD (will not obtain informed consent)
- Michael T. Collins, MD (will obtain informed consent)
- Mary Scott Ramnitz, MD (will obtain informed consent)

The following investigator is a licensed physician with a specialty in endocrinology. He has expert training in bone densitometry. He will be responsible for performing and interpreting DXA scans.

- James C. Reynolds, MD

The following investigators are licensed registered nurses with expertise in clinical research and treatment of endocrine disorders. They are qualified to recruit and screen subjects, perform assessments, assess adverse events, order and interpret tests within the scope of their clinical credentials, administer prescribed treatments including HPTH, handle specimens, perform regulatory reporting/paperwork, evaluate and interpret data, and obtain informed consent.

- Beth Brillante, RN, MBA
- Lori Guthrie, RN

The following investigator is a board certified orthopedic surgeon who will perform iliac crest bone biopsies. She will also order and interpret tests, handle specimens, prescribe treatments, and evaluate and interpret data.

- Laura L. Tosi, MD

The following investigator is board eligible in oral and maxillofacial surgery. This investigator will perform assessments, perform bone biopsies, order medications, order tests, and interpret tests.

- Andrea Burke, MD, DMD

11.7 Qualifications of Non-NIH Collaborators

The following non-NIH collaborators are scientists with expertise in the study of bone specimens. They will perform analyses on iliac crest bone biopsies outside of NIH.

- Hua Zhou, MD
- David Dempster, PhD
- Klaus Klaushofer, MD
- Paul Roschger, PhD

The following non-NIH collaborator is a board-certified nephrologist. This investigator will analyze data and will not have access to patient identifying information.

- Craig Langman, MD

12 ANTICIPATED BENEFIT

It is anticipated that participants in this study will benefit directly from their treatments with conventional therapy and may benefit from therapy with the investigational drug, HPTH. As described in Section 4.5,

subjects will be monitored throughout the study period in order to optimize the effects of conventional and investigational treatments on their calcium metabolism.

13 CLASSIFICATION OF RISK

13.1 Adults

This study is classified as research involving more than minimal risk. This risk is justified as the current treatment is inadequate and associated with morbidity.

13.2 Overall Risk and Benefit Consideration

Risks of the study are reasonable in relation to the anticipated benefit.

14 CONSENT DOCUMENTS AND PROCESS

14.1 Designation of Those Obtaining Consent

Informed consent will be obtained by study investigators as designated in Section 11.6.

14.2 Consent Procedures

All subjects (or their legally authorized representative) will be required to sign and date a consent form before participating in any portion of the study. Subjects previously enrolled in this protocol will be re-consented at their first study visit, as described in Sections 4.5.1-4.5.3. All participants will receive a verbal explanation in terms used to their comprehension of the purposes, procedures, and potential risks of the study and their rights as research participants. Participants will also have the opportunity to carefully review the written consent form and ask questions regarding this study prior to signing. A copy of the informed consent will be given to the prospective subject for review, and the principal investigator or an associate investigator, will review the consent form with the subject. In the presence of a witness, the investigator will request the subject's signature, indicating consent. The subject will be informed that participation is voluntary and that he/she may withdraw from the study at any time, for any reason.

14.3 Consent Documents

The consent document captures all required elements, including the purposes, procedures, benefits, and potential risks of the study (see Section 25). The consent process will be documented in the subjects' medical records. The documentation of the consent process will include the following elements:

- Date and time of consent
- Topics discussed with the subject (e.g. risk, benefits, alternatives)

- Confirmation that subject had adequate time to review the consent, that the subject's questions were answered, and that a copy of the consent was provided to the subject

The consent forms will be updated or revised whenever important new safety information is available, whenever the protocol is amended, or whenever any new information becomes available that may affect participation in the study. The original forms will become part of the permanent medical record and copies will be provided to the subjects.

15 DATA AND SAFETY MONITORING

15.1 Data and Safety Monitor

The principal investigator will be responsible for monitoring the data and accruing safety information. Serious adverse event (SAE) monitoring will be supported by an independent medical monitor and support team from the Clinical Research Operations and Management Support (CROMS) at Rho. Clinical monitoring for this study will be done by CROMS at Rho in collaboration with the NICDR Clinical Director and Principal Investigator.

The NIDCR Division of Intramural Research Data and Safety Monitoring Committee (DSMC) will provide data and safety review and recommendations to the NIDCR Clinical Director for the study. The DSMC will include members with expertise in a broad range of areas, including human subjects' protection, research ethics, clinical trial implementation, biostatistics, and medical bone and mineral metabolism.

15.2 Data and Safety Monitoring Plan

Data and safety will be monitored by the Principal Investigator along with the NIDCR Clinical Director and the independent medical monitor from CROMS.

The PI is responsible for monitoring the study progress and study data. The PI will also maintain responsibility for ensuring the accuracy, completeness, timeliness, and legibility of the data. The PI and associate investigators are also required to keep accurate and timely records to ensure that the conduct of the study is fully documented. The PI will review individual study subject data upon each patient encounter; she will review aggregate data reports on monthly basis to review enrollment progress and adverse events. Trends will be discussed with the protocol team to ensure subject safety, study compliance and recruitment goals are met.

Safety monitoring for this study will be the responsibility of the PI and supported by CROMS. The CROMS independent medical monitor will review serious adverse events that are reported to CROMS.

1022 The CROMS medical monitor will review the SAE report, request additional information about the event
1023 if necessary and provide a medical monitor assessment within 2 business days of receipt of the SAE
1024 report. The investigator and independent medical monitor may discuss specific events or trends if noted.
1025 The investigator will determine the appropriate clinical action for the subject.

1026 The DSMC will review data approximately annually related to enrollment progress, trial implementation,
1027 subject safety, and clinical efficacy. The DSMC will also consider current information from other sources
1028 on the biology of the disease, the investigational product, and the patient population under study. Based
1029 on these reviews, the DSMC will make recommendations to the NIDCR Clinical Director concerning the
1030 continuation, modification, or termination of the trial. The NIDCR Clinical Director determines which
1031 recommendations from the DSMC will be accepted and required of the principal investigator to address.
1032 The roles and responsibilities of committee members and meeting procedures will be formally described
1033 in a charter.

1034 The DSMC and the investigator will review the semi-annual DSMC reports to determine whether the
1035 aggregate safety data should be reported to the FDA in an expedited manner.

1036 Aggregate data will be reported in an expedited manner to the FDA if the DSMC or the investigator
1037 believes those data represent an unexpected set of related SAEs for which there is a reasonable possibility
1038 that they were caused by the study product (see Appendix 24.1 for a definition of expectedness).

1039 See Section 17 for a description of expedited FDA, IND reports of individual SAEs.

1040 **15.3 Criteria for Stopping the Study or Suspending Enrollment or Procedures**

1041 The study will be temporarily halted for any of the following reasons:

- 1042 • A fatal or life-threatening event (including osteosarcoma) assessed as related to use of the
1043 investigational product
- 1044 • Two or more similar grade 3 AEs/SAEs that are permanent or not easily reversible and assessed
1045 as related to the use of the investigational product. Easily reversible is defined as responding to
1046 treatment or dose titration such that the severity grade of the AE is reduced to 1 or 2.
- 1047 • Five or more treatment failures, defined as significant deterioration in metabolic control on PTH
1048 as defined by repeated measurements of serum calcium < 7 mg/dL for more than 4 weeks.

1049 The principal investigator will be responsible for monitoring accruing safety data related to stopping
1050 criteria and for notifying the DSMC chair when a halting rule is met. The DSMC Chair will be informed

by email within 1 business day that a halting rule has been reached and confirmed. When a halting rule is met, enrollment will be temporarily suspended while the DSMC considers the data. During this hold period, ongoing subjects will continue to receive HPTH and conventional care for hypoparathyroidism and will continue to be followed for clinical and safety outcomes. The DSMC will assemble an emergency meeting within one month of being notified that a study halting criterion has been met. Prior to the receipt of the DSMC decision, the study team will actively manage the subject(s) who triggered the alert by both treating the AE and titrating the dose, as clinically appropriate. The DSMC will issue a recommendation on study continuation to the NIDCR Clinical Director after reviewing data related to the halting rule. If NIDCR leadership terminates the study based on DSMC recommendations, subjects will be weaned off study drug and transitioned to conventional therapy. The principal investigator and the clinical director will provide the recommendations of the DSMC to the IRB.

15.4 Data and Safety Monitoring Committee Oversight

The NIDCR Data and Safety Monitoring Committee (DSMC) will have oversight responsibilities for the study. The committee will include members with expertise in a broad range of areas, including human subjects protection, research ethics, clinical trial implementation, biostatistics, and medical bone and mineral metabolism. In addition to any safety alerts, as defined in Section 15.3, the DSMC will review data approximately once a year related to enrollment progress, trial implementation, subject safety (including BMD), and clinical efficacy. The DSMC will also consider current information from other sources on the biology of the disease, the investigational product, and the patient population under study. Based on these reviews, the DSMC will make recommendations to the principal investigator and the NIDCR clinical director concerning the continuation, modification, or termination of the trial. The roles and responsibilities of committee members and meeting procedures will be formally described in a charter.

The DSMC and the investigator will review the annual DSMC reports to determine whether the aggregate safety data should be reported to the FDA in an expedited manner.

Aggregate data will be reported in an expedited manner to the FDA if the DSMC or the investigator believes those data represent an unexpected set of related SAEs for which there is a reasonable possibility that they were caused by the study drug (see Appendix 24.1 for a definition of expectedness).

See Section 17 for a description of expedited IND reports of individual SAEs.

16 QUALITY ASSURANCE

16.1 Quality Assurance Monitor

The NIDCR Office of Clinical Trials Operations and Management (OCTOM) is responsible for ensuring an appropriate clinical monitoring plan is developed that is specific for this study and data management system. Clinical site monitoring will be coordinated with the NIDCR Clinical Director and the Principal Investigator. OCTOM and its designee, CROMS, will conduct clinical monitoring according the clinical monitoring plan and will provide a report of monitoring findings associated with each visit.

16.2 Quality Assurance Plan

Clinical monitoring for this study is based on a Clinical Monitoring Plan that was developed by CROMS in collaboration with the National Institute of Dental and Craniofacial Research (NIDCR), Office of Clinical Trials Operations and Management (OCTOM) project officer and the NIDCR Clinical Director. The purpose of the clinical monitoring activities is to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol, and that the integrity of study data is maintained. The plan specifies the frequency, procedures, and levels of monitoring activities. Some monitoring activities will be performed remotely (e.g. review of regulatory documents), while others will take place on site (e.g. verification of study databases against source documentation, review of consent documentation, study drug administration). Staff from CROMS will provide a final site visit report to the principal investigator in approximately 21 calendar days from the last day of the visit. The frequency of other reports based on other monitoring activities will be specified in the monitoring plan.

Monitoring activities will include a study initiation visit prior to study start-up, interim site monitoring visits, a close-out visit and, if necessary, for-cause visits. Interim monitoring visits will take place at least annually and based on rate of accrual. During interim monitoring visits, the clinical research associate will complete a review of subject medical and research records, electronic case report forms, consent documents, unanticipated problems, adverse events, site regulatory documents, etc. Final monitoring visit reports will be provided to the PI, NIDCR Clinical Director, and OCTOM after monitoring visit completion.

The components of the data quality control and assurance program are 1) real-time detection and correction of errors within the EDC system, 2) verification of key outcome measurements during clinical monitoring visits, and 3) periodic data review by CROMS. At the time of data entry, the EDC system alerts the user to missing, out-of-range, and inconsistent values and provides the user the opportunity to correct errors in real time. In accordance with federal regulations, the system records all elements of data

1112 entry (i.e., time, date, verbatim text, and the name of the person performing the data entry). During
1113 periodic clinical monitoring visits, monitors will verify key outcome measurements by comparing data in
1114 the EDC system to source documentation. The frequency of monitoring visits and the number of records
1115 and data fields monitored are described in the study Clinical Monitoring Plan (CMP). Data managers at
1116 CROMS will generate periodic summary reports for the study staff to review.

1117 Data fields in the EDC that are the initial source of the data record (i.e. no source documentation is
1118 maintained) include those captured in the telephone prescreening (yes/no qualification information only).

1119 **17 UNANTICIPATED PROBLEM, ADVERSE EVENT, AND PROTOCOL**
1120 **DEVIATION REPORTING**

1121 The Principal Investigator is responsible for detecting, documenting, and reporting unanticipated
1122 problems (UPs), adverse events (AEs), including serious adverse events (SAEs), and protocol deviations
1123 in accordance with the protocol, IRB requirements, NIH Policy, and federal regulations. Definitions and
1124 additional reporting guidelines are provided in NIH SOP 16. Relatedness to the research of all serious
1125 adverse events will be determined by the PI in consultation with the Clinical Director's office.

1126 Definitions of the different types and characteristics of safety events, protocol deviations, and additional
1127 reporting guidelines are provided in Appendix 24.1. In the event of a discrepancy, NIH SOP 16 will be
1128 the prevailing document.

1129 Serious unanticipated problems and serious protocol deviations will be reported to the IRB and CD as
1130 soon as possible and in writing on the Problem Report Form no more than 7 days after the PI first learns
1131 of the event. Non- serious unanticipated problems and non -serious protocol deviations will be reported
1132 to the IRB and Clinical Director as soon as possible and in writing on the Problem Report Form not more
1133 than 14 days after the PI first learns of the event.

1134 Deaths will be reported to the Clinical Director as soon as possible, but not more than 7 days after the PI
1135 first learns of the event.

1136 All UPs, adverse events, and protocol deviations will be summarized and reported to the IRB at the time
1137 of continuing review with the following exceptions: hospitalizations for elective procedures or surgeries,
1138 hospitalizations for psychosocial or convenience reasons will not be reported. In this population,
1139 symptoms of hypocalcemia (a comorbidity of hypoparathyroidism), such as numbness, cramping, and
1140 fatigue are characteristic of the underlying disorder and may be present continually. Kidney stones may
1141 be as frequent as several times a year in the study population. Therefore, these incidents and the
1142 hospitalizations mentioned above will not be reported at the time of continuing review unless they occur

at a greater severity or frequency than expected. Adverse events occurring at a greater severity or frequency than expected will be reported as Unanticipated Problems as delineated above.

SAEs that are unexpected and for which there is a reasonable possibility that they are related to the use of the investigational product will be reported to the FDA in an expedited manner. If the event is also life-threatening or results in death, the FDA will be notified of the event no later than 7 calendar days after the investigator becomes aware of the event. All other qualifying SAEs will be reported to the FDA within 15 calendar days. All adverse events, including other non-expedited serious adverse events will be reported to the FDA at least annually in a summary format.

17.1 Pregnancy Reporting and Follow-Up

Pregnancies will be recorded from the time written informed consent is obtained until the subject is withdrawn from the study. Results of all pregnancy tests will be given to the subject and/or legally authorized representative, as appropriate. Subjects who become pregnant during the study will be weaned off of PTH and will be followed until a pregnancy outcome is reached at which time they will be withdrawn from the safety follow-up portion of the study. The subjects will be referred to a physician outside of NIH for care. If the pregnancy results in anything other than a normal birth or elective abortion of a healthy fetus, it will be reported as an SAE. At the end of the pregnancy follow-up period, the subjects will be withdrawn from the trial.

18 ALTERNATIVES TO PARTICIPATION OR ALTERNATIVE THERAPIES

Alternative to participation is use of current standard-of-care therapy for hypoparathyroidism: oral calcium and vitamin D analogues. There are no PTH preparations that are FDA-approved for the treatment of hypoparathyroidism. Subjects may be eligible for participation in other clinical trials evaluating treatment for hypoparathyroidism or patients may be able to convince their personal physicians to prescribe PTH off-label

19 CONFIDENTIALITY

19.1 Research Data and Investigator Medical Records

A subject's privacy and confidentiality will be respected throughout the study. Each subject will be assigned a code number. That number, rather than the participant's name, will be used on CRFs, the study database, and on samples collected for research (see Section 5). Individual research charts, which contain the link between the subject's name and code, will be kept in locked cabinets or rooms, and computer research databases will be on computer networks that are password protected and encrypted.

19.2 Stored Samples

All samples are coded and do not have personal identifiers. The codes for identifiers are contained in a subject code log that is maintained in secure research files. The key (i.e. list) that links each subject's name to his/her code will be stored in secured computer files. Only study investigators and their delegates, such as the study staff, laboratory staff, and the DCC, will have access to the study samples or data.

19.3 Special Precautions

Access to study data will be restricted as described above. The study PI, Associate Investigators, and NIDCR Site personnel will have access to research records, study data and research samples. Clinical Research Operations and Management Support and OCTOM will be able to access study data. Clinical Research Associates from CROMS will also have access to research records for monitoring purposes only. A summary of study results will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law.

20 CONFLICT OF INTEREST / TECHNOLOGY TRANSFER

20.1 Distribution of NIH Guidelines

NIH guidelines on conflict of interest have been distributed to all investigators. The principal investigator is responsible for ensuring that NIH policies and guidelines are followed.

20.2 Conflict of Interest

There are no conflicts of interest to report.

20.3 Role of a Commercial Company or Sponsor

Not applicable.

21 TECHONOLOGY TRANSFER

A material transfer agreement exists between NIH and David Dempster (via Helen Hayes Hospital) and Klaus Klaushofer (via Ludwig Boltzmann Institute of Osteology) who will be analyzing the bone biopsy specimens.

1198 **22 RESEARCH AND TRAVEL COMPENSATION**

1199 There will be no financial compensation for participating in the study; however, travel/subsistence
1200 expenses and research-related co-pays will be reimbursed according to the NIH policy established
1201 January 5, 2009.

1202

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1268

1269 **24 APPENDICES**

1270 **24.1 Adverse Event and Unanticipated Problem, and Protocol Deviation**
1271 **Definitions, Characteristics and Additional Reporting Details**

1272 **24.2 Pre-Screening Questionnaire and Eligibility Checklist**

1273 **24.3 Study Schema**

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1275 **24.5 Calcium Questionnaire**

1276 **24.6 DNA Consent Documents**

1277 **24.7 SF-36 Survey**

1278 **24.8 Fatigue Symptom Inventory**

1279 **24.9 6-Minute Walk Test**

1280 **24.10 Dosing Algorithm**

1281 **24.11 Discharge Instructions**

1282 **24.12 Bone Labeling Instructions**

1283 **24.13 Forteo Package Insert**

1284 **24.14 Study Blood Draw Amounts**

1285 **25 CONSENT FORMS**

1286 Consent forms are attached.

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24.1 Adverse Event and Unanticipated Problem Definitions, Characteristics and Reporting Details

**Adverse Event, Unanticipated Problem, & Protocol Deviation Definitions, Characteristics,
& Additional Reporting Details
Protocol Number 07-D-0016¹**

1 DEFINITIONS

1.1 Adverse Event

An AE is any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. In the context of FDA reporting, an AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

1.2 Serious Adverse Event (SAE)

A Serious Adverse Event is defined as any adverse event that:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity Results in congenital anomaly/birth defect OR
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

¹ All AE, SAE, UP, and PD definitions are based on NIH HRPP Standard Operating Procedure #16, v 1, entitled "Reporting Requirements for Unanticipated Problems, Adverse Events, and Protocol Deviations." Likewise, all event reporting described in the protocol and this Appendix complies with SOP #16. Additional text has been included to clarify the concepts of expectedness and relatedness as they are differentially used by the NIH, for purposes of unanticipated problem reporting, and by the FDA, for purposes of SAE reporting.

1.3 Unanticipated Problem

The Office for Human Research Protections considers unanticipated problems to be any incident, experience, or outcome that meets *all* of the following criteria:

- Is unexpected in terms of nature, severity, or frequency given a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent, and b) the characteristics of the subject population being studied;
- Is related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at **a greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

Expected adverse events may become unanticipated problems if they occur at a greater frequency or severity than was previously expected for an individual subject, as detailed in Section 17 of the protocol.

An incident, experience, or outcome that meets the 3 criteria above will generally warrant consideration of substantive changes in order to protect the safety, welfare, or rights of subjects or others. Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include the following:

- Changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects.
- Modification of inclusion or exclusion criteria to mitigate the newly identified risks.
- Implementation of additional procedures for monitoring subjects.
- Suspension of enrollment of new subjects.
- Suspension of research procedures in currently enrolled subjects.

- Modification of informed consent documents to include a description of newly recognized risks.
- Provision of additional information about newly recognized risks to previously enrolled subjects.

Per the definition, only a subset of AEs would be further characterized as unanticipated problems. Additionally, there are other sorts of events that, while not AEs, would also be characterized as unanticipated problems (e.g., contaminated investigational product).

1.4 Protocol Deviation

The Office of Human Subjects Research Protection defines a protocol deviation as any change, divergence, or departure from the IRB approved research protocol.

A serious protocol deviation is a deviation that “meets the definition of a serious adverse event or if it compromises the safety, welfare, or rights of subjects or others.” More specifically, a deviation is serious if it meets any of the following criteria:

- Has harmed or poses a significant or substantive risk of harm to the research subject
- Compromises the scientific integrity of the data collected for the study
- Is a breach of human subject protection regulations, or NIH policies or procedures
- Involves serious or continuing non-compliance with applicable federal, state, local or institutional human subject protection laws, regulations, or policies, or procedures
- Is inconsistent with the NIH Human Research Protection Program’s research, medical, and ethical principles.

Protocol deviations will be reported to the IRB and NIDCR Clinical Director as described in protocol Section 15.5.

2 EVENT CHARACTERISTICS

2.1 Severity of AE/SAEs

The severity of AE/SAEs will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The CTCAE provides a standard framework for recording, analyzing, and reporting events. Following CTCAE convention, AE/SAEs will be graded on a 5-point scale. If the severity of an event cannot be graded using CTCAE convention, the following guidelines will be used:

1. Mild: no intervention required
2. Moderate: minimal, local, or noninvasive intervention
3. Severe: significant symptoms requiring invasive intervention
4. Life-threatening: need for intensive care or emergent invasive procedure
5. Death: resulting from an adverse event

2.2 Relationship to the Investigational Product

For all AEs, the investigator will determine the degree to which an event may have been caused by the investigational product. "Relationship to the investigational product" is a factor used to guide SAE reporting to FDA. The investigator's assessment will be based on clinical judgment and information available in the study and investigational product documentation (e.g., Risks section of the protocol, Investigator's Brochure or Drug Fact Sheet). Alternative causes such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors will also be considered and investigated. The following guidelines will be used to aid this determination:

1. Related (Possible, probable, definite)
 - a. The event is not commonly associated with hypoparathyroidism or with one of the study procedures
 - b. The event is known to occur with administration of the product or similar products
 - c. There is a temporal relationship between product administration and event onset
 - d. The event abates when the investigational product is discontinued

- e. The event reappears upon a re-challenge with the product
2. Not Related (Not related, Unlikely)
- a. The event is commonly associated with hypoparathyroidism or with one of the study procedures
 - b. There is no temporal relationship between product administration and event onset
 - c. An alternate etiology has been established

2.3 Relationship to the Research

For all AEs, the investigator will determine the degree to which an event may have been caused by participation in the research. “Relationship to the research” is a factor used to identify unanticipated problems. An event would be considered related to the research if the investigator believes that it may have been caused by the investigational product, by a study procedure, by another study assessment, or any other aspect of study participation.

Relationship to the research will also partly determine whether a non-AE event might be qualified as an unanticipated problem.

2.4 Expected, Based on the Investigational Product

Serious adverse events that are considered to be at least possibly related to investigational product will be evaluated for expectedness based on the investigational product. For purposes of reporting, the Principal Investigator will be responsible for determining whether SAEs are expected or unexpected based on safety information in the Investigator’s Brochure (or Drug Fact Sheet) and the protocol. An SAE will be considered unexpected if the specificity or severity is not described in the available safety information for the investigational product, published medical literature, the protocol, or the informed consent document.

2.5 Expected, Based on the Study

Potential unanticipated problems (i.e., AEs or other events related to participation in the research that potentially place the subject at greater risk of harm) will be evaluated by the principal investigator to determine whether they were expected, based on the study. This broad definition includes documented risks of HPTH and study procedures and assessments; it also includes

consideration of the nature of the subject population being studied. Events that are expected based on any or all of these considerations are considered to be expected, based on the study. Such events would therefore not be considered UPs, because they would not satisfy the unexpectedness criterion.

3 RECORDING AND REPORTING DETAILS

3.1 All Adverse Events

All AE/SAEs will be recorded from the time written informed consent is obtained until subject withdrawal (for non-treated subjects) and through the conclusion of the HPTH post-stabilization phase (for HPTH treated subjects).

At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. The principal investigator will also review all source documentation related to inpatient study procedures for evidence of AEs. If subjects exhibit medical symptoms or conditions outside of the purview of the study (e.g., depression), they will be referred to their primary care provider or other appropriate medical personnel. Events will be followed until they return to baseline or until stabilization of the event. Participants who have AEs that are ongoing at the time their study participation ends will be referred to physicians outside of the NIH for care and follow-up.

All AE/SAEs will be captured in CRFs that document the event term, severity, duration, relationship to use of the investigational product, relationship to the research, actions taken in response to the event, and outcome. Potential UPs (i.e., events that are related to the research) will be evaluated for expectedness, based on the study. SAEs related to the investigational product will also be evaluated for expectedness, based on that investigational product.

See Section 17.0 for details of AE annual reporting to the IRB and to the FDA.

3.2 Clinically Significant Laboratory Abnormalities

The principal investigator will evaluate all clinical laboratory results for clinically significant abnormalities and document the evaluation in a CRF. Clinically significant findings (e.g., increase in calcium-citrate ratio to >0.7) will be recorded and reported as AEs regardless of their

association with the use of the investigational product. The principal investigator will follow significant abnormalities until they return to baseline or stabilization.

3.3 SAE & UP Reporting

See Section 17 for details of reporting timeframes for SAEs and UPs to the IRB, Clinical Director, and FDA.

SAEs and UPs will be reported to CROMS product safety via the study specific electronic data capture system. SAEs and UPs should be entered into the EDC within 1 business day of learning of the event. Once submitted, CROMS Product Safety will send a confirmation email to the investigator within 1 business day. The investigator should contact the CROMS product safety if this confirmation is not received. The Product Safety Associate will review the event report, gather additional information from the site, as necessary, and consult with the medical monitor or the physician designee.

Together, this Product Safety Team will determine for SAEs whether there is a reasonable possibility that the event is related to the investigational product and if so, whether the event was expected for the investigational product. The Product Safety Team will also review the intensity of the SAE in order to determine follow-up actions.

24.2 Pre-Screening Questionnaire and Eligibility Checklist

Gafni 07-D-0016	Prescreening	Subject ID #:
	Telephone Pre-Screening	

Screening Eligibility Questions

1. [Interviewer] Date of interview: / /
dd mmm yyyy

2. [Interviewer] What is the subject's gender?

☐ Male☐ Female

3. What is your date of birth? / / OR Age at time of Pre-Screening
 dd mmm yyyy If subject is permanently ineligible for the study or does not provide
 informed consent, enter Age and leave Date of Birth blank.

4. Have you been diagnosed with hypoparathyroidism by a physician?

☐ Yes☐ No (*Ineligible, skip to end*)

4a. Were you diagnosed at least one year ago?

☐ Yes☐ No (Ineligible, skip to Q16)

5. Do you have any of the following health problems?

Diabetes ☐ Yes ☐ No

Celiac disease ☐ Yes ☐ No

Crohn's disease ☐ Yes ☐ No

Cushing's syndrome ☐ Yes ☐ No

Active thyroid cancer ☐ Yes ☐ No

Seizure disorder ☐ Yes ☐ No

Osteoporosis ☐ Yes ☐ No

Osteosarcoma ☐ Yes ☐ No

Paget's disease ☐ Yes ☐ No

Metastatic bone disease ☐ Yes ☐ No

Liver disease ☐ Yes ☐ No

Adrenal insufficiency ☐ Yes ☐ No

Retinoblastoma ☐ Yes ☐ No

Li-Fraumeni Syndrome ☐ Yes ☐ No

Other ☐ Yes ☐ No Specify permanently disqualifying condition:

If any health problem is Yes, subject is ineligible and skip to end.

6. Are you currently taking any medications?

☐ Yes

☐ No (Skip to Q7)

6a. What medications are you taking?

List medications:

Exclusionary medications: PTH (for more than 2 weeks prior to study entry), thyroid hormone to suppress thyroid stimulating hormone below the assay's detection limit, bisphosphonates, calcitonin, tamoxifen, selective-estrogen receptor modulators, oral or intravenous corticosteroids (>3 weeks in last 6 months), estrogen replacement therapy, or medication for a seizure disorder

6b. [Interviewer] Is the subject taking any exclusionary medications?

☐ Yes (Ineligible, skip to Q16)

☐ No

7. Are you allergic to any antibiotics?

☐ Yes

☐ No (Skip to Q8)

7a. Which antibiotics are you allergic to?

List antibiotics:

7b. [Interviewer] Were tetracycline antibiotic allergies noted?

☐ Yes (Ineligible, skip to end)

☐ No

8. Have you received bone radiation treatment?

☐ Yes (Ineligible, skip to end)

☐ No

9. [Females only] Have you been post-menopausal for more than 6 months?

[Removed per protocol amendment]

9a. [Interviewer, Females only] Is the subject peri-menopausal as defined by no menses for 6 months to 5 years?

☐ Yes (Ineligible, skip to Q16)

☐ No

10. [Females only] Are you pregnant or breast-feeding?

☐ Yes (Ineligible, skip to Q16)

☐ No

11. [Females only] Have you received an injection for birth control in the last 12 months?

☐ Yes (Ineligible, skip to Q16)

☐ No

12. [Interviewer] Are there any other reasons to exclude this subject?

☐ Yes (Ineligible, provide Comment and skip to Q16)

☐ No (Skip to Q13)

12a. Comment on reason or exclusion:

13. [Interviewer] Is the subject eligible for a screening visit?

☐ Yes

☐ No (*Skip to Q16*)

14. [Interviewer] Is the subject interested in attending a screening visit?

☐ Yes

☐ No (*Skip to end*)

15. [Interviewer] Was an inpatient visit scheduled?

☐ Yes

☐ No (*Skip to Q16*)

16. [Interviewer] Will the subject be contacted later to reassess eligibility for the study?

☐ Yes

☐ No

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Gafni 07-D-0016		Subject ID #:
	Inclusion/Exclusion	

Inclusion Criteria

Subjects may only be included if all applicable inclusion questions are answered "Yes".

- | | |
|---|---|
| 1. Adult female aged 18-45 years or adult male aged 18-50 years | [Removed per protocol amendment] |
| 1a. Pre-menopausal female aged 18-45 years or adult male aged 18-70 years | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A |
| 1b. Postmenopausal woman aged ≥ 53 years to 70 years and 5 years since last menses | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A |
| [2.] Adolescent female with bone age ≥ 14 years (x-ray of the hand and wrist) or adolescent male with bone age ≥ 16 years (x-ray of the hand and wrist) | [Removed per protocol amendment] |
| 3. Physician-diagnosed hypoparathyroidism of at least 1-year duration, confirmed by medical record review | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A |
| 4. Intact PTH < 30 pg/mL | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A |
| 5. Woman without a uterus with a clinical history of menopause for at least 5 years and an FSH > 30 u/L | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A |

Exclusion Criteria

Subjects must be excluded if any responses to questions 1 - 18 are answered "Yes".

- | | |
|--|---|
| 1. Moderate to severe hepatic disease defined as hepatic transaminases (ALT and AST) > 2 times the upper limit of normal | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A |
| 2. Severe renal insufficiency defined as a calculated GFR < 25 mL/min/1.73 m ² using the CKD-EPI equation | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A |
| 3. Allergy or intolerance to tetracycline antibiotics | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A |
| 4. Pregnant or lactating | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A |

5. Peri- or post-menopausal as defined by no menses for > 6 months and an FSH > 20 U/L at the screening and/or baseline visits [Removed per protocol amendment]
- 5a. Peri-menopausal defined by no menses for 6 months to 5 years and an FSH > 20 U/L at the screening and/or baseline visits ☐ Yes ☐ No ☐ N/A
6. Chronic diseases that might affect mineral metabolism such as diabetes, celiac disease, Crohn's disease, Cushing's syndrome, or adrenal insufficiency ☐ Yes ☐ No ☐ N/A
7. Concurrent treatment with doses of thyroid hormone intended to suppress thyroid stimulating hormone below the assay's detection limit or persistent thyroid cancer ☐ Yes ☐ No ☐ N/A
- [8.] History of a skeletal disease unrelated to hypoparathyroidism, such as osteoporosis/low bone density (defined as a DXA Z-score or T-score < -2), osteosarcoma, Paget's disease, or metastatic bone disease [Removed per protocol amendment]
- 8a. History of a skeletal disease unrelated to hypoparathyroidism, such as osteoporosis or low bone density (defined as a DXA Z-score < -2 in all subjects or T-score < -2 in subjects ≥ 20 years old), osteosarcoma, Paget's disease, alkaline phosphatase > 1.5 times the upper limit of normal, or metastatic bone disease ☐ Yes ☐ No ☐ N/A
9. History of treatment with bisphosphonates, calcitonin, tamoxifen, selective-estrogen receptor modulators, or directed skeletal irradiation ☐ Yes ☐ No ☐ N/A
10. Use of oral or intravenous corticosteroids for more than 3 weeks within the last 6 months [Removed per protocol amendment]
- 10a. Use of oral or intravenous corticosteroids or estrogen replacement therapy for more than 3 weeks within the last 6 months ☐ Yes ☐ No ☐ N/A
11. Use of depot medoxyprogesterone for contraception within the past 12 months ☐ Yes ☐ No ☐ N/A
12. Chronic inadequate biochemical control with conventional therapy and/or calcium infusion dependent ☐ Yes ☐ No ☐ N/A
13. Seizure disorder requiring antiepileptic medications ☐ Yes ☐ No ☐ N/A
14. Treatment with PTH for more than 2 weeks prior to study entry [Removed per protocol amendment]
- 14a. Treatment with PTH for more than 2 weeks continuously at any time prior to study entry ☐ Yes ☐ No ☐ N/A
15. Any cognitive impairment that limits the subject's ability to comply, independently or through the assistance of a legally authorized representative, with protocol procedures. ☐ Yes ☐ No ☐ N/A

16. Unwillingness or inability to comply with protocol procedures

[Removed per
protocol amendment]

17. History of retinoblastoma or Li-Fraumeni syndrome

☐ Yes ☐ No ☐ N/A

18. Open epiphyses as determined by an x-ray of the hand and wrist in subjects <21 years of age ☐ Yes ☐ No ☐ N/A

Eligibility Status

Review all responses to the inclusion and exclusion criteria to determine subject eligibility.

19. Is the patient eligible for the study

☐ Yes ☐ No

Comments associated with this page:

Submit Query

Cancel

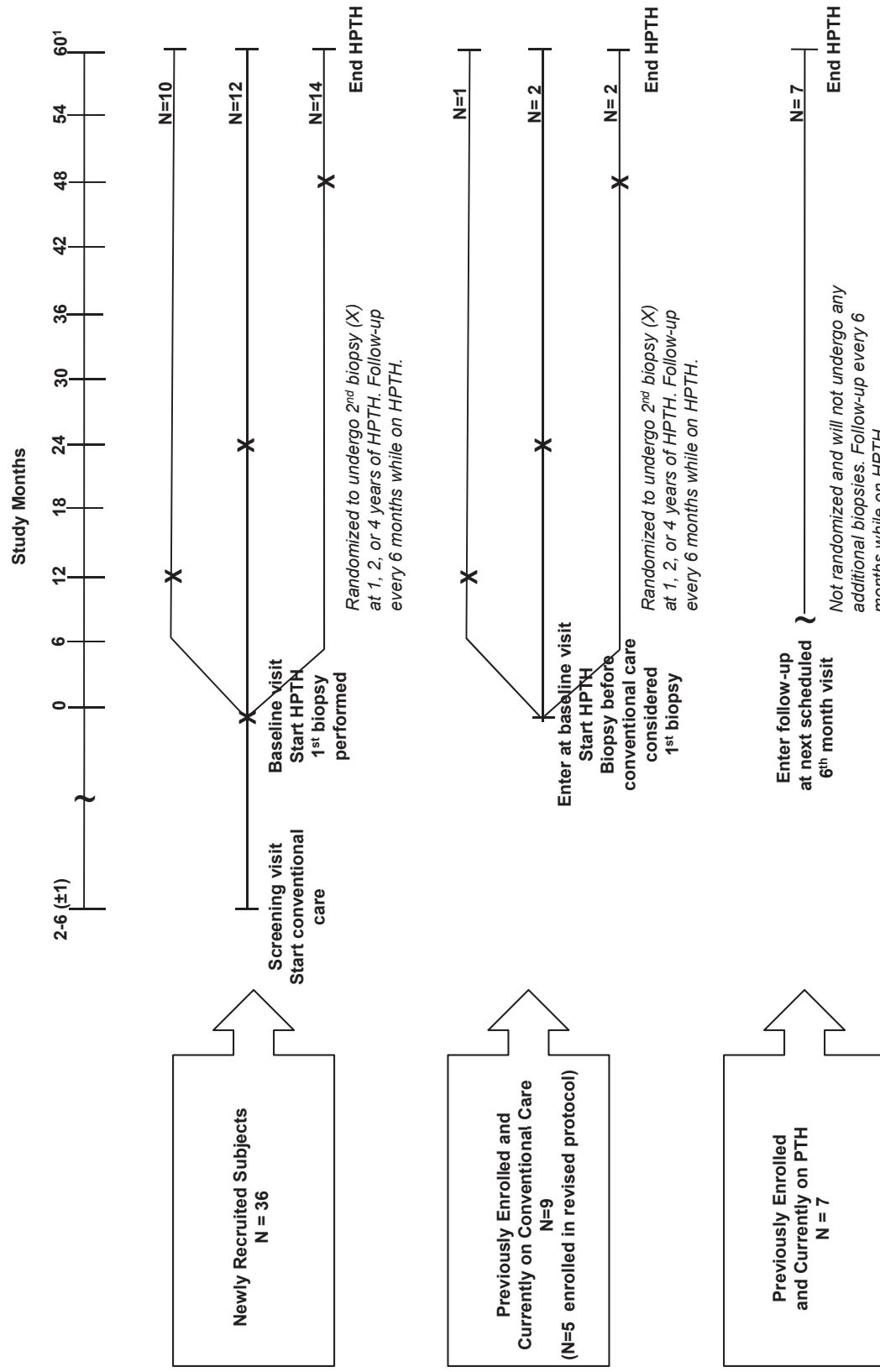
Form Completion Help

Print

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24.3 Study Schema

Effects of HPTH on Bone in Hypoparathyroidism



¹ At this time, subjects will be weaned off HPTH and provided with standard of care medication for a minimum of 3 months (±2weeks) and until the subject has stabilized. AE/SAE related to the down titration of HPTH will be reported during this Post-HPTH safety follow-up period. Version Date: 15FEB2011

24.4 Schedule of Events

Gafni 07-D-0016: Schedule of Events

	Prescreen	Screening ₈	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10 ⁹	V11 ¹⁰
Target Date (months)		2-6	0	6	12	18	24	30	36	42	48	54	60	66
Visit Window (weeks)		±4	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2
Recruitment and Enrollment														
Telephone pre-screening	X													
Informed consent ¹		X												
Medical History														
Medical history		X	X	X	X	X	X	X	X	X	X	X	X	X
Dietician consultation		X	X	X	X	X	X	X	X	X	X	X	X	X
Short Calcium Questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X
SF-36			X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X
Fitness Measures														
Fatigue Symptom Inventory			X	X	X	X	X	X	X	X	X	X	X	X
6-Minute Walk Test			X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam														
Height/weight		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination		X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Tests														
DNA testing (if indicated)		X												
Chem 20 panel		X	X	X	X	X	X	X	X	X	X	X	X	X
Complete blood count		X	X	X	X	X	X	X	X	X	X	X	X	X
Mineral panel or calcium level ²		X	X	X	X	X	X	X	X	X	X	X	X	X
Thyroid panel		X	X	X	X	X	X	X	X	X	X	X	X	X
25-OH-vitamin D		X	X	X	X	X	X	X	X	X	X	X	X	X
1,25 (OH) ₂ vitamin D ¹¹		X	X	X	X	X	X	X	X	X	X	X	X	X
Intact PTH		X	X	X	X	X	X	X	X	X	X	X	X	X
Bone-specific alkaline phosphate			X	X	X	X	X	X	X	X	X	X	X	X
Osteocalcin			X	X	X	X	X	X	X	X	X	X	X	X
Ionized calcium		X	X	X	X	X	X	X	X	X	X	X	X	X
Research blood samples for storage			X	X	X	X	X	X	X	X	X	X	X	X
24-hr blood sampling ³					X									

	Gafni 07-D-0016: Schedule of Events (continued)													
	Prescreen	Screening⁸	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10⁹	V11¹⁰
Target Date (months)		2-6	0	6	12	18	24	30	36	42	48	54	60	66
Visit Window (weeks)		±4	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2
Blood Tests														
Acute care and mineral panels ¹¹			X											
FGF23 ¹¹			X											
Urine Tests														
Urine pregnancy test		X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis		X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour urine ⁴		X	X	X	X	X	X	X	X	X	X	X	X	X
Spot Urine ¹²			X											
Imaging														
Radiographs to assess bone age ⁵		X												
Renal ultrasound		X	X		X		X		X		X		X	X
DXA ⁶		X	X	X	X	X	X	X	X	X	X	X	X	X
CT of the kidney without contrast			X		X		X		X		X		X	
Quantitative CT (L1 and L2 spine)			X		X		X		X		X		X	
Biopsy														
Baseline bone biopsy			X											
Follow-up bone biopsy ⁷					X		X				X			
PTH														
Conventional care		X											X	X
PTH therapy			X	X	X	X	X	X	X	X	X	X		

¹ Patients enrolled under the previous version of the protocol who are on conventional therapy will re-enter the study at V0 and be re-consented at V0. Patients enrolled under the previous version of the protocol who are on HPTH will re-enter the study during their next scheduled follow-up visit and will be re-consented at that visit.

² Mineral panels and calcium levels may be repeated as needed to monitor response to PTH therapy.

³ Blood will be drawn every 2 hours (± 15 minutes) for 24 hours to measure calcium, magnesium, phosphorus, and albumin.

⁴ At the Screening Visit, single 24-hour urine sample will be collected for calcium, phosphorus, creatinine, magnesium, sodium, citrate, pH, and potassium. At all subsequent visits, two 24-hour urine samples will be collected for the same measurements plus the measurement of N-Telopeptide.

⁵ Radiographs of the hand and wrist to assess bone age will be required for subjects <21 years of age.

⁶ DXA scan of the spine, femur, radius, and total body.

⁷ Subjects will be randomized to receive a single follow-up bone biopsy after 1, 2, or 4 years of HPTH therapy.

⁸ The duration of the screening period will be 2 to 6 months (±1 month) prior to first HPTH dosing.

⁹ At this time point, subjects will have been weaned off HPTH and provided with standard of care medication for a minimum of 3 months (\pm 2weeks) and until the subject has stabilized. Only AE/SAEs related to the weaning/termination of HPTH will be reported during this Post HPTH stabilization phase.

¹⁰ Visit will be completed 6 months after the start of the Post HPTH stabilization phase.

¹¹ Blood draws for an acute care panel, mineral panel, 1,25 (OH)₂ vitamin D, and FGF23 will be completed at 8AM, 12PM, 4PM, and 8PM on the first day of PTH therapy (Day 0). Blood draws for an acute care panel, mineral panel, 1, 25 (OH)₂ vitamin D, and FGF23 will also be collected at 8AM on the second day of PTH therapy (Day 1). One-hour windows are permitted on either side of each specified sampling time.

A morning blood draw will be completed on subsequent in-patient days during V0 for an acute care panel.

¹² Spot urine will be collected for cAMP, creatinine, phosphorus, calcium, and pH at 8AM, 12PM, 4PM, and 8PM on the first day of PTH therapy (Day 0). Spot urine for cAMP, creatinine, phosphorus, calcium, and pH will also be collected at 8AM on the second day of PTH therapy (Day 1). One-hour windows are permitted on either side of each specified sampling time.

A morning spot urine will be collected on subsequent in-patient days during V0 for cAMP, creatinine, phosphorus, calcium, and pH.

24.5 Calcium Questionnaire

Name:

Date:

Patient number:

Directions: In the yellow (shaded) boxes below, write in the number of servings of each of the following foods you eat in a typical week.

<u>Food or Beverage</u>	<u>Reference serving</u>	<u>Number servings per week</u>
"Total"® brand dry cereals (not other brands)	1 cup	<input type="text"/>
Instant breakfast drinks, shakes, diet shakes, liquid supplements	12 fl oz	<input type="text"/>
Milk, any kind, including on cereal, in beverages, etc	1 cup	<input type="text"/>
Yogurt (not frozen)	1 cup	<input type="text"/>
Calcium-fortified orange juice	1 cup	<input type="text"/>
Latte, cappuccino, frappuccino, etc	12 fl oz	<input type="text"/>
Meal replacement or energy bars	1 med	<input type="text"/>
Cheese: Swiss, cheddar, provolone, American, others (including on sandwiches and burgers)	1 oz/1 slice	<input type="text"/>
Sardines or salmon with bones	3 ounces	<input type="text"/>
Pizza with cheese	1 slice	<input type="text"/>
Lasagna, etc with cheese	1 cup	<input type="text"/>
Macaroni and cheese	1 cup	<input type="text"/>
Taco, burritos, etc, with cheese	1 each	<input type="text"/>
Soup made with milk	1 cup	<input type="text"/>
Breakfast bars	1 medium	<input type="text"/>
Tofu, firm, processed with calcium sulfate	½ cup	<input type="text"/>
Broccoli, collards, turnip greens, kale, bok choy	½ cup	<input type="text"/>
Beans: kidney, navy, black, baked, etc	1 cup	<input type="text"/>
Ice cream, frozen yogurt	½ cup	<input type="text"/>
Cottage cheese	¾ cup	<input type="text"/>
Pudding, made with milk	½ cup	<input type="text"/>
Pancakes, waffles, French toast	2 each	<input type="text"/>
Other dry cereals (not including Total®)	1 cup	<input type="text"/>
Almonds	¼ cup	<input type="text"/>
Other calcium-fortified drinks and juices	1 cup	<input type="text"/>

Have you taken any of the following in the past month?

Vitamin/mineral supplements	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Calcium supplements or pills	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Tums®, Rolaids®, etc.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

If yes, complete the following:

Name of product # 1:

Calcium (mg) per dose:

Average number doses taken per week:

Average calcium (mg/day)

Name of product # 2:

Calcium (mg) per dose:

Average number doses taken per week:

Average calcium (mg/day)

Name of product # 3:

Calcium (mg) per dose:

Average number doses taken per week:

Average calcium (mg/day)

For office use only:

Number of servings ____ x 1000 = Number of servings ____ x 400 = Number of servings ____ x 300 = Number of servings ____ x 200 = Number of servings ____ x 100 = Subtotal from diet mg/wkDivide by 7 to get daily average / 7Subtotal from diet mg/dayMiscellaneous from diet [add 200] + 200 mg/dayDaily calcium intake from food mg/dayDaily calcium intake from suppl + mg/day**TOTAL DAILY CALCIUM INTAKE** mg/day

Short Calcium Questionnaire (version SCQ 2002)

Nutrition Department, NIH Clinical Center

National Institutes of Health, Bethesda, MD 20892-1078 USA

24.6 DNA Consent Documents

I, _____, request DNA-based testing for [circle] MYSELF and/or MY CHILD or CHILDREN for **Calcium Homeostasis Disorder/CASR** (name of disease/gene). I understand that biological samples (blood, cheek cells, or skin) will be removed using standard techniques which carry very little risk. In addition, if prenatal diagnosis is being performed, fetal cells obtained by chorionic villus sampling or amniocentesis will be used. I understand that the blood, cheek cells, skin, or fetal samples will be used for the purpose of attempting to determine if I and/or members of my family are carriers of the disease gene, or are affected with, or at increased risk to someday be affected with this genetic disease. The minor children for which I hereby give permission to collect biological samples for this test are named below:

Child's Name	Date of Birth	Gender (M/F)
_____	_____	_____
_____	_____	_____
_____	_____	_____

I understand that:

1. In some cases the DNA test directly detects an abnormality, called a mutation, in the gene, and the test is better than 99% accurate.

In other cases, the DNA test is unable to identify an abnormality although the abnormality may still exist. This event may be due to our current lack of knowledge of the complete gene structure or an inability of the current technology to identify certain types of changes (mutations) in the gene.

Ninety percent of families with familial (benign) hypocalciuric hypercalcemia, type 1 (HHC1/FHH) have an identifiable mutation in the CASR gene. Most cases of autosomal recessive neonatal severe primary hyperparathyroidism (NSHPT) also harbor mutations in the CASR gene. In autosomal dominant hypocalcemia (ADH), one small study found that 42% of patients with isolated hypoparathyroidism had a CASR mutation. Test sensitivity in familial isolated hypoparathyroidism (FIH) has not been established. Studies in some families with calcium homeostasis disorders have found that mutation in another gene (or genes), rather than CASR, is likely to underlie the disease; however those other genes have yet to be identified.

I have been informed of the likelihood of finding a mutation in the gene for which I am being tested. _____ (Initial)

2. In rare cases, GeneDx may use an indirect method called linkage analysis. If linkage analysis is being used, naturally occurring rearrangements in the DNA (known as "recombination") may produce an uncertainty in predicting carrier status or diagnosis. Rare variations in the DNA of individuals can also cause uncertainty in predicting carrier status or diagnosis. Thus, linkage

analysis is not 100% accurate, and the results will be reported as a probability. In some families, the markers used for the linkage analysis may not be informative. In these cases, the DNA test will not be useful for that family or for some family members.

3. An error in the diagnosis of disease status may occur if the true biological relationships of the family members being tested are not as I have stated. For example, non-paternity means that the stated father of an individual is not the true biological father. This test may detect non-paternity, and it may be necessary to report this finding to the individual who requested testing. Any erroneous diagnosis in a family member can lead to an incorrect diagnosis for other related individuals who are being tested.
4. I understand that the DNA analysis performed by GeneDx is specific for this disease and in no way guarantees my health or the health of my living or unborn children. The accuracy of DNA analysis is entirely dependent on the clinical diagnosis made elsewhere, and GeneDx cannot be responsible for an erroneous clinical diagnosis made elsewhere.
5. In order to perform accurate prenatal diagnosis on a fetal sample, biological samples are also required from the affected individual in the family, the mother, and in some cases the father.
6. These tests are relatively new and are being improved and expanded continuously. The tests are not considered research, but are considered to be the best and newest laboratory service that can be offered. This testing is complex and utilizes specialized materials so that there is always some very small possibility that the test will not work properly or that an error will occur. There is a low error rate (perhaps 1 in 1000 samples) even in the best laboratories. My signature below acknowledges my voluntary participation in this test, but in no way releases the laboratory and staff of GeneDx from their professional and ethical responsibility to me.
7. I understand that my sample is not being banked. GeneDx does not return DNA samples to individuals or physicians. However, in some cases it may be possible for GeneDx to reanalyze the remaining DNA upon request. The request for additional testing must be ordered and there will be an additional fee.
8. Because of the complexity of DNA based testing and the important implications of the test results, results will only be reported to me through a physician, genetic counselor, or certified genetics professional. The result reports are confidential and will only be released to other medical professionals or other parties with my express written consent. All laboratory data is confidential and will not be released from GeneDx. Participation in DNA testing is completely voluntary.
9. I will receive a copy of this consent form.

Signature: _____ Date: _____

Witnessed by: _____

Physician's/Counselor's Statement: I have explained DNA testing to this individual. I have addressed the limitation outlined above, and I have answered this person's questions.

Signature: _____ Date: _____

I, _____, request DNA-based testing for [circle] MYSELF and/or MY CHILD or CHILDREN for **Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy / AIRE gene** (name of disease/gene). I understand that biological samples (blood, cheek cells, or skin) will be removed using standard techniques which carry very little risk. In addition, if prenatal diagnosis is being performed, fetal cells obtained by chorionic villus sampling or amniocentesis will be used. I understand that the blood, cheek cells, skin, or fetal samples will be used for the purpose of attempting to determine if I and/or members of my family are carriers of the disease gene, or are affected with, or at increased risk to someday be affected with this genetic disease. The minor children for which I hereby give permission to collect biological samples for this test are named below:

Child's Name	Date of Birth	Gender (M/F)
_____	_____	_____
_____	_____	_____
_____	_____	_____

I understand that:

1. In some cases the DNA test directly detects an abnormality, called a mutation, in the gene, and the test is better than 99% accurate.

In other cases, the DNA test is unable to identify an abnormality although the abnormality may still exist. This event may be due to our current lack of knowledge of the complete gene structure or an inability of the current technology to identify certain types of changes (mutations) in the gene.

Tier 1 of the AIRE test (sequencing of exons 2, 3, 6, 8, and 10) is expected to detect at least one mutation in 90% of patients in most ethnic groups. Tier 2 testing (sequencing of the remainder of the gene plus exon-level array CGH if indicated) is available for patients who are negative or have only one mutation with Tier 1. Altogether the methods use by GeneDx are expected to detect at least 98% of mutations.

I have been informed of the likelihood of finding a mutation in the gene for which I am being tested.
_____ (Initial)

2. In rare cases, GeneDx may use an indirect method called linkage analysis. If linkage analysis is being used, naturally occurring rearrangements in the DNA (known as "recombination") may produce an uncertainty in predicting carrier status or diagnosis. Rare variations in the DNA of individuals can also cause uncertainty in predicting carrier status or diagnosis. Thus, linkage analysis is not 100% accurate, and the results will be reported as a probability. In some families, the markers used for the linkage analysis may not be informative. In these cases, the DNA test will not be useful for that family or for some family members.

3. An error in the diagnosis of disease status may occur if the true biological relationships of the family members being tested are not as I have stated. For example, non-paternity means that the stated father of an individual is not the true biological father. This test may detect non-paternity, and it may be necessary to report this finding to the individual who requested testing. Any erroneous diagnosis in a family member can lead to an incorrect diagnosis for other related individuals who are being tested.
4. I understand that the DNA analysis performed by GeneDx is specific for this disease and in no way guarantees my health or the health of my living or unborn children. The accuracy of DNA analysis is entirely dependent on the clinical diagnosis made elsewhere, and GeneDx cannot be responsible for an erroneous clinical diagnosis made elsewhere.
5. In order to perform accurate prenatal diagnosis on a fetal sample, biological samples are also required from the affected individual in the family, the mother, and in some cases the father.
6. These tests are relatively new and are being improved and expanded continuously. The tests are not considered research, but are considered to be the best and newest laboratory service that can be offered. This testing is complex and utilizes specialized materials so that there is always some very small possibility that the test will not work properly or that an error will occur. There is a low error rate (perhaps 1 in 1000 samples) even in the best laboratories. My signature below acknowledges my voluntary participation in this test, but in no way releases the laboratory and staff of GeneDx from their professional and ethical responsibility to me.
7. I understand that my sample is not being banked. GeneDx does not return DNA samples to individuals or physicians. However, in some cases it may be possible for GeneDx to reanalyze the remaining DNA upon request. The request for additional testing must be ordered and there will be an additional fee.
8. Because of the complexity of DNA based testing and the important implications of the test results, results will only be reported to me through a physician, genetic counselor, or certified genetics professional. The result reports are confidential and will only be released to other medical professionals or other parties with my express written consent. All laboratory data is confidential and will not be released from GeneDx. Participation in DNA testing is completely voluntary.
9. I will receive a copy of this consent form.

Signature: _____ Date: _____

Witnessed by: _____

Physician's/Counselor's Statement: I have explained DNA testing to this individual. I have addressed the limitation outlined above, and I have answered this person's questions.

Signature: _____ Date: _____

24.7 SF-36 Survey

Protocol: 07-D-0016 Effects of Calcitriol vs. PTH Replacement Therapy on Bone Patients with Hypoparathyroidism

Form Name:

SF-36 HEALTH SURVEY V2

Form Description:

SF-36

This survey asks for your views about your health. Answer every question by selecting the appropriate answer.

SF-36 Done

☐ Yes☐ No

1. In general would you say your health is:

☐ Excellent☐ Very good☐ Good☐ Fair☐ Poor

2. Compared to one year ago, how would you rate your health in general now?

☐ Much better now than one year ago☐ Somewhat better now than one year ago☐ About the same☐ Somewhat worse now than one year ago☐ Much worse now than one year ago

3. The following questions are about activities you might do during a day. Does your health now limit you in these activities?

a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports

☐ Yes, limited a lot☐ Yes, limited a little☐ No, not limited at all

b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

☐ Yes, limited a lot☐ Yes, limited a little☐ No, not limited at all

c. Lifting or carrying groceries

☐ Yes, limited a lot☐ Yes, limited a little☐ No, not limited at all

d. Climbing several flights of stairs

☐ Yes, limited a lot

- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

d. Had difficulty performing the work or other activities (for example, it took extra effort)

- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

5. During the past 4 weeks, have you had any of the following problems as a result of any emotional problems?

a. Cut down the amount of time you spent on work or other activities

- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

b. Accomplished less than you would like

- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

c. Didn't do work or other activities as carefully as usual

- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

7. How much bodily pain have you had during the past 4 weeks?

7. How much bodily pain have you had during the past 4 weeks?

- ☐ None
- ☐ Very mild
- ☐ Mild

- ☐ Moderate
- ☐ Severe
- ☐ Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including work outside the home and housework)?

- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

9. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks

a. Did you feel full of life?

- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

b. Have you been a very nervous person?

- ☐ All the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

c. Have you felt so down in the dumps that nothing could cheer you up?

- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

d. Have you felt calm and peaceful?

- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

e. Did you have a lot of energy?

- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time

f. Have you felt downhearted and blue?

- ☐ None of the time
☐ All of the time
☐ Most of the time
☐ Some of the time
☐ A little of the time
☐ None of the time

g. Did you feel worn out?

- ☐ All of the time
☐ Most of the time
☐ Some of the time
☐ A little of the time
☐ None of the time

h. Have you been a happy person?

- ☐ All of the time
☐ Most of the time
☐ Some of the time
☐ A little of the time
☐ None of the time

i. Did you feel tired?

- ☐ All of the time
☐ Most of the time
☐ Some of the time
☐ A little of the time
☐ None of the time

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relative, etc.)?

- ☐ All of the time
☐ Most of the time
☐ Some of the time
☐ A little of the time
☐ None of the time

11. How TRUE or FALSE is each of the following statements for you?

a. I seem to get sick a little easier than other people

- ☐ Definitely true
☐ Mostly true
☐ Don't know
☐ Mostly false
☐ Definitely false

b. I am as healthy as anybody I know

- ☐ Definitely true
☐ Mostly true
☐ Don't know

c. I expect my health to get worse

- ☐ Mostly false
- ☐ Definitely false

- ☐ Definitely true
- ☐ Mostly true
- ☐ Don't know
- ☐ Mostly false
- ☐ Definitely false

d. My health is excellent

- ☐ Definitely true
- ☐ Mostly true
- ☐ Don't know
- ☐ Mostly false
- ☐ Definitely false

24.8 Fatigue Symptom Inventory

Measurement of fatigue in cancer patients: Further validation of the Fatigue Symptom Inventory

Danette M. Hann, Maxine M. Denniston & Frank Baker
Behavioral Research Center, American Cancer Society, Atlanta, GA, USA

Accepted in revised form 20 October 2000

Abstract

Fatigue is one of the most common and debilitating symptoms experienced by cancer patients, yet until recent years it has received little systematic attention, due in part to the lack of adequate instruments to measure fatigue. The primary aim of this report is to further validate a recently developed measure of fatigue for use with cancer patients: the Fatigue Symptom Inventory (FSI). This 13-item self-report measure was designed to measure the intensity and duration of fatigue and its interference with quality of life. The FSI was originally validated in a sample of breast cancer patients and a sample of healthy individuals. In this study, the FSI was evaluated in an outpatient sample that included male and female cancer patients, as well as some older patients, with a variety of cancer diagnoses. A seven-item interference scale was found to have good internal consistency, with α coefficients above 0.90. Convergent validity was demonstrated via comparisons with an existing measure of fatigue. Construct validity was demonstrated via comparisons with measure of life satisfaction and depression as well as comparisons among subgroups of patients expected to differ in their experience of fatigue. Overall, the FSI was further established as a valid and reliable measure of fatigue in cancer patients. The potential application of this measure in psychosocial oncology research is discussed.

Key words: Fatigue, Neoplasms, Quality of life

Introduction

Fatigue is among the most common and debilitating symptoms that cancer patients experience [1, 2]. In recent years, the severity of fatigue and its impact on quality of life have received increased attention. As more studies of fatigue have been undertaken, there have been a number of different measures developed to assess fatigue in cancer patients. These measures range from one-item scales of intensity (i.e., visual analog scales) to multidimensional measures such as the Piper Fatigue Scale (PFS) [3]. Other measures include the fatigue subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [4] and the Multidimensional Fatigue Inventory [5]. The advantages and psy-

chometric limitations of the aforementioned measures were reviewed in a previous report [6]. Recently, the Piper scale has been revised, and additional measures have been developed; a review of these follows.

The revised PFS is a 22-item self-report measure used to assess the subjective experience of fatigue. Four subscales measure the behavioral, affective, sensory, and cognitive aspects of fatigue [7]. The PFS also contains three open-ended questions about what patients have used to relieve fatigue, what they believe causes fatigue, and symptoms associated with fatigue. Reliability of the PFS is strong, with α coefficients ranging from 0.85 to 0.95. While briefer than the original measure, the wording of some of the PFS items still presumes that respondents are currently experiencing fatigue

and therefore can only be used reliably if respondents are first screened for the presence of fatigue.

A fatigue subscale has been added to the Functional Assessment for Cancer Therapy scale (FACT-F) [8]. The fatigue subscale demonstrated strong internal consistency ($\alpha = 0.95$) as well as convergent, discriminant, and construct validity. However, the instrument was validated using only 50 patients, and conclusions drawn from the sample should be replicated with a larger sample. Also, the author of the scale points out that the fatigue subscale can be used as an 'independent, brief, unidimensional measure of fatigue', i.e., while the subscale provides an index of current fatigue, it does not provide information about the multidimensional impact of fatigue on quality of life.

The Schwartz Cancer Fatigue Scale (SCFS) [9] is a 28-item scale with four subscales: physical, emotional, cognitive, and temporal. The scale includes a list of symptoms that reflect the various dimensions. Reliability is reported to be between 0.82 and 0.93. Lacking in this scale is an index of the impact of fatigue on various aspects of quality of life, e.g., ability to work and participation in social activities.

In summary, there are a number of instruments that measure cancer-related fatigue, but none that provide an assessment that includes information about fatigue intensity, duration, and impact on quality of life. The fatigue symptom inventory (FSI) offers the unique opportunity to assess fatigue intensity, fatigue duration, and the interference of fatigue with various aspects of quality of life [6]. The psychometric properties of the FSI were originally assessed in a sample of women undergoing treatment for breast cancer, women who had completed treatment for breast cancer and women with no history of cancer. The average age of all three groups of women was under 55 years. In this study, the seven-item interference subscale was found to have good internal consistency, with α coefficients above 0.90 in all three groups. The complete FSI was found to have rather weak to moderate test-retest reliability in cancer patients and healthy controls assessed on three separate occasions. Convergent validity was demonstrated using comparisons with an existing standardized fatigue measure. Construct validity was demonstrated using comparisons between and within groups as well as comparisons with

measures of anxiety and depression. Overall, the FSI was established as a valid and reliable measure of fatigue in breast cancer patients and in healthy individuals. However, until the present study, the FSI had not been assessed in other cancer patients. The purpose of this report is to describe the psychometric properties of the FSI when used with male patients as well as female patients, patients 55 years of age and older as well as patients under 55 years of age, and patients with other types of cancer as well as patients with breast cancer.

Method

Subjects

To be eligible for this sample, patients had to be 18 years of age or older, have no known psychiatric or neurological disorders which would interfere with completion of the measures, and be able to read English. Patients were recruited at outpatient clinics in four states (Iowa, Wisconsin, Minnesota, and Georgia) after approval of the Institutional Review Board at each facility had been obtained. Across the four clinics there was an average response rate of 60%. A total of 342 cancer patients participated in this study.

Procedure

Each subject was individually recruited by a clinic staff member or research assistant. After informed consent was obtained, participants were given a self-report questionnaire to complete while waiting for their appointment. Patients who wished to complete the questionnaire at home were provided a stamped envelope with which to return it. In addition to the FSI, the questionnaire also included the fatigue scale from the Profile of Mood States (POMS-F) [10], the Satisfaction with Life Domains scale-Cancer (SLDS-C) [11, 12], the Center for Epidemiological Studies-Depression Scale (CES-D) [13], and a demographic and medical background form.

Measures

A copy of the FSI is presented in Table 1. The FSI includes measures of fatigue intensity (four items)

Table 1. The Fatigue Symptom Inventory (FSI)

For each of the following, circle the **one number** that best indicates how that item applies to you.

1. Rate your level of fatigue on the day you **felt** most fatigued during the past week.
0 1 2 3 4 5 6 7 8 9 10
Not at all As fatigued as
fatigued I could be
2. Rate your level of fatigue on the day you felt **least** fatigued during the past week.
0 1 2 3 4 5 6 7 8 9 10
Not at all As fatigued as
fatigued I could be
3. Rate your level of fatigue on the **average** in the last week.
0 1 2 3 4 5 6 7 8 9 10
Not at all As fatigued as
fatigued I could be
4. Rate your level of fatigue **right now**.
0 1 2 3 4 5 6 7 8 9 10
Not at all As fatigued as
fatigued I could be
5. Rate how much, in the past week, fatigue interfered with your **general level of activity**.
0 1 2 3 4 5 6 7 8 9 10
No Extreme
interference interference
6. Rate how much, in the past week, fatigue interfered with your **ability to bathe and dress yourself**.
0 1 2 3 4 5 6 7 8 9 10
No Extreme
interference interference
7. Rate how much, in the past week, fatigue interfered with your normal work activity (**includes both work outside the home and housework**).
0 1 2 3 4 5 6 7 8 9 10
No Extreme
interference interference
8. Rate how much, in the past week, fatigue interfered with your **ability to concentrate**.
0 1 2 3 4 5 6 7 8 9 10
No Extreme
interference interference
9. Rate how much, in the past week, fatigue interfered with your **relations with other people**.
0 1 2 3 4 5 6 7 8 9 10
No Extreme
interference interference
10. Rate how much, in the past week, fatigue interfered with your **enjoyment of life**.
0 1 2 3 4 5 6 7 8 9 10
No Extreme
interference interference

Table 1. (Continued)

11. Rate how much, in the past week, fatigue interfered with your **mood**:
0 1 2 3 4 5 6 7 8 9 10
No Extreme
interference interference
12. Indicate **how many days**, in the past week, you felt fatigued for any part of the day.
0 1 2 3 4 5 6 7
Days Days
13. Rate **how much of the day**, on average you felt fatigued in the past week.
0 1 2 3 4 5 6 7 8 9 10
None of The entire
the day day

and duration (two items) during the past week as well as a subscale (seven items) which measures the extent to which fatigue interfered with quality of life. The intensity items require a respondent's rating of the most, least, and average fatigue in the past week, and current fatigue on an 11 point scale (0 = not at all fatigued and 10 = extreme fatigue). The interference items assess the extent to which fatigue interfered with a respondent's general activity level, ability to bathe and dress, work activity, ability to concentrate, relations with others, enjoyment of life and mood during the previous week using an 11 point rating scale (0 = no interference and 10 = extreme interference). The last two items assess fatigue duration, i.e., number days in the past week (0–7 days) and the percent of time each day (0 = none of the day and 10 = the entire day) fatigue was present [6].

The POMS-F is a reliable and valid measure of feelings of weariness and low energy [10]. Respondents indicate the extent to which they have experienced each of seven symptoms of fatigue during the previous week on five-point intensity scales (0 = not at all and 4 = extremely). The POMS-F has been widely used to measure fatigue in cancer patients, and was used as the standard measure against which to evaluate convergent validity in the original validation of the FSI [6].

The SLDS-C is a reliable and valid 18-item measure of life satisfaction in cancer patients. This scale covers a variety of life domains relevant to patients with cancer, and uses a picture response format. Respondents are asked to express their satisfaction with each of 18 life areas by choosing

one of seven 'smiley' faces, ranging from a 'very unhappy' face with a deep, down-turned frown (scored 1) to a 'delighted' face with a large smile (scored 7) [11, 12].

The CES-D is a reliable and valid 20-item measure of the severity of depressive symptoms during the past week [13]. Items are ranked on a four-point frequency scale (1 = rarely or none of the time; 4 = most or all of the time). Although originally developed for use with the general population, recent psychometric evaluations support the use of the CES-D to assess depressive symptoms in cancer patients [14, 15].

Psychometric analyses

The internal consistency of the FSI interference scale was evaluated by computing coefficient α [16]. To examine the reliability of the FSI in various patient subgroups, we computed coefficient α separately for male and female patients; for younger (18–54 years) and older (55 or more years) patients, and for patients with breast cancer and patients with any other type of cancer. To further evaluate the reliability of the interference scale, item–total correlations were calculated for the sample as a whole.

The convergent validity of the FSI was evaluated by computing the correlation between the FSI items (fatigue intensity items, duration items, and interference scale) and the POMS-F total score. It was expected that significant positive correlations between the measures would support the validity of the FSI. Correlations were computed for the group as a whole as well as for subgroups by gender, age and type of cancer.

Construct validity was evaluated by computing the correlations between the FSI and measures of life satisfaction and depression: the SLDS-C and CES-D. Since increased fatigue has been associated with increased depressive symptoms [6, 12, 17] and with lower life satisfaction [18], it was expected that significant positive correlations between the FSI and CES-D and significant negative correlations between FSI and SLDS-C would demonstrate construct validity. Correlations were computed for the sample as a whole and for subgroups by gender, age and type of cancer.

Further, the construct validity of the FSI was evaluated by comparing subgroups of patients

who might be expected to differ in the extent to which they are experiencing fatigue. Separate ANOVAs were conducted to evaluate the differences among three patient subgroups on measures of fatigue intensity, duration and interference. The scores of patients on active treatment and those of patients who were less than 1 year post-treatment were expected to be higher than those of patients who were more than 1 year post-treatment.

Results

Demographic characteristics of the sample

The demographic characteristics of the sample are presented in Table 2. The average age of the

Table 2. Demographic characteristics of the sample

	N	%
Age (years)		
18–54	121	36
55 or older	216	64
Gender		
Female	239	71
Male	99	29
Type of cancer		
Breast	147	43
Other	143	42
Ethnic background		
African–American	63	19
Caucasian	271	80
Asian/other	3	1
Marital status		
Married/living with partner	239	71
Widowed	29	9
Separated	8	2
Divorced	38	11
Single, never married	22	7
Education		
Some high school or less	39	12
High school graduate/GED	84	25
Vocational or some college	103	31
College graduate	62	18
Professional/graduate school	49	14
Household income		
\$10,000 or less	20	7
\$10,001–\$20,000	47	15
\$20,001–\$40,000	93	29
\$40,001–\$75,000	100	32
More than \$75,000	53	17

patients was 59 (SD = 12.7; range 27–91). The majority of patients were female (71%), Caucasian (80%), and married (71%). Patients reported a variety of cancer diagnoses, including breast (42%), colorectal (19%), and prostate (9%). The average time since most recent diagnosis was 1.8 years (SD = 1.8; range 0.1–8.6 years).

Reliability

The α coefficient for the interference scale in the sample as a whole was 0.94. In the subgroups of female patients and male patients, α coefficients were 0.93 and 0.95, respectively. For younger patients and older patients, the values were 0.92 and 0.94, respectively. For breast cancer patients and patients with another type of cancer, the values were 0.93 and 0.94, respectively. These values are well above the acceptable range determined by Nunnally (0.70–0.80) [16]. The item–total correlations for the interference scale, computed using the entire sample, were above 0.75, with the exception of the item asking about the ability to bathe and dress, which had a correlation of 0.60.

Convergent and construct validity

The convergent validity of the FSI was evaluated using the entire sample as well as the patient subgroups; results are presented in Table 3. As expected, significant positive correlations between the FSI (intensity items, duration items, and interference scale) and POMS-F support the

convergent validity of the FSI. The correlations were consistently strong and positive across age, gender, and type of cancer.

With regard to construct validity, it was expected that fatigue would be significantly related to depressive symptoms and life satisfaction. The results are presented in Table 4. As expected, significant positive correlations were found between the fatigue intensity ratings, fatigue duration ratings, and interference scale score and depressive symptoms (CES-D). The correlations were moderate, positive, and significant for the entire sample as well as across age, gender and type of cancer. Also as expected, significant negative correlations were found between fatigue ratings and life satisfaction (SLDS-C) which were moderate to strong, negative, and significant for the entire sample as well as across subgroups by age, gender and type of cancer.

Construct validity was also tested by comparing fatigue intensity, duration, and interference among subgroups of patients who were either in active treatment ($n = 181$), within one year of treatment ($n = 75$), or more than one year post-treatment ($n = 71$). The mean FSI scores for the three groups are presented in Table 5. As expected, patients who were in active treatment reported significantly worse fatigue than patients who were more than one year post-treatment. Specifically, patients in active treatment or within one year of treatment reported fatigue that was significantly more severe (average fatigue), longer in duration (more days and more time each day) and produced greater interference with quality of life.

Table 3. Correlations of FSI ratings with POMS-F score

FSI	Entire group	18–54 years (n = 119)	55+ years (n = 209)	Female (n = 231)	Male (n = 97)	Breast (n = 142)	Other (n = 141)
<i>Intensity ratings</i>							
Most fatigue	0.71	0.65	0.75	0.68	0.81	0.67	0.72
Least fatigue	0.65	0.58	0.71	0.65	0.68	0.62	0.70
Average fatigue	0.75	0.72	0.76	0.72	0.81	0.73	0.72
Fatigue now	0.66	0.69	0.64	0.61	0.78	0.71	0.63
<i>Duration ratings</i>							
Number of days fatigued	0.71	0.53	0.69	0.59	0.74	0.56	0.68
Time fatigued	0.64	0.64	0.75	0.69	0.74	0.72	0.69
<i>Interference scale</i>	0.78	0.79	0.77	0.79	0.74	0.78	0.73

All correlations are significant at $p = 0.01$.

Table 4. Correlations of fatigue ratings with depression and life satisfaction scores

FSI	Entire group	18–54 years (n = 119)	55+ years (n = 209)	Female (n = 231)	Male (n = 97)	Breast (n = 142)	Other (n = 141)
<i>Intensity ratings</i>							
Most fatigue							
CES-D	0.47	0.45	0.46	0.43	0.54	0.39	0.53
SLDS-C	–0.53	–0.45	–0.56	–0.51	–0.57	–0.47	–0.59
Least fatigue							
CES-D	0.40	0.43	0.42	0.41	0.39	0.45	0.36
SLDS-C	–0.46	–0.34	–0.55	–0.48	–0.41	–0.49	–0.43
Average fatigue							
CES-D	0.55	0.55	0.55	0.53	0.59	0.52	0.58
SLDS-C	–0.54	–0.50	–0.56	–0.53	–0.56	–0.53	–0.57
Fatigue now							
CES-D	0.45	0.41	0.48	0.41	0.54	0.47	0.51
SLDS-C	–0.47	–0.42	–0.50	–0.42	–0.59	–0.52	–0.47
<i>Duration ratings</i>							
Number days fatigued							
CES-D	0.37	0.40	0.37	0.37	0.39	0.36	0.35
SLDS-C	–0.49	–0.42	–0.52	–0.45	–0.56	–0.42	–0.52
Time fatigued							
CES-D	0.52	0.50	0.52	0.50	0.54	0.55	0.50
SLDS-C	–0.49	–0.45	–0.56	–0.50	–0.56	–0.57	–0.48
<i>Interference scale</i>							
CES-D	0.63	0.66	0.60	0.63	0.63	0.68	0.59
SLDS-C	–0.61	–0.55	–0.63	–0.61	–0.58	–0.63	–0.56

All correlations are significant at $p = 0.01$.

Table 5. Differences in fatigue between patients in active treatment, less than 1 year post-treatment, or more than 1 year post-treatment

	Active treatment (n = 179) Mean (SD)	1 year post-treatment (n = 74) Mean (SD)	More than 1 year post-treatment (n = 70) Mean (SD)	F-Value
<i>Intensity ratings</i>				
Most fatigue	5.5 (2.9)	5.3 (2.8)	4.9 (2.6)	0.96
Least fatigue	2.2 (2.0)	2.2 (1.9)	1.6 (1.7)	2.8
Average fatigue	3.7 (2.2)A	3.8 (2.3)B	3.0 (2.0)AB	3.2*
Fatigue now	3.2 (2.7)	3.1 (2.7)	2.5 (2.6)	1.8
<i>Duration ratings</i>				
Number of days	3.9 (2.4)A	3.9 (2.5)B	3.0 (2.3)AB	4.1*
Time fatigued	3.7 (2.7)A	3.6 (2.5)B	2.7 (2.0)AB	4.1*
<i>Interference scale</i>				
	2.5 (2.3)A	2.0 (2.0)B	1.6 (1.8)AB	5.7**

* $p < 0.05$; ** $p < 0.01$; Within rows, cells with the same letters are significantly different between groups.

Discussion

The purpose of this report is to further describe the psychometric properties of the FSI. The FSI was

originally validated in a sample of women with breast cancer who on average were under 55 years of age. In this study, the sample was heterogeneous, which gave us the opportunity to evaluate

the reliability of the FSI in male patients and patients 55 years of age or more. We could also evaluate the FSI when used in a sample of patients with cancer diagnoses other than breast cancer.

The FSI interference scale exhibited high internal consistency in the sample as a whole as well as in the subgroups of patients broken down by age, gender and type of cancer. The convergent validity of the FSI was demonstrated via significant correlations with an established measure of fatigue. The construct validity of the FSI was supported by significant associations with life satisfaction and depression as well as by comparisons among patients expected to differ in their experience of fatigue. For the purpose of these psychometric analyses, the interference items were combined into one subscale. Perhaps use of these items independently may offer a richer view of the various ways that fatigue affects quality of life in cancer patients; this is an area for further study.

A limitation of this study is that we were unable to assess test-retest reliability, since respondents were asked to complete the questionnaires just one time as part of a cross-sectional study of quality of life in cancer survivors in an outpatient setting. In addition, it should be noted that we received only a 60% response rate. This may have produced some bias, for example, only patients who were feeling well enough to complete the questionnaire responded and thus less severe fatigue was reported. In addition, while the FSI was established as reliable with male and with older patients as well as with female and younger patients, and across a wide variety of cancer diagnoses, it would be beneficial to evaluate how well the FSI performs across multiple assessments. In the original validation report, the test-retest reliability in a group of breast cancer patients was found to be only weak to moderate, which highlights the need for further investigation into this area. Finally, the original validation study of the FSI included a healthy comparison group of women with no history of cancer. This was helpful in demonstrating that the FSI can be used to measure fatigue in cancer samples as well as healthy samples. It also supported the construct validity of the FSI by showing that the breast cancer patients reported significantly worse fatigue than did healthy women of similar age. In fact, the FSI has been used in a number of studies to compare fatigue in cancer

patients vs. their healthy peers. Results from these studies indicated that compared to healthy women of about the same age, breast cancer patients who received bone marrow transplantation reported significantly worse fatigue that interferes with their quality of life [20, 21]. In contrast, breast cancer patients who received radiotherapy reported a level of fatigue that was similar to that of their healthy peers [17]. We did not gather data from an age-matched group of healthy individuals for comparisons in this study.

Overall, however, in this report we were able to further establish the FSI as a reliable and valid tool which can be used to measure fatigue intensity, duration, and impact on quality of life in cancer patients. Also, it appears that the FSI can be used in studies of adult patients of either gender; thus, it would be a useful tool in studies of gender and age-related differences in fatigue. Also, since the measure was established as useful in a sample of patients with variety of diagnoses, the FSI could be used to compare the characteristics of fatigue across groups of patients with different diagnoses. The FSI was recently used to evaluate the physical and psychosocial correlates of fatigue [19] and could continue to be used in this manner. One goal of research into treatment side effects is to evaluate the effectiveness of interventions designed to alleviate those symptoms. If shown to be sensitive to change over time, the FSI could be used in mixed cancer samples in intervention studies to reduce fatigue.

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Address for correspondence: Danette Hann, C/o Behavioral Research Center, American Cancer Society, 1599 Clifton Road, NE, Atlanta, GA 30329, USA
Phone: (404) 329-7769; Fax: (404) 320-6262

24.9 Six-Minute Walk Test

The Six-Minute Walk Test

Paul L Enright MD

Introduction

Standards and Indications

6-Minute Walk Test Versus Shuttle Walk Test

Safety

Variables Measured

Conducting the Test

Ensuring Quality

Factors That Influence 6-Minute Walk Distance

Interpreting the Results

Improving the 6-Minute Walk Distance

Summary

The American Thoracic Society has issued guidelines for the 6-minute walk test (6MWT). The 6MWT is safer, easier to administer, better tolerated, and better reflects activities of daily living than other walk tests (such as the shuttle walk test). The primary measurement is 6-min walk distance (6MWD), but during the 6MWT data can also be collected about the patient's blood oxygen saturation and perception of dyspnea during exertion. When conducting the 6MWT do not walk with the patient and do not assist the patient in carrying or pulling his or her supplemental oxygen. The patient should walk alone, not with other patients. Do not use a treadmill on which the patient adjusts the speed and/or the slope. Do not use an oval or circular track. Use standardized phrases while speaking to the patient, because your encouragement and enthusiasm can make a difference of up to 30% in the 6MWD. Count the laps with a lap counter. If the 6MWD is low, thoroughly search for the cause(s) of the impairment. Better 6MWD reference equations will be published in the future, so be sure you are using the best available reference equations. *Key words: step test, exercise test, pulmonary rehabilitation.* [Respir Care 2003;48(8):783–785.

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Introduction

Walking tests have been around since the 1960s, when the 12-min walk was popularized by aerobics fitness enthusiast,

Paul L Enright MD is affiliated with the Respiratory Science Center, College of Medicine, University of Arizona, Tucson, Arizona.

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Paul L Enright MD, University of Arizona, AHSC 2342, PO Box 245030, 1501 N Campbell Avenue, Tucson AZ 85724-3030. E-mail: lungguy@aol.com.

Kenneth H Cooper, as a quick and easy fitness test. There's a full range of tests that you could perform to assess a patient's functional capacity. The easiest is just a questionnaire or self-report of how much work the patient can do. You might ask, "How many flights of stairs can you climb or how many blocks can you walk?" But patients differ in their ability to recall that kind of information and may overestimate or underestimate their true functional capacity, so objective measurements are usually better than self-reports. Another easy test of fitness is the number of stairs the patient can climb. Many surgeons have said that if the patient can walk up 2–3 flights of stairs, then he or she can survive surgery. The ease of performing a 6-minute walk test (6MWT) falls between stair climbing and testing for exercise-induced asthma.

Standards and Indications

Recently the American Thoracic Society Pulmonary Function Standards Committee developed guidelines for the 6MWT in clinical settings.¹ Carl Mottram, a respiratory therapist working at the Mayo Clinic in Rochester, Minnesota, helped to review the document. The 6MWT was chosen because it is easier to administer, better tolerated, and better reflects activities of daily living than other walk tests.²

Table 1 lists the indications for the 6MWT, the most important of which is to measure outcomes before and after treatment in people with moderate to severe heart and lung disease. The 6MWT can also be used to measure functional status and for epidemiologic purposes. A short 6-minute walk distance (6MWD) fairly accurately predicts morbidity and mortality from heart or lung disease.

Table 1. Indications for the 6-Minute Walk Test

Before-and-After Treatment Comparisons

- Lung transplantation or lung resection
- Lung volume reduction surgery
- Pulmonary rehabilitation
- Drug therapy for chronic obstructive pulmonary disease
- Pulmonary hypertension
- Heart failure

To Measure Functional Status

- Chronic obstructive pulmonary disease
- Cystic fibrosis
- Heart failure
- Peripheral vascular disease
- In elderly patients

To Predict Hospitalization and Death

- From heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension

6-Minute Walk Test Versus Shuttle Walk Test

How does the 6MWT compare to the shuttle walk test, which is frequently used in Great Britain? With the 6MWT the instructions to the patient are to “walk as far as you can during 6-minutes,” whereas the shuttle walk test pressures the patient to meet multiple deadlines, according to beeps from an audio cassette tape.³ The 6MWT is self-paced, and a patient is probably less likely to push himself beyond his endurance or through angina or other pain than during the shuttle walk test. The shuttle walk test is better correlated with peak oxygen uptake, as measured by a full cardiopulmonary exercise test, but not as many people are using the shuttle walk test.

Safety

What about safety? Absolute contraindications for the 6MWT include a history of unstable angina or a heart attack during the previous month. Relative contraindications include resting tachycardia (heart rate > 120 beats/min) or uncontrolled hypertension. Two large studies of thousands of elderly people who performed the 6MWT reported no untoward events.^{4,5} A physician need not be present during the test, but it is recommended that technicians administering the test be certified in cardiopulmonary resuscitation and that medications be available to treat angina, bronchospasm, and severe shortness of breath. Electrocardiographic and oxygen saturation monitoring are not necessary, and the patient should not be tethered with cables during the test.

Variables Measured

What variables can be measured in the 6MWT? The primary measurement is the total distance walked. Secondary measures can include fatigue and dyspnea, measured with a modified Borg or visual analog scale. Arterial oxygen saturation can also be measured via pulse oximetry, as long as the oximeter is portable and not heavy. However, I have used 3 different pulse oximeters in large epidemiologic studies during the past 10 years, and I found an unacceptably high failure rate, due to motion artifact. For the last 2 studies I chose fourth-generation pulse oximeters specifically designed to compensate for motion artifact. They are reliable for determining the oxygen saturation before and after the 6MWT test, but, in my opinion, you should be very cautious in interpreting oxygen saturation readings obtained *during* exercise.

Conducting the Test

When you schedule a walk test, ask the patient to wear comfortable footwear. During the test do not walk with the patient, because even if you walk behind them, it will alter their pace. If the patient is using supplemental oxygen during the walk, don't help push the oxygen tank or the 6MWD will not be the same as if the patient was pushing the tank, as he or she would do at home. In one study the investigators walked 6 people at the same time, which created competition among the study participants, resulting in a 30% larger mean 6MWD than tests in which the patients walked alone.⁴

Ensuring Quality

What should you do to obtain good quality results? Follow the recently published American Thoracic Society guidelines.¹ Do not use a treadmill or bike on which the

patient adjusts the speed and/or the slope. Do not walk with the patient. Do not use an oval or circular track. You must use standardized phrases for speaking to the patient, because the amount of encouragement and enthusiasm given can make a difference of up to 30% in the 6MWD. Count the laps with a lap counter.

Factors That Influence 6-Minute Walk Distance

Table 2 lists factors that influence 6MWD.⁵ Not surprisingly, short people and women have a shorter stride length and therefore have shorter 6MWDs. Older and heavier subjects usually have reduced muscle mass and, therefore, shorter 6MWDs, as do those who are less motivated or have impaired cognition. Arthritis and other musculoskeletal diseases also decrease the 6MWD.

Table 2. Factors That Affect 6-Minute Walk Distance

Factors Associated with Shorter 6-Minute Walk Distance

Shorter height (shorter legs)
Old age
Higher body weight
Female gender
Impaired cognition
Shorter walking corridor (more turns)
Chronic obstructive pulmonary disease, asthma, cystic fibrosis, interstitial lung disease
Angina, myocardial infarction, congestive heart failure, stroke, transient ischemic attack, peripheral vascular disease, ankle-arm index
Arthritis; ankle, knee, or hip injuries; muscle wasting

Factors Associated with Longer 6-Minute Walk Distance

Taller height (longer legs)
Male gender
High motivation
Patient has previously performed the test
Medication for a disabling disease taken just before the test
Oxygen supplementation

Interpreting the Results

Once you have measured 6MWD for a given patient, how do you interpret the result? Ideally, you would calculate the predicted distance using equations from a published study of healthy people of the same age group, much like for spirometry tests. Healthy subjects' 6MWDs range from 400 to 700 m. However, the few published studies have all used different methods, and the predicted distances differ by up to 30% between the studies.⁵⁻⁷ Look for better 6MWD reference equations to be published in the future. A low 6MWD is nonspecific and nondiagnostic (just like a low maximum voluntary ventilation). If the

6MWD is low, thoroughly search for the cause(s) of the impairment. The following tests may then be helpful: pulmonary function, cardiac function, ankle-arm index, muscle strength, nutritional status, orthopedic function, and cognitive function.

Improving the 6-Minute Walk Distance

How much will an intervention improve the 6MWD? One good study showed that an improvement of more than 70 m walked was clinically important to the patients.⁸ Mean improvements of 70–170 m (12–40% longer 6MWD) have been published for various interventions. Supplemental oxygen for chronic obstructive pulmonary disease and interstitial lung disease was shown to improve 6MWD, despite the extra weight of the ambulatory oxygen source. Lung volume reduction surgery has also been shown to improve 6MWD. In patients with chronic obstructive pulmonary disease, inhaled bronchodilators and rehabilitation programs can increase 6MWD.

Summary

The 6MWT is a useful measure of functional capacity, targeted at people with at least moderately severe impairment. It has been widely used for measuring the response to therapeutic interventions for pulmonary and cardiac disease. The new American Thoracic Society guidelines provide a standardized approach for performing the test.

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24.10 Dosing Algorithm

PTH Dosing Algorithm

Serum Calcium Level	Dose Titration
< 6.0 mg/dL < 1.5 mmol/L	<ul style="list-style-type: none"> Calcium 1000-1800 mg PO as a single dose. Refer to the Emergency Department for calcium infusion Increase PTH dose by 20-50% Check serum calcium within 2 – 3 days
6.1 to 6.9 mg/dL 1.52 to 1.73 mmol/L	<ul style="list-style-type: none"> Increase PTH dose 10 to 20% Calcium 1000mg to 1800 mg PO as a single dose Check serum calcium within 2 – 3 days
7.0 – 7.5 mg/dL 1.75 – 1.88 mmol/L	<ul style="list-style-type: none"> Increase PTH dose 5 to 20% and/or Calcium 500 – 1200 mg PO as a single dose Check serum calcium at least once within a week of dosing change
7.6 – 9.0 mg/dL 1.9 – 2.25 mmol/L	<ul style="list-style-type: none"> No change or 5% increase/decrease in PTH dose or increase/decrease in calcium supplements Check serum calcium at least once a month If change in dose was made, recheck calcium within one week
9.1 – 10.9 mg/dL 2.28 – 2.73 mmol/L	<ul style="list-style-type: none"> Decrease PTH dose 5 to 20% and/or decrease oral calcium supplements Check serum calcium once a week until calcium level is back to target range.
11.0 - 11.9 mg/dL 2.75 – 2.98 mmol/L	<ul style="list-style-type: none"> Temporarily suspend PTH dosing and calcium supplements Check serum calcium within 2 – 3 days Resume PTH dosing, decreased 20-40 % when serum calcium < 11.0 mg/dL, 2.75 mmol/L
> 12.0 mg/dL > 3 mmol/L	<ul style="list-style-type: none"> Temporarily suspend dosing and calcium supplements Refer to the Emergency Department for IV fluids Check serum calcium within 2 – 3 days Resume dosing, decreased 20-40 % when serum calcium < 11.0 mg/dL, 2.75 mmol/L

Prior to any change in PTH dose, subject compliance, symptoms, and general state of health must be assessed by a member of the protocol team.

If the current dose of PTH is < 5 mcg/dose, PTH will be adjusted at the investigator's discretion.

24.11 Discharge Instructions

Discharge Instructions for Patients on Protocol 07-D-0016

Name: _____

Date of Discharge: _____

Diet:

Please make sure to get at least 1000-2000 mg of calcium every day. If you are unable to get enough calcium through your diet, you may take supplements as directed below. Please do not drink a lot of cola as it contains lots of phosphorus which is not good in hypoparathyroidism. Limiting your salt intake may help to decrease the amount of calcium in your urine and is recommended in general for good health.

Medication doses and instructions:

HPTH (100 mcg/mL): Inject _____ mL twice a day (this is ____ on an insulin syringe)

Calcium supplements: _____

Magnesium supplements: _____

Other: _____

Outside Laboratory Tests:

1. Please use the slip that we have given you to obtain laboratory tests near your home.
 2. **You must do blood tests at least once a month and urine tests every three months.**
- Please make sure that your lab has faxed the results to 301-435-7598.

Your next blood test is due the week of: _____

Your next 24-hour urine collection is due the week of: _____

Illnesses or other issues:

Please contact Dr. Rachel Gafni (301-594-9924) or Nurse Lori Guthrie (301-594-0844) as soon as possible if you are sick, injured, or start taking any new medications. Please have someone contact us immediately if you need to go to the emergency room or are hospitalized. For evening and weekend emergencies, please call the NIH page operator at 301-496-1211 and ask to page Dr. Gafni.

I understand that if I am unable to follow the instructions above, I may be taken off of HPTH and withdrawn from this protocol.

Subject and date

Investigator and date

Witness and date

24.12 Bone Labeling Instructions

Bone “Labeling” Instruction Sheet for Biopsy - Tetracycline

Certain antibiotics are taken-up by bone. When a specimen of bone that has incorporated these antibiotics is subjected to light of a particular wave length, it is fluorescent. When these antibiotics are given in a specific sequence with a length of time between doses, the bone is “labeled” in such a way that an enormous amount of information can be gained about the bone’s biology. During this study there will be two biopsies. Different antibiotics and combinations of antibiotics will be used for different biopsies

For this biopsy, we will use the antibiotic tetracycline according to the following schedule: 3 days of tetracycline (250 mg 4 times per day), 12 days off drug, 3 days of tetracycline (250 mg 4 times per day), four days off drug and biopsy on the fifth day.

Your schedule is indicated below. You should not take these antibiotics if you have an allergy to tetracycline-type antibiotics, are under 6 years of age or pregnant. In addition, you should avoid extensive direct sun light while you are actively taking these antibiotics.

Patient: _____

Day #	Date	Drug
1		tetracycline 250 mg 4 times/day
2		tetracycline 250 mg 4 times/day
3		tetracycline 250 mg 4 times/day
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		tetracycline 250 mg 4 times/day
17		tetracycline 250 mg 4 times/day
18		tetracycline 250 mg 4 times/day
19		
20		
21		
22		
23 Biopsy		Biopsy

Bone “Labeling” Instruction Sheet Biopsy - Demeclocycline

Certain antibiotics are taken-up by bone. When a specimen of bone that has incorporated these antibiotics is subjected to light of a particular wave length, it is fluorescent. When these antibiotics are given in a specific sequence with a length of time between doses, the bone is “labeled” in such a way that an enormous amount of information can be gained about the bone’s biology. During this study there will be two biopsies. Different antibiotics and combinations of antibiotics will be used for different biopsies

For this biopsy, we will use the antibiotic demeclocycline according to the following schedule: 3 days of demeclocycline (150 mg 4 times per day), 12 days off drug, 3 days of demeclocycline (150 mg 4 times per day), four days off drug and biopsy on the fifth day.

Your schedule is indicated below. You should not take these antibiotics if you have an allergy to tetracycline-type antibiotics, are under 6 years of age or pregnant. In addition, you should avoid extensive direct sun light while you are actively taking these antibiotics.

Patient: _____

Day #	Date	Drug
1		demeclocycline 150 mg 4 times/day
2		demeclocycline 150 mg 4 times/day
3		demeclocycline 150 mg 4 times/day
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		demeclocycline 150 mg 4 times/day
17		demeclocycline 150 mg 4 times/day
18		demeclocycline 150 mg 4 times/day
19		
20		
21		
22		
23 Biopsy		Biopsy

24.13 Forteo Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FORTEO safely and effectively. See full prescribing information for FORTEO.

FORTEO (teriparatide [rDNA origin] injection) for subcutaneous use
Initial U.S. Approval: 2002

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

See full prescribing information for complete boxed warning.

- In rats, teriparatide caused an increase in the incidence of osteosarcoma, a malignant bone tumor. (5.1, 13.1)
- Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO only for patients for whom potential benefits outweigh potential risk. (5.1)
- FORTEO should not be prescribed for patients at increased baseline risk for osteosarcoma (e.g., those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton). (5.1)

RECENT MAJOR CHANGES

None.

INDICATIONS AND USAGE

FORTEO is recombinant human parathyroid hormone analog (1-34), [rhPTH(1-34)] indicated for:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture (1.1)
- Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture (1.2)
- Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture (1.3)

DOSAGE AND ADMINISTRATION

- Recommended dose is 20 mcg subcutaneously once a day (2.1, 2.2, 2.3)
- Administer as a subcutaneous injection into the thigh or abdominal wall (2.4)
- Administer initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur (2.4)
- Use of the drug for more than 2 years during a patient's lifetime is not recommended (2.5)

DOSAGE FORMS AND STRENGTHS

Multi-dose prefilled delivery device (pen) containing 28 daily doses of 20 mcg (3)

CONTRAINDICATIONS

- Patients with hypersensitivity to teriparatide or to any of its excipients (4)

WARNINGS AND PRECAUTIONS

- Patients with Paget's disease of bone, pediatric and young adult patients with open epiphyses, and patients with prior external beam or implant radiation involving the skeleton: Should not be treated with FORTEO (5.1, 8.4)
- Treatment duration: Use of FORTEO for more than 2 years during a patient's lifetime is not recommended. (5.2)
- Patients with bone metastases, history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or hypercalcemic disorders: Should not be treated with FORTEO (5.3, 5.4, 5.5)
- Laboratory alterations: FORTEO may increase serum calcium, urinary calcium, and serum uric acid (5.5, 5.6)
- Urolithiasis: Use with caution in patients with active or recent urolithiasis because of risk of exacerbation (5.6)
- Orthostatic hypotension: Transient orthostatic hypotension may occur with initial doses of FORTEO (5.7)

ADVERSE REACTIONS

Most common adverse reactions (>10%) include: arthralgia, pain, and nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-545-5979 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Digoxin: Use FORTEO with caution in patients receiving digoxin. Transient hypercalcemia may predispose patients to digitalis toxicity (5.8, 7.1, 12.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal studies, may cause fetal harm (8.1)
- Nursing Mothers: Discontinue nursing or FORTEO, taking into account the importance of treatment to the mother (8.3)
- Pediatric Use: FORTEO should not be used in pediatric and young adult patients with open epiphyses due to increased baseline risk of osteosarcoma (5.1, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 03/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

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- 1.1 Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture
- 1.2 Increase of Bone Mass in Men with Primary or Hypogonadal Osteoporosis at High Risk for Fracture
- 1.3 Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis at High Risk for Fracture

2 DOSAGE AND ADMINISTRATION

- 2.1 Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture
- 2.2 Increase of Bone Mass in Men with Primary or Hypogonadal Osteoporosis at High Risk for Fracture
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- 2.4 Administration
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FULL PRESCRIBING INFORMATION

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO® only for patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton) [see *Warnings and Precautions (5.1), Adverse Reactions (6.2), and Nonclinical Toxicology (13.1)*].

1 INDICATIONS AND USAGE

1.1 Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture

FORTEO is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, FORTEO reduces the risk of vertebral and nonvertebral fractures [see *Clinical Studies (14.1)*].

1.2 Increase of Bone Mass in Men with Primary or Hypogonadal Osteoporosis at High Risk for Fracture

FORTEO is indicated to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy [see *Clinical Studies (14.2)*].

1.3 Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis at High Risk for Fracture

FORTEO is indicated for the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy [see *Clinical Studies (14.3)*].

2 DOSAGE AND ADMINISTRATION

2.1 Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture

The recommended dose is 20 mcg subcutaneously once a day.

2.2 Increase of Bone Mass in Men with Primary or Hypogonadal Osteoporosis at High Risk for Fracture

The recommended dose is 20 mcg subcutaneously once a day.

2.3 Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis at High Risk for Fracture

The recommended dose is 20 mcg subcutaneously once a day.

2.4 Administration

- FORTEO should be administered as a subcutaneous injection into the thigh or abdominal wall. There are no data available on the safety or efficacy of intravenous or intramuscular injection of FORTEO.
- FORTEO should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur [see *Warnings and Precautions (5.7)*].

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. FORTEO is a clear and colorless liquid. Do not use if solid particles appear or if the solution is cloudy or colored.
- Patients and caregivers who administer FORTEO should receive appropriate training and instruction on the proper use of the FORTEO delivery device from a qualified health professional [*see Patient Counseling Information (17.5)*].

2.5 Treatment Duration

The safety and efficacy of FORTEO have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years during a patient's lifetime is not recommended.

3 DOSAGE FORMS AND STRENGTHS

Multi-dose prefilled delivery device (pen) for subcutaneous injection containing 28 daily doses of 20 mcg.

4 CONTRAINDICATIONS

Do not use FORTEO in patients with:

- Hypersensitivity to teriparatide or to any of its excipients. Reactions have included angioedema and anaphylaxis [*see Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Osteosarcoma

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration [*see Boxed Warning and Nonclinical Toxicology (13.1)*]. FORTEO should not be prescribed for patients at increased baseline risk of osteosarcoma.

These include:

- Paget's disease of bone. Unexplained elevations of alkaline phosphatase may indicate Paget's disease of bone.
- Pediatric and young adult patients with open epiphyses.
- Prior external beam or implant radiation therapy involving the skeleton.

Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Enrollment information can be obtained by calling 1-866-382-6813, or by visiting www.forteoregistry.rti.org

5.2 Treatment Duration

The safety and efficacy of FORTEO have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years during a patients' lifetime is not recommended.

5.3 Bone Metastases and Skeletal Malignancies

Patients with bone metastases or a history of skeletal malignancies should not be treated with FORTEO.

5.4 Metabolic Bone Diseases

Patients with metabolic bone diseases other than osteoporosis should not be treated with FORTEO.

5.5 Hypercalcemia and Hypercalcemic Disorders

FORTEO has not been studied in patients with pre-existing hypercalcemia. These patients should not be treated with FORTEO because of the possibility of exacerbating hypercalcemia. Patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, should not be treated with FORTEO.

5.6 Urolithiasis or Pre-existing Hypercalciuria

In clinical trials, the frequency of urolithiasis was similar in patients treated with FORTEO and placebo. However, FORTEO has not been studied in patients with active urolithiasis. If active urolithiasis or pre-existing hypercalciuria are suspected, measurement of urinary calcium excretion should be considered. FORTEO should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

5.7 Orthostatic Hypotension

FORTEO should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur. In short-term clinical pharmacology studies with teriparatide, transient episodes of symptomatic orthostatic hypotension were observed in 5% of patients. Typically, an event began within 4 hours of dosing and spontaneously resolved within a few minutes to a few hours. When transient orthostatic hypotension occurred, it happened within the first several doses, it was relieved by placing the person in a reclining position, and it did not preclude continued treatment.

5.8 Drug Interactions

Hypercalcemia may predispose patients to digitalis toxicity. Because FORTEO transiently increases serum calcium, patients receiving digoxin should use FORTEO with caution [*see Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Treatment of Osteoporosis in Men and Postmenopausal Women

The safety of FORTEO in the treatment of osteoporosis in men and postmenopausal women was assessed in two randomized, double-blind, placebo-controlled trials of 1382 patients (21% men, 79% women) aged 28 to 86 years (mean 67 years). The median durations of the trials were 11 months for men and 19 months for women, with 691 patients exposed to FORTEO and 691 patients to placebo. All patients received 1000 mg of calcium plus at least 400 IU of vitamin D supplementation per day.

The incidence of all cause mortality was 1% in the FORTEO group and 1% in the placebo group. The incidence of serious adverse events was 16% in FORTEO patients and 19% in placebo patients. Early discontinuation due to adverse events occurred in 7% of FORTEO patients and 6% of placebo patients.

Table 1 lists adverse events from the two principal osteoporosis trials in men and postmenopausal women that occurred in $\geq 2\%$ of FORTEO-treated and more frequently than placebo-treated patients.

Table 1. Percentage of Patients with Adverse Events Reported by at Least 2% of FORTEO-Treated Patients and in More FORTEO-Treated Patients than Placebo-Treated Patients from the Two Principal Osteoporosis Trials in Women and Men
Adverse Events are Shown Without Attribution of Causality

	FORTEO N=691	Placebo N=691
Event Classification	(%)	(%)
Body as a Whole		
Pain	21.3	20.5
Headache	7.5	7.4
Asthenia	8.7	6.8
Neck pain	3.0	2.7
Cardiovascular		
Hypertension	7.1	6.8
Angina pectoris	2.5	1.6
Syncope	2.6	1.4
Digestive System		
Nausea	8.5	6.7
Constipation	5.4	4.5
Diarrhea	5.1	4.6
Dyspepsia	5.2	4.1
Vomiting	3.0	2.3
Gastrointestinal disorder	2.3	2.0
Tooth disorder	2.0	1.3
Musculoskeletal		
Arthralgia	10.1	8.4
Leg cramps	2.6	1.3
Nervous System		
Dizziness	8.0	5.4
Depression	4.1	2.7
Insomnia	4.3	3.6
Vertigo	3.8	2.7
Respiratory System		
Rhinitis	9.6	8.8
Cough increased	6.4	5.5
Pharyngitis	5.5	4.8
Dyspnea	3.6	2.6
Pneumonia	3.9	3.3
Skin and Appendages		

Rash	4.9	4.5
Sweating	2.2	1.7

Immunogenicity — In the clinical trial, antibodies that cross-reacted with teriparatide were detected in 3% of women (15/541) receiving FORTEO. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions or allergic reactions among these patients. Antibody formation did not appear to have effects on serum calcium, or on bone mineral density (BMD) response.

Laboratory Findings

Serum Calcium — FORTEO transiently increased serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. Serum calcium measured at least 16 hours post-dose was not different from pretreatment levels. In clinical trials, the frequency of at least 1 episode of transient hypercalcemia in the 4 to 6 hours after FORTEO administration was increased from 2% of women and none of the men treated with placebo to 11% of women and 6% of men treated with FORTEO. The number of patients treated with FORTEO whose transient hypercalcemia was verified on consecutive measurements was 3% of women and 1% of men.

Urinary Calcium — FORTEO increased urinary calcium excretion, but the frequency of hypercalciuria in clinical trials was similar for patients treated with FORTEO and placebo [see *Clinical Pharmacology* (12.2)].

Serum Uric Acid — FORTEO increased serum uric acid concentrations. In clinical trials, 3% of FORTEO patients had serum uric acid concentrations above the upper limit of normal compared with 1% of placebo patients. However, the hyperuricemia did not result in an increase in gout, arthralgia, or urolithiasis.

Renal Function — No clinically important adverse renal effects were observed in clinical studies. Assessments included creatinine clearance; measurements of blood urea nitrogen (BUN), creatinine, and electrolytes in serum; urine specific gravity and pH; and examination of urine sediment.

Studies in Men and Women with Glucocorticoid-Induced Osteoporosis

The safety of FORTEO in the treatment of men and women with glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥ 5 mg per day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months with 214 patients exposed to FORTEO and 214 patients exposed to oral daily bisphosphonate (active control). All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day.

The incidence of all cause mortality was 4% in the FORTEO group and 6% in the active control group. The incidence of serious adverse events was 21% in FORTEO patients and 18% in active control patients, and included pneumonia (3% FORTEO, 1% active control). Early discontinuation because of adverse events occurred in 15% of FORTEO patients and 12% of active control patients, and included dizziness (2% FORTEO, 0% active control).

Adverse events reported at a higher incidence in the FORTEO group and with at least a 2% difference in FORTEO-treated patients compared with active control-treated patients were: nausea (14%, 7%), gastritis (7%, 3%), pneumonia (6%, 3%), dyspnea (6%, 3%), insomnia (5%, 1%), anxiety (4%, 1%), and herpes zoster (3%, 1%), respectively.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of FORTEO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Osteosarcoma: Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period. The causality to FORTEO use is unclear. Long term osteosarcoma surveillance studies are ongoing [see *Warnings and Precautions* (5.1)]
- Hypercalcemia: Hypercalcemia greater than 13.0 mg/dL has been reported with FORTEO use.

Adverse events reported since market introduction that were temporally (but not necessarily causally) related to FORTEO therapy include the following:

- Allergic Reactions: Anaphylactic reactions, drug hypersensitivity, angioedema, urticaria
- Investigations: Hyperuricemia
- Respiratory System: Acute dyspnea, chest pain
- Musculoskeletal: Muscle spasms of the leg or back
- Other: Injection site reactions including injection site pain, swelling and bruising; oro-facial edema

7 DRUG INTERACTIONS

7.1 Digoxin

A single FORTEO dose did not alter the effect of digoxin on the systolic time interval (from electrocardiographic Q-wave onset to aortic valve closure, a measure of digoxin's calcium-mediated cardiac effect). However, because FORTEO may transiently

increase serum calcium, FORTEO should be used with caution in patients taking digoxin [see *Warnings and Precaution (5.8) and Clinical Pharmacology (12.3)*].

7.2 Hydrochlorothiazide

The coadministration of hydrochlorothiazide 25 mg with teriparatide did not affect the serum calcium response to teriparatide 40 mcg. The effect of coadministration of a higher dose of hydrochlorothiazide with teriparatide on serum calcium levels has not been studied [see *Clinical Pharmacology (12.3)*].

7.3 Furosemide

Coadministration of intravenous furosemide (20 to 100 mg) with teriparatide 40 mcg in healthy people and patients with mild, moderate, or severe renal impairment (CrCl 13 to 72 mL/min) resulted in small increases in the serum calcium (2%) and 24-hour urine calcium (37%) responses to teriparatide that did not appear to be clinically important [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C — There are no adequate and well-controlled studies of FORTEO in pregnant women. In animal studies, teriparatide increased skeletal deviations and variations in mouse offspring at doses more than 60 times the equivalent human dose and produced mild growth retardation and reduced motor activity in rat offspring at doses more than 120 times the equivalent human dose. FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In animal studies, pregnant mice received teriparatide during organogenesis at subcutaneous doses 8 to 267 times the human dose. At doses ≥ 60 times the human dose, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib). When pregnant rats received subcutaneous teriparatide during organogenesis at doses 16 to 540 times the human dose, the fetuses showed no abnormal findings.

In a perinatal/postnatal study, pregnant rats received subcutaneous teriparatide from organogenesis through lactation. Mild growth retardation in female offspring at doses ≥ 120 times the human dose (based on surface area, mcg/m²). Mild growth retardation in male offspring and reduced motor activity in both male and female offspring occurred at maternal doses 540 times the human dose. There were no developmental or reproductive effects in mice or rats at doses 8 or 16 times the human dose, respectively.

Exposure multiples were normalized based on body surface area (mcg/m²). Actual animal doses: mice (30 to 1000 mcg/kg/day); rats (30 to 1000 mcg/kg/day).

8.3 Nursing Mothers

It is not known whether teriparatide is excreted in human milk. Because of the potential for tumorigenicity shown for teriparatide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of FORTEO have not been established in any pediatric population. FORTEO should not be prescribed in patients at an increased baseline risk of osteosarcoma which include pediatric and young adult patients with open epiphyses. Therefore, FORTEO is not indicated for use in pediatric or young adult patients with open epiphyses [see *Warnings and Precautions (5.1)*].

8.5 Geriatric Use

Of the patients receiving FORTEO in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and over and 23% were 75 years of age and over. Of the patients receiving FORTEO in the osteoporosis trial of 437 men, 39% were 65 years of age and over and 13% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

No studies have been performed in patients with hepatic impairment. [see *Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

In 5 patients with severe renal impairment (CrCl < 30 mL/min), the AUC and T_{1/2} of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Incidents of overdose in humans have not been reported in clinical trials. Teriparatide has been administered in single doses of up to 100 mcg and in repeated doses of up to 60 mcg/day for 6 weeks. The effects of overdose that might be expected include a delayed hypercalcemic effect and risk of orthostatic hypotension. Nausea, vomiting, dizziness, and headache might also occur.

In postmarketing spontaneous reports, there have been cases of medication errors in which the entire contents (up to 800 mcg) of the FORTEO delivery device (pen) have been administered as a single dose. Transient events reported have included nausea,

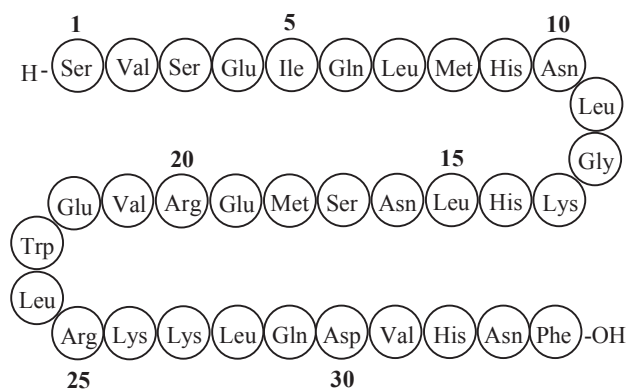
weakness/lethargy and hypotension. In some cases, no adverse events occurred as a result of the overdose. No fatalities associated with overdose have been reported.

Overdose Management — There is no specific antidote for teriparatide. Treatment of suspected overdose should include discontinuation of FORTEO, monitoring of serum calcium and phosphorus, and implementation of appropriate supportive measures, such as hydration.

11 DESCRIPTION

FORTEO (teriparatide [rDNA origin] injection) contains recombinant human parathyroid hormone (1-34), and is also called rhPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

Teriparatide has a molecular weight of 4117.8 daltons and its amino acid sequence is shown below:



Teriparatide (rDNA origin) is manufactured using a strain of *Escherichia coli* modified by recombinant DNA technology. FORTEO is supplied as a sterile, colorless, clear, isotonic solution in a glass cartridge which is pre-assembled into a disposable delivery device (pen) for subcutaneous injection. Each prefilled delivery device is filled with 2.7 mL to deliver 2.4 mL. Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4.

Each cartridge, pre-assembled into a delivery device, delivers 20 mcg of teriparatide per dose each day for up to 28 days.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous 84-amino acid parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. Physiological actions of PTH include regulation of bone metabolism, renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. The biological actions of PTH and teriparatide are mediated through binding to specific high-affinity cell-surface receptors. Teriparatide and the 34 N-terminal amino acids of PTH bind to these receptors with the same affinity and have the same physiological actions on bone and kidney. Teriparatide is not expected to accumulate in bone or other tissues.

The skeletal effects of teriparatide depend upon the pattern of systemic exposure. Once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. In monkey studies, teriparatide improved trabecular microarchitecture and increased bone mass and strength by stimulating new bone formation in both cancellous and cortical bone. In humans, the anabolic effects of teriparatide manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength. By contrast, continuous excess of endogenous PTH, as occurs in hyperparathyroidism, may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation.

12.2 Pharmacodynamics

Pharmacodynamics in Men and Postmenopausal Women with Osteoporosis

Effects on Mineral Metabolism — Teriparatide affects calcium and phosphorus metabolism in a pattern consistent with the known actions of endogenous PTH (e.g., increases serum calcium and decreases serum phosphorus).

Serum Calcium Concentrations — When teriparatide 20 mcg is administered once daily, the serum calcium concentration increases transiently, beginning approximately 2 hours after dosing and reaching a maximum concentration between 4 and 6 hours (median increase, 0.4 mg/dL). The serum calcium concentration begins to decline approximately 6 hours after dosing and returns to baseline by 16 to 24 hours after each dose.

In a clinical study of postmenopausal women with osteoporosis, the median peak serum calcium concentration measured 4 to 6 hours after dosing with FORTEO (teriparatide 20 mcg) was 2.42 mmol/L (9.68 mg/dL) at 12 months. The peak serum calcium remained below 2.76 mmol/L (11.0 mg/dL) in >99% of women at each visit. Sustained hypercalcemia was not observed.

In this study, 11.1% of women treated with FORTEO had at least 1 serum calcium value above the upper limit of normal [2.64 mmol/L (10.6 mg/dL)] compared with 1.5% of women treated with placebo. The percentage of women treated with FORTEO whose serum calcium was above the upper limit of normal on consecutive 4- to 6-hour post-dose measurements was 3.0% compared with 0.2% of women treated with placebo. In these women, calcium supplements and/or FORTEO doses were reduced. The timing of these dose reductions was at the discretion of the investigator. FORTEO dose adjustments were made at varying intervals after the first observation of increased serum calcium (median 21 weeks). During these intervals, there was no evidence of progressive increases in serum calcium.

In a clinical study of men with either primary or hypogonadal osteoporosis, the effects on serum calcium were similar to those observed in postmenopausal women. The median peak serum calcium concentration measured 4 to 6 hours after dosing with FORTEO was 2.35 mmol/L (9.44 mg/dL) at 12 months. The peak serum calcium remained below 2.76 mmol/L (11.0 mg/dL) in 98% of men at each visit. Sustained hypercalcemia was not observed.

In this study, 6.0% of men treated with FORTEO daily had at least 1 serum calcium value above the upper limit of normal [2.64 mmol/L (10.6 mg/dL)] compared with none of the men treated with placebo. The percentage of men treated with FORTEO whose serum calcium was above the upper limit of normal on consecutive measurements was 1.3% (2 men) compared with none of the men treated with placebo. Although calcium supplements and/or FORTEO doses could have been reduced in these men, only calcium supplementation was reduced [see *Warnings and Precautions* (5.5) and *Adverse Reactions* (6.1)].

In a clinical study of women previously treated for 18 to 39 months with raloxifene (n=26) or alendronate (n=33), mean serum calcium >12 hours after FORTEO injection was increased by 0.09 to 0.14 mmol/L (0.36 to 0.56 mg/dL), after 1 to 6 months of FORTEO treatment compared with baseline. Of the women pretreated with raloxifene, 3 (11.5%) had a serum calcium >2.76 mmol/L (11.0 mg/dL), and of those pretreated with alendronate, 3 (9.1%) had a serum calcium >2.76 mmol/L (11.0 mg/dL). The highest serum calcium reported was 3.12 mmol/L (12.5 mg/dL). None of the women had symptoms of hypercalcemia. There were no placebo controls in this study.

In the study of patients with glucocorticoid-induced osteoporosis, the effects of FORTEO on serum calcium were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

Urinary Calcium Excretion — In a clinical study of postmenopausal women with osteoporosis who received 1000 mg of supplemental calcium and at least 400 IU of vitamin D, daily FORTEO increased urinary calcium excretion. The median urinary excretion of calcium was 4.8 mmol/day (190 mg/day) at 6 months and 4.2 mmol/day (170 mg/day) at 12 months. These levels were 0.76 mmol/day (30 mg/day) and 0.3 mmol/day (12 mg/day) higher, respectively, than in women treated with placebo. The incidence of hypercalciuria (>7.5 mmol Ca/day or 300 mg/day) was similar in the women treated with FORTEO or placebo.

In a clinical study of men with either primary or hypogonadal osteoporosis who received 1000 mg of supplemental calcium and at least 400 IU of vitamin D, daily FORTEO had inconsistent effects on urinary calcium excretion. The median urinary excretion of calcium was 5.6 mmol/day (220 mg/day) at 1 month and 5.3 mmol/day (210 mg/day) at 6 months. These levels were 0.5 mmol/day (20 mg/day) higher and 0.2 mmol/day (8.0 mg/day) lower, respectively, than in men treated with placebo. The incidence of hypercalciuria (>7.5 mmol Ca/day or 300 mg/day) was similar in the men treated with FORTEO or placebo.

Phosphorus and Vitamin D — In single-dose studies, teriparatide produced transient phosphaturia and mild transient reductions in serum phosphorus concentration. However, hypophosphatemia (<0.74 mmol/L or 2.4 mg/dL) was not observed in clinical trials with FORTEO.

In clinical trials of daily FORTEO, the median serum concentration of 1,25-dihydroxyvitamin D was increased at 12 months by 19% in women and 14% in men, compared with baseline. In the placebo group, this concentration decreased by 2% in women and increased by 5% in men. The median serum 25-hydroxyvitamin D concentration at 12 months was decreased by 19% in women and 10% in men compared with baseline. In the placebo group, this concentration was unchanged in women and increased by 1% in men.

In the study of patients with glucocorticoid-induced osteoporosis, the effects of FORTEO on serum phosphorus were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

Effects on Markers of Bone Turnover — Daily administration of FORTEO to men and postmenopausal women with osteoporosis in clinical studies stimulated bone formation, as shown by increases in the formation markers serum bone-specific alkaline phosphatase (BSAP) and procollagen I carboxy-terminal propeptide (PICP). Data on biochemical markers of bone turnover were available for the first 12 months of treatment. Peak concentrations of PICP at 1 month of treatment were approximately 41% above baseline, followed by a decline to near-baseline values by 12 months. BSAP concentrations increased by 1 month of treatment and continued to rise more slowly from 6 through 12 months. The maximum increases of BSAP were 45% above baseline in women and 23% in men. After discontinuation of therapy, BSAP concentrations returned toward baseline. The increases in formation markers were accompanied by secondary increases in the markers of bone resorption: urinary N-telopeptide (NTX) and urinary deoxypyridinoline (DPD), consistent with the physiological coupling of bone formation and resorption in skeletal remodeling.

Changes in BSAP, NTX, and DPD were lower in men than in women, possibly because of lower systemic exposure to teriparatide in men.

In the study of patients with glucocorticoid-induced osteoporosis, the effects of FORTEO on serum markers of bone turnover were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

12.3 Pharmacokinetics

Absorption — Teriparatide is absorbed after subcutaneous injection; the absolute bioavailability is approximately 95% based on pooled data from 20-, 40-, and 80- mcg doses. The rates of absorption and elimination are rapid. The peptide reaches peak serum concentrations about 30 minutes after subcutaneous injection of a 20-mcg dose and declines to non-quantifiable concentrations within 3 hours.

Distribution — Systemic clearance of teriparatide (approximately 62 L/hr in women and 94 L/hr in men) exceeds the rate of normal liver plasma flow, consistent with both hepatic and extra-hepatic clearance. Volume of distribution, following intravenous injection, is approximately 0.12 L/kg. Intersubject variability in systemic clearance and volume of distribution is 25% to 50%. The half-life of teriparatide in serum is 5 minutes when administered by intravenous injection and approximately 1 hour when administered by subcutaneous injection. The longer half-life following subcutaneous administration reflects the time required for absorption from the injection site.

Metabolism and Excretion — No metabolism or excretion studies have been performed with teriparatide. However, the mechanisms of metabolism and elimination of PTH(1-34) and intact PTH have been extensively described in published literature. Peripheral metabolism of PTH is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys.

Pediatric Patients — Pharmacokinetic data in pediatric patients are not available [*see Warnings and Precautions (5.1)*].

Geriatric Patients — No age-related differences in teriparatide pharmacokinetics were detected (range 31 to 85 years).

Gender — Although systemic exposure to teriparatide was approximately 20% to 30% lower in men than women, the recommended dose for both genders is 20 mcg/day.

Race — The populations included in the pharmacokinetic analyses were 98.5% Caucasian. The influence of race has not been determined.

Renal Impairment — No pharmacokinetic differences were identified in 11 patients with mild or moderate renal impairment [creatinine clearance (CrCl) 30 to 72 mL/min] administered a single dose of teriparatide. In 5 patients with severe renal impairment (CrCl < 30 mL/min), the AUC and $T_{1/2}$ of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased. No studies have been performed in patients undergoing dialysis for chronic renal failure [*see Use in Specific Populations (8.7)*].

Hepatic Impairment — No studies have been performed in patients with hepatic impairment. Non-specific proteolytic enzymes in the liver (possibly Kupffer cells) cleave PTH(1-34) and PTH(1-84) into fragments that are cleared from the circulation mainly by the kidney [*see Use in Specific Populations (8.6)*].

Drug Interactions

Digoxin — In a study of 15 healthy people administered digoxin daily to steady state, a single FORTEO dose did not alter the effect of digoxin on the systolic time interval (from electrocardiographic Q-wave onset to aortic valve closure, a measure of digoxin's calcium-mediated cardiac effect). However, sporadic case reports have suggested that hypercalcemia may predispose patients to digitalis toxicity. Because FORTEO may transiently increase serum calcium, FORTEO should be used with caution in patients taking digoxin [*see Drug Interactions (7.1)*].

Hydrochlorothiazide — In a study of 20 healthy people, the coadministration of hydrochlorothiazide 25 mg with teriparatide did not affect the serum calcium response to teriparatide 40 mcg. The 24-hour urine excretion of calcium was reduced by a clinically unimportant amount (15%). The effect of coadministration of a higher dose of hydrochlorothiazide with teriparatide on serum calcium levels has not been studied [*see Drug Interactions (7.2)*].

Furosemide — In a study of 9 healthy people and 17 patients with mild, moderate, or severe renal impairment (CrCl 13 to 72 mL/min), coadministration of intravenous furosemide (20 to 100 mg) with teriparatide 40 mcg resulted in small increases in the serum calcium (2%) and 24-hour urine calcium (37%) responses to teriparatide that did not appear to be clinically important [*see Drug Interactions (7.3)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Two carcinogenicity bioassays were conducted in Fischer 344 rats. In the first study, male and female rats were given daily subcutaneous teriparatide injections of 5, 30, or 75 mcg/kg/day for 24 months from 2 months of age. These doses resulted in systemic exposures that were, respectively, 3, 20, and 60 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 mcg (based on AUC comparison). Teriparatide treatment resulted in a marked dose-related increase in the incidence of osteosarcoma, a rare malignant bone tumor, in both male and female rats. Osteosarcomas were observed at all doses and the incidence reached 40% to 50% in the high-dose groups. Teriparatide also caused a dose-related increase in

osteoblastoma and osteoma in both sexes. No osteosarcomas, osteoblastomas or osteomas were observed in untreated control rats. The bone tumors in rats occurred in association with a large increase in bone mass and focal osteoblast hyperplasia.

The second 2-year study was carried out in order to determine the effect of treatment duration and animal age on the development of bone tumors. Female rats were treated for different periods between 2 and 26 months of age with subcutaneous doses of 5 and 30 mcg/kg (equivalent to 3 and 20 times the human exposure at the 20-mcg dose, based on AUC comparison). The study showed that the occurrence of osteosarcoma, osteoblastoma and osteoma was dependent upon dose and duration of exposure. Bone tumors were observed when immature 2-month old rats were treated with 30 mcg/kg/day for 24 months or with 5 or 30 mcg/kg/day for 6 months. Bone tumors were also observed when mature 6-month old rats were treated with 30 mcg/kg/day for 6 or 20 months. Tumors were not detected when mature 6-month old rats were treated with 5 mcg/kg/day for 6 or 20 months. The results did not demonstrate a difference in susceptibility to bone tumor formation, associated with teriparatide treatment, between mature and immature rats.

The relevance of these animal findings to humans is uncertain.

Mutagenesis — Teriparatide was not genotoxic in any of the following test systems: the Ames test for bacterial mutagenesis; the mouse lymphoma assay for mammalian cell mutation; the chromosomal aberration assay in Chinese hamster ovary cells, with and without metabolic activation; and the in vivo micronucleus test in mice.

Impairment of Fertility — No effects on fertility were observed in male and female rats given subcutaneous teriparatide doses of 30, 100, or 300 mcg/kg/day prior to mating and in females continuing through gestation Day 6 (16 to 160 times the human dose of 20 mcg based on surface area, mcg/m²).

13.2 Animal Toxicology

In single-dose rodent studies using subcutaneous injection of teriparatide, no mortality was seen in rats given doses of 1000 mcg/kg (540 times the human dose based on surface area, mcg/m²) or in mice given 10,000 mcg/kg (2700 times the human dose based on surface area, mcg/m²).

In a long-term study, skeletally mature ovariectomized female monkeys (N=30 per treatment group) were given either daily subcutaneous teriparatide injections of 5 mcg/kg or vehicle. Following the 18-month treatment period, the monkeys were removed from teriparatide treatment and were observed for an additional 3 years. The 5 mcg/kg dose resulted in systemic exposures that were approximately 6 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 mcg (based on AUC comparison). Bone tumors were not detected by radiographic or histologic evaluation in any monkey in the study.

14 CLINICAL STUDIES

14.1 Treatment of Osteoporosis in Postmenopausal Women

The safety and efficacy of once-daily FORTEO, median exposure of 19 months, were examined in a double-blind, multicenter, placebo-controlled clinical study of 1637 postmenopausal women with osteoporosis (FORTEO 20 mcg, n=541).

All women received 1000 mg of calcium and at least 400 IU of vitamin D per day. Baseline and endpoint spinal radiographs were evaluated using the semiquantitative scoring. Ninety percent of the women in the study had 1 or more radiographically diagnosed vertebral fractures at baseline. The primary efficacy endpoint was the occurrence of new radiographically diagnosed vertebral fractures defined as changes in the height of previously undeformed vertebrae. Such fractures are not necessarily symptomatic.

Effect on Fracture Incidence

New Vertebral Fractures — FORTEO, when taken with calcium and vitamin D and compared with calcium and vitamin D alone, reduced the risk of 1 or more new vertebral fractures from 14.3% of women in the placebo group to 5.0% in the FORTEO group. This difference was statistically significant ($p < 0.001$); the absolute reduction in risk was 9.3% and the relative reduction was 65%. FORTEO was effective in reducing the risk for vertebral fractures regardless of age, baseline rate of bone turnover, or baseline BMD (see Table 2).

Table 2. Effect of FORTEO on Risk of Vertebral Fractures in Postmenopausal Women with Osteoporosis

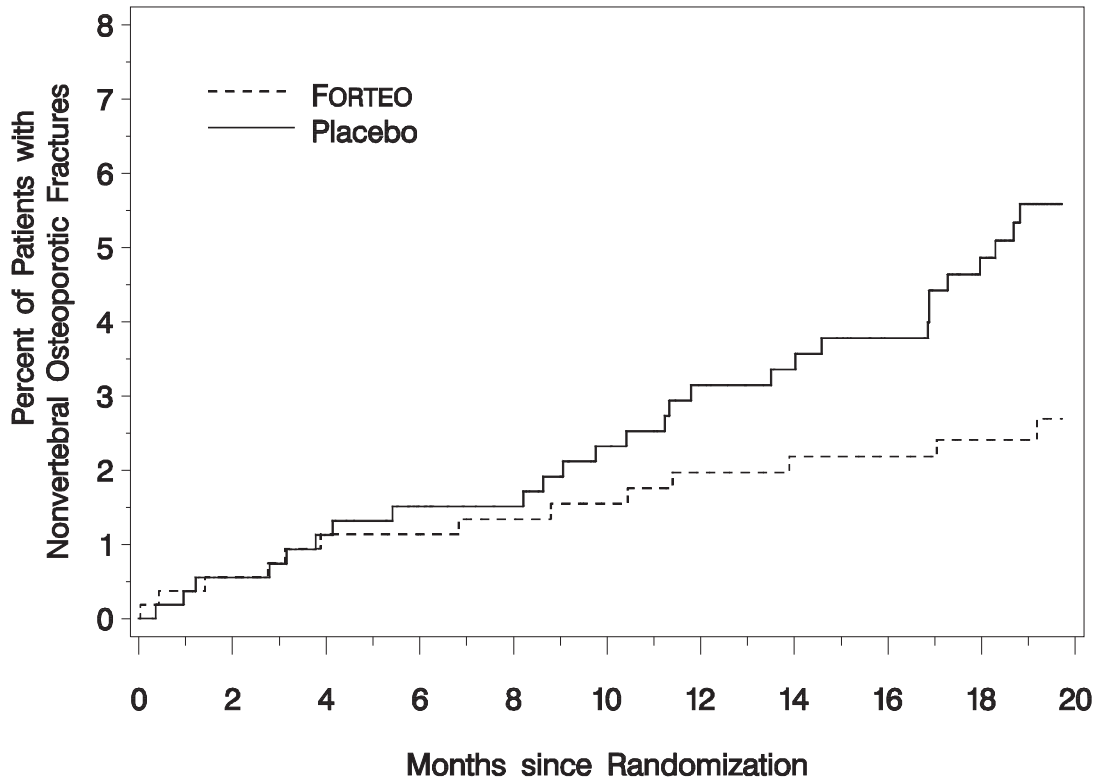
	Percent of Women With Fracture			
	FORTEO (N=444)	Placebo (N=448)	Absolute Risk Reduction (%, 95% CI)	Relative Risk Reduction (%, 95% CI)
New fracture (≥1)	5.0 ^a	14.3	9.3 (5.5-13.1)	65 (45-78)
1 fracture	3.8	9.4		
2 fractures	0.9	2.9		
≥3 fractures	0.2	2.0		

^a $p \leq 0.001$ compared with placebo.

New Nonvertebral Osteoporotic Fractures — FORTEO significantly reduced the risk of any nonvertebral fracture from 5.5% in the placebo group to 2.6% in the FORTEO group ($p<0.05$). The absolute reduction in risk was 2.9% and the relative reduction was 53%. The incidence of new nonvertebral fractures in the FORTEO group compared with the placebo group was ankle/foot (0.2%, 0.7%), hip (0.2%, 0.7%), humerus (0.4%, 0.4%), pelvis (0%, 0.6%), ribs (0.6%, 0.9%), wrist (0.4%, 1.3%), and other sites (1.1%, 1.5%), respectively.

The cumulative percentage of postmenopausal women with osteoporosis who sustained new nonvertebral fractures was lower in women treated with FORTEO than in women treated with placebo (*see* Figure 1).

Figure 1. Cumulative Percentage of Postmenopausal Women with Osteoporosis Sustaining New Nonvertebral Osteoporotic Fractures



Effect on Bone Mineral Density (BMD)

FORTEO increased lumbar spine BMD in postmenopausal women with osteoporosis. Statistically significant increases were seen at 3 months and continued throughout the treatment period. Postmenopausal women with osteoporosis who were treated with FORTEO had statistically significant increases in BMD from baseline to endpoint at the lumbar spine, femoral neck, total hip, and total body (*see* Table 3).

Table 3. Mean Percent Change in BMD from Baseline to Endpoint^a in Postmenopausal Women with Osteoporosis, Treated with FORTEO or Placebo for a Median of 19 Months

	FORTEO N=541	Placebo N=544
Lumbar spine BMD	9.7 ^b	1.1
Femoral neck BMD	2.8 ^c	-0.7
Total hip BMD	2.6 ^c	-1.0
Trochanter BMD	3.5 ^c	-0.2
Intertrochanter BMD	2.6 ^c	-1.3

Ward's triangle BMD	4.2 ^c	-0.8
Total body BMD	0.6 ^c	-0.5
Distal 1/3 radius BMD	-2.1	-1.3
Ultradistal radius BMD	-0.1	-1.6

^a Intent-to-treat analysis, last observation carried forward.

^b p<0.001 compared with placebo.

^c p<0.05 compared with placebo.

FORTEO treatment increased lumbar spine BMD from baseline in 96% of postmenopausal women treated.

Seventy-two percent of patients treated with FORTEO achieved at least a 5% increase in spine BMD, and 44% gained 10% or more.

Both treatment groups lost height during the trial. The mean decreases were 3.61 and 2.81 mm in the placebo and FORTEO groups, respectively.

Bone Histology

The effects of teriparatide on bone histology were evaluated in iliac crest biopsies of 35 postmenopausal women treated for 12 to 24 months with calcium and vitamin D and teriparatide 20 or 40 mcg/day. Normal mineralization was observed with no evidence of cellular toxicity. The new bone formed with teriparatide was of normal quality (as evidenced by the absence of woven bone and marrow fibrosis).

14.2 Treatment to Increase Bone Mass in Men with Primary or Hypogonadal Osteoporosis

The safety and efficacy of once-daily FORTEO, median exposure of 10 months, were examined in a double-blind, multicenter, placebo-controlled clinical study of 437 men with either primary (idiopathic) or hypogonadal osteoporosis (FORTEO 20 mcg, n=151). All men received 1000 mg of calcium and at least 400 IU of vitamin D per day. The primary efficacy endpoint was change in lumbar spine BMD.

FORTEO increased lumbar spine BMD in men with primary or hypogonadal osteoporosis. Statistically significant increases were seen at 3 months and continued throughout the treatment period. FORTEO was effective in increasing lumbar spine BMD regardless of age, baseline rate of bone turnover, and baseline BMD. The effects of FORTEO at additional skeletal sites are shown in Table 4.

FORTEO treatment for a median of 10 months increased lumbar spine BMD from baseline in 94% of men treated.

Fifty-three percent of patients treated with FORTEO achieved at least a 5% increase in spine BMD, and 14% gained 10% or more.

Table 4. Mean Percent Change in BMD from Baseline to Endpoint^a in Men with Primary or Hypogonadal Osteoporosis, Treated with FORTEO or Placebo for a Median of 10 Months

	FORTEO N=151	Placebo N=147
Lumbar spine BMD	5.9 ^b	0.5
Femoral neck BMD	1.5 ^c	0.3
Total hip BMD	1.2	0.5
Trochanter BMD	1.3	1.1
Intertrochanter BMD	1.2	0.6
Ward's triangle BMD	2.8	1.1
Total body BMD	0.4	-0.4
Distal 1/3 radius BMD	-0.5	-0.2
Ultradistal radius BMD	-0.5	-0.3

^a Intent-to-treat analysis, last observation carried forward.

^b p<0.001 compared with placebo.

^c p<0.05 compared with placebo.

14.3 Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis

The efficacy of FORTEO for treating glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥5 mg/day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months with 214 patients exposed to FORTEO. In the FORTEO group, the baseline median glucocorticoid dose was 7.5 mg/day and the median duration of glucocorticoid use was 1.5 years. The mean (SD) baseline lumbar spine BMD was 0.85 ± 0.13 g/cm² and lumbar spine BMD T-score was -2.5 ± 1 (number of

standard deviations below the mean BMD value for healthy adults). A total of 30% of patients had prevalent vertebral fracture(s) and 43% had prior non-vertebral fracture(s). The patients had chronic rheumatologic, respiratory or other diseases that required sustained glucocorticoid therapy. All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day.

Because of differences in mechanism of action (anabolic vs. anti-resorptive) and lack of clarity regarding differences in BMD as an adequate predictor of fracture efficacy, data on the active comparator are not presented.

Effect on Bone Mineral Density (BMD)

In patients with glucocorticoid-induced osteoporosis, FORTEO increased lumbar spine BMD compared with baseline at 3 months through 18 months of treatment. In patients treated with FORTEO, the mean percent change in BMD from baseline to endpoint was 7.2% at the lumbar spine, 3.6% at the total hip, and 3.7% at the femoral neck ($p < 0.001$ all sites). The relative treatment effects of FORTEO were consistent in subgroups defined by gender, age, geographic region, body mass index, underlying disease, prevalent vertebral fracture, baseline glucocorticoid dose, prior bisphosphonate use, and glucocorticoid discontinuation during trial.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

The FORTEO delivery device (pen) is available in the following package size:

- 2.4 mL prefilled delivery device NDC 0002-8400-01 (MS8400).

16.2 Storage and Handling

- The FORTEO delivery device should be stored under refrigeration at 2° to 8°C (36° to 46°F) at all times.
- Recap the delivery device when not in use to protect the cartridge from physical damage and light.
- During the use period, time out of the refrigerator should be minimized; the dose may be delivered immediately following removal from the refrigerator.
- Do not freeze. Do not use FORTEO if it has been frozen.

17 PATIENT COUNSELING INFORMATION

See Medication Guide.

17.1 Potential Risk of Osteosarcoma and Voluntary FORTEO Patient Registry

Patients should be made aware that in rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Enrollment information can be obtained by calling 1-866-382-6813, or by visiting www.forteoregistry.rti.org.

17.2 Orthostatic Hypotension

FORTEO should be administered initially under circumstances where the patient can immediately sit or lie down if symptoms occur. Patients should be instructed that if they feel lightheaded or have palpitations after the injection, they should sit or lie down until the symptoms resolve. If symptoms persist or worsen, patients should be instructed to consult a physician before continuing treatment [*see Warnings and Precautions (5.7)*].

17.3 Hypercalcemia

Although symptomatic hypercalcemia was not observed in clinical trials, physicians should instruct patients taking FORTEO to contact a health care provider if they develop persistent symptoms of hypercalcemia (e.g., nausea, vomiting, constipation, lethargy, muscle weakness).

17.4 Other Osteoporosis Treatment Modalities

Patients should be informed regarding the roles of supplemental calcium and/or vitamin D, weight-bearing exercise, and modification of certain behavioral factors such as cigarette smoking and/or alcohol consumption.

17.5 Use of Delivery Device (Pen)

Patients and caregivers who administer FORTEO should be instructed on how to properly use the delivery device (refer to *User Manual*), properly dispose of needles, and be advised not to share their delivery device with other patients. The contents of the delivery device should NOT be transferred to a syringe.

Each FORTEO delivery device can be used for up to 28 days including the first injection from the delivery device. After the 28-day use period, discard the FORTEO delivery device, even if it still contains some unused solution.

17.6 Availability of Medication Guide and User Manual

Patients should read the *Medication Guide* and delivery device (pen) *User Manual* before starting therapy with FORTEO and re-read them each time the prescription is renewed. Patients need to understand and follow the instructions in the FORTEO delivery device *User Manual*. Failure to do so may result in inaccurate dosing.

Literature revised: March 21, 2012

Marketed by: Lilly USA, LLC
Indianapolis, IN 46285, USA
www.forteo.com

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PA097FSAM01

24.14 Blood Draw Amounts

07-D-0016 Blood Draw Amounts

	Screening	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Cumulative mls
	2-6 weeks	Month 0	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	Month 54	Month 60	Month 66	
Blood Tests														
DNA Testing - if indicated (not included in protocol)														
Chem 20 (4ml)	4	4	4	4	4	4	4	4	4	4	4	4	4	52
Complete blood count (3ml)	3	3	3	3	3	3	3	3	3	3	3	3	3	39
Mineral panel or calcium level (4ml) - as needed	8	32	4	4	4	4	4	4	4	4	4	4	4	84
Thyroid Panel (4ml)	4	4	4	4	4	4	4	4	4	4	4	4	4	52
25-OH-VitD (5ml)	5	5	5	5	5	5	5	5	5	5	5	5	5	65
1,25 (OH) ₂ (4ml)	4	4	4	4	4	4	4	4	4	4	4	4	4	52
Intact PTH (3ml)	3	3	3	3	3	3	3	3	3	3	3	3	3	39
BSAP (4ml)		4	4	4	4	4	4	4	4	4	4	4	4	48
Osteocalcin (3ml)		3	3	3	3	3	3	3	3	3	3	3	3	36
Ionized calcium (1ml)	1	1	1	1	1	1	1	1	1	1	1	1	1	13
Research Blood for sample storage (4 ml)		4	4	4	4	4	4	4	4	4	4	4	4	48
24-hr blood sampling (4 mls X 13= 52ml)				52										52
Acute care and mineral panels for day 1 at 8 am, 12 pm, 4 pm, 8 pm, 8am on day 2 FGF-23 (4ml)		20												20
		4												4
Total (ml)	32	91	39	91	39	39	39	39	39	39	39	39	39	604

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient
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INSTITUTE: National Institute of Dental and Craniofacial Research

STUDY NUMBER: 07-D-0016 PRINCIPAL INVESTIGATOR: Rachel I. Gafni, M.D.

STUDY TITLE: Effects of PTH Replacement on Bone in Hypoparathyroidism

Continuing Review Approved by the IRB on 03/25/15

Amendment Approved by the IRB on 09/11/15 (Z)

Date Posted to Web: 09/17/15

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Purpose of the Study

The purpose of this study is to see how treatment with parathyroid hormone (PTH) affects bones of people with hypoparathyroidism.

Background

You have a disorder called hypoparathyroidism. People with this disorder do not make enough PTH. PTH is a hormone made by the parathyroid glands, which are located in the neck. Sometimes, hypoparathyroidism starts during childhood. It can also begin later in life. If it begins later, it is usually due to damage or removal of the parathyroid glands during surgery.

PTH helps control the amount of calcium in blood, kidneys, and bones. When there is not enough PTH, the calcium level in the blood can be too low and the level in the kidneys, urine, and bones can be too high. Low levels of calcium in the blood can cause a person to feel sick. It can cause cramping or tingling in the hands, feet, or other parts of the body. A very low blood calcium can cause fainting or seizures. The standard treatment for hypoparathyroidism is a form of vitamin D (usually calcitriol) and calcium supplements. Most patients take these medications by mouth several times a day. Calcitriol helps the body absorb calcium from the supplements and food. Keeping blood calcium levels normal can be

PATIENT IDENTIFICATION

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

• Adult Patient or • Parent, for Minor Patient

NIH-2514-1 (07-09)

P.A.: 09-25-0099

File in Section 4: Protocol Consent (1)

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate in A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study
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difficult and sometimes impossible. Sometimes there is too much calcium in the urine even if the calcium levels in the blood are low. High calcium in the kidneys and urine can cause problems such as calcium deposits in the kidney (nephrocalcinosis) or kidney stones. High levels of calcium in the kidney may keep the kidney from functioning normally.

There is a manufactured form of PTH that is similar to the hormone that the body makes. Unlike calcitriol, PTH must be given as a shot under the skin using a small needle. Previous research has shown that PTH may improve calcium levels in blood and urine. However, how PTH affects the bones of people with hypoparathyroidism is not well understood. This study will examine the effects of PTH treatment on bone in people with hypoparathyroidism.

Study Population

This study will enroll about 36 people with hypoparathyroidism.

Who Can Be In This Study

You may be eligible to participate if you:

1. Have had hypoparathyroidism for at least one year.
2. Are a man between 18-70 years old at the first visit;
3. Are a woman between 18-45 years old and have not started menopause at the first visit. Or are a woman between 53-70 years old and have not had a menstrual cycle within the past 5 years.

Who May Not Be In This Study

You may not be eligible to be in this study if you:

1. Have decreased liver or kidney function
2. Have allergy or inability to take certain types of antibiotics (such as tetracycline)
3. Are pregnant or nursing, or if you are planning to become pregnant during the course of the study. Women who are able to get pregnant must agree to use an effective form of birth control while in this study.
4. Are in menopause or are starting menopause
5. Have another disease or condition that may affect bone, such as diabetes, celiac disease, Crohn's disease, Cushing syndrome, or adrenal insufficiency.
6. Have active thyroid cancer and/or are receiving treatment with suppressive doses of thyroid hormone
7. Have taken medicines or received radiation that affect the bones
8. Used steroid medicine or estrogen replacement for more than 3 weeks in the past 6 months.
9. Have uncontrollable low calcium levels requiring frequent intravenous calcium
10. Are taking medicine for a seizure disorder
11. Have cancer of the retina
12. Have a genetic condition that increases your risk for bone cancer.
13. Have bones that have not stopped growing. (We'll check this by an x-ray of your hand).
14. Have ever had previous treatment with PTH for more than 2 weeks

Procedures

The study includes 13 visits to the NIH Clinical Center over a 6 year period. Those 13 visits include one inpatient visit for tests to see if you can be in the study. It also includes one baseline inpatient visit, 10 follow-up visits (1 visit about every 6 months), and one follow-up visit after you have stopped PTH. Follow-up visits could be inpatient or outpatient. The NIH visits vary in length from 1 to 10 days. In between visits, you will also need to have regular blood and urine tests at a doctor or laboratory near your home.

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Screening Period

For the first visit you will be admitted to the NIH clinical Center for 2-3 days. We will do tests to see if you qualify for the study. If you qualify and agree to participate, you will be placed on calcium and calcitriol. You will take calcium and calcitriol for 1-7 months before your first dose of PTH. Your return visit will be scheduled at your convenience.

Baseline Visit

This baseline visit will occur after the doses of calcium and calcitriol are stable. This inpatient visit at the NIH Clinical Center may last 7 – 10 days. At this visit you will start taking PTH. You will take PTH twice a day for up to 5 years. You will take PTH by shot. You will be taught how to give yourself a shot under the skin using a small needle. At this visit you will have a bone biopsy from your hip. The month before the biopsy, you will be given antibiotics to take for a few days.

Follow-up Visits

You will come to the NIH for a follow-up visit every 6 months while you are taking PTH. One follow-up visit will occur after you stop taking PTH. The follow-up visit with the bone biopsy will be inpatient and will last 5-7 days. Other follow-up visit will last 1-3 days and may be inpatient or outpatient. The purpose of these visits is to run tests and to make sure your PTH dose is correct. We may also adjust your other medications or add medications based on the results of the blood and urine tests.

During one of those follow-up visits, you will have a second bone biopsy taken from the other hip. That second biopsy will be done after 1 year, 2 years, or 4 years of taking PTH. The timing of the second biopsy will be determined randomly. Doing this in a random way makes the scientific information we get from the biopsies more accurate. The month before the biopsy, you will be given antibiotics to take for a few days.

Research Test Procedures

This section details the procedures and assessments that will be completed. The section also clarifies at which visits the procedures will be done.

1. **Medical History, Vital Signs and Physical Exam.** (Each study visit) The study doctor will ask you about your health, check your vital signs such as heart rate and blood pressure, temperature, and breathing rate. You will also have a physical exam. These will take about 60-90 minutes.
2. **Blood tests.** (Each study visit) Blood will be drawn through a needle in your arm. We will draw no more than 2 tablespoons of blood at any one time. You may be asked not to eat after midnight the night before these are done. The total blood drawn during most study visits is approximately 2 tablespoons.

Blood tests will be used to monitor your safety. Blood will also be drawn for future research. It may also be drawn to test for genetic causes of hypoparathyroidism. You will be asked to sign a separate consent form for this test.

On the day you start taking the PTH shots, you may have up to 4 blood draws throughout the day. If you would like, an intravenous catheter can be placed for the purpose of painless blood draws through the day.

On subsequent visit days, there will be only one or two blood draws per day. The total blood drawn during the entire Baseline visit will be approximately 6 tablespoons.

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Genetic Testing. You may be asked to give 3-5 ml (1 teaspoon) of blood for genetic testing. The genetic material, DNA, will be extracted from the sample and analyzed in order to identify the genes causing the hypoparathyroidism in your family.

24-Hour Blood Sampling. After you have been taking PTH for one year, you will have blood drawn every 2 hours over a 24-hour period. The purpose is to monitor the changes in different minerals throughout the day and night while you are taking PTH. The amount of blood drawn over the 24-hour period will be about 3 tablespoons. An intravenous catheter will be placed for the purpose of painless blood draws through the day. For the IV, a needle will be used to guide a thin plastic tube (catheter) into one of your veins. The needle will be removed, leaving only the catheter in the vein. The catheter will be taped to the skin to hold it in place. Occasionally, there is difficulty placing the IV and we may need to place a longer catheter called, called a PICC line, into one of your larger veins.

3. **Questionnaires.** (Screening, Baseline, and Follow-up visits) You will be asked questions about your diet, overall health, and feelings of fatigue. It should take you less than an hour to complete these questionnaires.
4. **6-Minute Walk Test.** (Baseline and Follow-up visits) You will be asked to complete a 6 minute walking test. For the walking test, you will be asked to walk back and forth on an indoor walking course. You will be asked to walk as briskly as is comfortable for you. The walk will continue for 6 minutes or until you are unable to continue. You will be monitored by a rehabilitation specialist throughout the test.
5. **Bone Age X-ray.** (Screening Visit) People less than 21 years of age will have a bone age X-ray of the one hand. We will use this x-ray to see if your bones have stopped growing. It takes only a few minutes.
6. **Bone Density (DXA) Scan.** (Screening and all follow-up visits) This is an X-ray of your bones to measure bone mineral density. For this test, you will lie on an open table while an X-ray machine moves around you. You will only need to stay still for a few minutes at a time. The test will take about 30 minutes.
7. **CT Scan.** (Baseline, Year 1, Year 2, Year 3, Year 4 and Year 5 visits) CT scanning uses x-rays to obtain an image of the kidneys and spine. The CT scanner is shaped like a metal cylinder. For the CT scan you will lie on a table that can slide in and out of the cylinder. You will be in the scanner for about 15 minutes. You will be able to communicate with the CT staff at all times, and you may ask to be moved out of the machine at any time.
8. **Kidney Ultrasound** (Baseline, Year 1, Year 2, Year 3, Year 4 and Year 5 visits) A kidney ultrasound to look for calcium deposits. For this test you will need to lie on a table for about 15-30 minutes while a technician moves a wand over your back to look at your kidneys.
9. **24-hour Urine Collection.** (Each study visit) Collection of urine for 24 hours. When you are in the Clinical Center the container may be stored in the bathroom. A nurse will collect the urine throughout the day. At other times, you will be asked to save and collect your urine for a 24 hour period.
10. **Urine Collection** (Baseline visit) Urine samples will be collected 4 times on the day that you start taking PTH and then once a day on the following days of this visit.
11. **Urine Pregnancy Test.** (Each study visit) Women who are able to become pregnant will have a pregnancy test at each study visit.
12. **Bone Biopsy Procedure.** (Baseline and only once during follow-up)

You will not have more than 2 biopsies in this study. The biopsy procedure can be uncomfortable. The bone biopsy will be done in the operating room. You will be given some medicine to make you sleepy. This can be

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given as: a pill; a suppository inserted into the rectum; or a shot under the skin, into a muscle, or by injection into your vein. The skin over the area of the hip will be cleaned. A numbing medication will be injected with a small needle into the skin. The needle will go through the underlying tissues, and onto the surface of the bone. A larger needle, about the width of a pencil (approximately 1/3 inch in diameter), will then be inserted through a small skin incision into the bone to remove bone tissue. The skin incision will be closed with several stitches that will dissolve within 2-3 weeks. After the biopsy is over, you will receive additional pain medicine as needed. The biopsies will be performed in the operating room by a qualified surgeon with an anesthesiologist on hand. The biopsy procedure usually takes less than an hour. You will be asked to sign a separate surgical consent form before the procedure.

The month before each biopsy you will be asked to take an antibiotic. You will take it for 3 days. Then you will stop taking it for 12 days. And then you will take it again for 3 more days. The schedule will be explained to you again when it comes time to take the antibiotic.

13. **Tests at Your Local Laboratory**

Between follow-up visits, you will be asked to go to your local laboratory for blood and urine tests. At first, you will need blood tests at least once a week. Later, you will need blood tests once a month. You will need urine tests every 3 months. You or your local laboratory will send the laboratory results to the study staff. One of the study doctors will contact you to adjust your medications, as needed.

Risks, Inconveniences and Discomforts

Some of the known risks and discomforts of the study drug and procedures are listed below. As with all studies, there may be risks or discomforts we don't know about.

PTH

The PTH used in this study has not been approved by the Food and Drug Administration (FDA). However, Forteo (recombinant human PTH), a drug almost identical to the PTH used in this study, has been approved by the FDA for the treatment of osteoporosis. Forteo has a proven bone-building effect in elderly people with osteoporosis. The most common side effects of Forteo include pain, joint pain, nausea, and high levels of calcium in the blood.

The known risks of taking PTH for hypoparathyroidism are described below. There may be additional risks from taking PTH injections that are not yet known.

- Daily shots of PTH under the skin may cause discomfort. If done properly, using small needles, these shots should not be painful.
- Some people may develop bone pain during their PTH therapy. This may be treated with a change in the PTH dose.
- PTH shots may cause enlargement of blood vessels in the skin. This may cause redness.
- Some people feel lightheaded or have a decrease in blood pressure, especially with the first dose. This will be monitored closely while you are at the NIH.
- Some people, both with osteoporosis or hypoparathyroidism, have decreases in the bone density of the wrist while they are taking PTH. However, there have not been reports of increased wrist fractures in people taking PTH. We will be monitoring your bone density every 6 months. If your bone density becomes low, you may have to stop taking PTH.

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- Some people develop resistance to PTH therapy. This means that the body does not respond to the medicine. These people may require gradual increases in PTH dose to keep the calcium levels in the target range. If this happens to you, you may be able to continue the therapy if the resistance is mild. Others may develop severe resistance and the calcium levels stay dangerously low. If that happens to you, PTH treatment will have to be stopped and you will have to go back to taking standard treatment.

When it is time to take you off PTH, we will gradually decrease the dose to keep your calcium levels where they need to be. We may need to check your blood levels frequently at your local laboratory during that time. Some people need to take higher doses of calcium and calcitriol than they did before joining the study for several months while they are switching off of the PTH. We will monitor you as long as necessary to make sure that your calcium levels are stable off of the PTH.

Since this study has started, we have noticed that the amount of citrate in the urine decreases in many patients after they start taking PTH. Some patients have low urine citrate levels even before starting PTH. Urine citrate helps to prevent calcium deposits and kidney stones. It is not known if the decrease in urine citrate increases the risk of calcium deposits in people with hypoparathyroidism, but it might. We will check the citrate level in your urine every time that you do a 24-hour urine test. If the level of citrate is not high enough compared to the urine calcium level, we may ask you to take potassium citrate pills, an FDA-approved treatment for low urine citrate that is used to prevent kidney stones. These pills may help to protect your kidneys from calcium deposits and kidney stones, even if your urine citrate levels do not become completely normal. The most common side effect of potassium citrate is stomach upset. If you cannot tolerate the potassium citrate tablets, you will not be required to take them.

You should be aware that in animal studies, some rats developed bone cancer after receiving high doses of Forteo. However, monkeys given high doses Forteo have not been shown to develop bone tumors. There have been two reports of bone cancer in patients treated with Forteo for osteoporosis. However, it is not known whether the Forteo actually caused the bone cancer. Over 1,000,000 people have been treated with Forteo around the world. No one knows if there is truly an increased risk for cancer, but there is a possibility. The risk of cancer may be greater if PTH is given for a long periods of time. As a result, the FDA has issued a warning for Forteo. The warning states that Forteo should not be prescribed for people with an increased risk of bone cancer. Those at increased risk include people with certain diseases, such as Paget's disease of bone, a history of radiation therapy to the bones, or a history of bone cancer and children or young adults with open growth plates in their bones. The safety and effectiveness of Forteo has not been established beyond two years.

Blood Draws

You may have discomfort and bruising at the site of the needle stick. There is a very small risk of fainting. Infection in the area of the needle stick is rare.

The risks of an intravenous catheter or PICC line include bleeding, infection, or inflammation of the skin and vein with pain and swelling. These will be treated if they occur.

Drawing blood every 2 hours (at the 1 year visit) may be inconvenient to you and may disrupt your sleep.

Urine collections

Urine collections are an inconvenience but do not involve risk.

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Walk test

The 6-minute walk test may make you tired. You can stop if you become too tired. A rehabilitation specialist will be present throughout the test.

Bone biopsy

The bone biopsy may cause discomfort and pain for several days. You will be given medicine to help you with the pain. The biopsy is performed through a small skin incision. Bleeding and infection at the site of the biopsy are possible but rare. The anesthesia used during the biopsy may cause nausea, vomiting or decreased appetite for a day or two after the biopsy. You will need to avoid doing any intense exercise or heavy lifting for about two weeks after the biopsy.

Antibiotic

Prior to the biopsy you will take tetracycline or demeclocycline. In some people, these antibiotics may cause nausea, vomiting, or diarrhea. The antibiotics may also make your skin more sensitive to sunlight, so you will need to avoid extensive exposure to direct sunlight while taking these antibiotics.

Radiation

This research study involves exposure to radiation from annual CT scans and DXA scans every 6 months. This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 1.1 rem, which is below the 5.0 rem per year NIH Radiation Safety Committee guideline for adults. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant you will not be permitted to participate in this research study.

Genetic Testing

If a genetic cause of hypoparathyroidism is suspected, you may be offered the option of genetic testing. Genetic testing will be done through another certified laboratory. You will be asked to sign a different consent form. The laboratory consent form lists additional testing procedures that are not part of this study and will not be done. We will discuss with you which tests will and will not be done for this research study. You can receive a copy of the genetic testing report if you wish. You do not have to have genetic testing to be in this study.

Genetic testing can provide information about how health or illness is passed on within your family. This knowledge may affect your emotional wellbeing. You might feel differently about your life if you learned that you or your children were at increased risk of a disease, especially if there were no treatments. Your children, brothers or sisters may find out that they are at risk for health problems because of information found out about you, which might affect your relationships with them. Other family members may also be affected by uncovering risks they have but did not want to know about. This information can cause stress, anxiety, or depression.

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH-2514-1 (10-84) NIH-2514-2 (10-84) P.A.: 09-25-0099
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MEDICAL RECORD**CONTINUATION SHEET for either:
NIH 2514-1, Consent to Participate in A Clinical Research Study
NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study**

STUDY NUMBER:

07-D-0016

CONTINUATION: Page 8 of 10 pages

Your genetic information will be kept confidential to the extent possible. The results of your genetic testing will be kept in a locked and secured manner at the NIH. Genetic information about you will not be revealed to others, including your relatives, without your written permission. Problems, such as with insurance or employment discrimination, may occur if you disclose information about yourself or agree to have your research records released. We will not release any information about you or your family to any physician, insurance company or employer unless you sign a document allowing release of the information.

Use of Stored Samples

Your blood, urine and bone samples will be stored in secured freezers on the NIH campus. Your name and identifying information will not be on the samples; we will assign them a code. The key to the code will be kept in a separate, secure area.

Your sample may be used for other research projects, including those not related to hypoparathyroidism if you agree. The samples may be shared with researchers at NIH and outside of NIH. Please initial on the line below that reflects your choice:

_____ My samples may be used for other research projects including those not related to hypoparathyroidism.

_____ I do not want my samples used for other research projects. Please destroy my samples once this project is complete.

If you withdraw from this research project before it is complete, you may request that any remaining samples you have contributed will be discarded. Results obtained before you withdraw will be kept and your privacy will be protected.

Commercial products may be developed from your and others' research samples. You or your beneficiaries will not be paid if a product, process, or service is developed from the use of your samples.

Anticipated Benefits

Treatment with PTH will replace the hormone you are missing. Your disease may be better controlled on PTH than on calcium and calcitriol.

Right of Withdrawal and Conditions for Early Withdrawal

You may decide to withdraw from the study at any time. The study doctor can withdraw you from the study at any time. You will be withdrawn if it is not in your best interest to continue. Or you will be withdrawn if you cannot comply with study requirements. If you become pregnant, if you do not respond well to PTH, or if you develop certain conditions, the study doctor will have to withdraw you from the study. The study doctor can tell you about those conditions. If you are planning to become pregnant within 5 years of starting the study, then you should not participate in this study.

If you or the study doctor elects to discontinue study medication, you may be asked to return to the NIH for tests or exams. You have the right to refuse these tests and exams.

Results from This Study

You will be informed of any new findings that develop during this study that might relate to your willingness to continue to participate. You will be informed of any new information about hypoparathyroidism that might affect your health.

Study Termination

If the study is stopped early, you will not continue to receive PTH from the NIH. The study may be stopped early for several reasons, including subject safety.

PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

NIH-2514-1 (10-84)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate in A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study
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Alternatives to Participation or Treatment

You do not have to be in this study to get treatment for hypoparathyroidism. The standard treatment is oral calcium and calcitriol. You may receive the standard treatment from doctors who treat patients with hypoparathyroidism. You might be able to persuade your personal doctor to prescribe PTH. Also, you may be eligible for participation in other clinical trials that are evaluating treatments.

Compensation and Travel Costs

You will not be paid to participate in this study. Travel/subsistence expenses and research-related co-pays will be reimbursed. This is based on to the NIH policy established January 5, 2009.

Posting of Research Results on www.ClinicalTrials.gov

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. 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.

Revision Copy

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH-2514-1 (10-84) NIH-2514-2 (10-84) P.A.: 09-25-0099
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MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY •Adult Patient or •Parent, for Minor Patient
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STUDY NUMBER: 07-D-0016

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OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Rachel I. Gafni, MD, Building 30, Room 228, Telephone: 301-594-9924. You may also call the Clinical Center Patient Representative at (301) 496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study. Signature of Adult Patient/Legal Representative _____ Date _____ Print Name _____	B. Parent's Permission for Minor Patient. I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study. (Attach NIH 2514-2, Minor's Assent, if applicable.) Signature of Parent(s)/Guardian _____ Date _____ Print Name _____
C. Child's Verbal Assent (If Applicable) The information in the above consent was described to my child and my child agrees to participate in the study. Signature of Parent(s)/Guardian _____ Date _____ Print Name _____	
THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM MARCH 25, 2015 THROUGH MARCH 24, 2016.	
Signature of Investigator _____ Date _____ Print Name _____	Signature of Witness _____ Date _____ Print Name _____

PATIENT IDENTIFICATION

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY (Continuation Sheet)

• Adult Patient or • Parent, for Minor Patient
 NIH-2514-1 (07-09)
 P.A.: 09-25-0099
 File in Section 4: Protocol Consent