STATISTICAL ANALYSIS PLAN
06 June 2018

Effects of PTH Replacement on Bone in Hypoparathyroidism

PROTOCOL NUMBER 07-D-0016

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DOCUMENT VERSION CONTROL

Version Number	Date	Comments/Changes
0.12	05-Jan-2017	First draft. This line will be updated to version 1.0, when the document is finalized.
1.0	17-Feb-2017	Planned as Final. Not finalized.
1.2	31-May-2018	Changed the name of the ITT Population to Secondary Efficacy Population which is more appropriate (Section 4). Clarified when the Bone Biospy or Secondary Efficacy Analysis Populations are used for the efficacy analyses (Section 7.4). Stated that the 4-year biopsy endpoints may be dropped from the bone biopsy analyses if they are qualitatively different from the 2-year biopsy endpoints. (Sections 7.4.1 and 7.4.2).
2.0	06-May-2018	Minor edits. Saved as Final

APPROVALS

By signing this document, I indicate that I have reviewed and hereby approve the contents, procedures and standards described herein.

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LIST OF ABBREVIATIONS

AjAR	Adjusted apposition rate
BMD	Bone mineralization density
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
Cn.BFR/BS	Cancellous bone formation rate
Cn.BV/TV	Cancellous Bone Volume
Cn.MS/BS	Cancellous mineralizing surface (bone surface based)
Cn.MAR	Cancellous bone mineral apposition rate
Cn.O.Th	Cancellous osteoid thickness
CT	Computed tomography
Ct.Ar	Total Area of Inner and Outer Cortices
Ct.BFR/BS	Intracortical bone formation rate
Ct.MAR	Intracortical bone mineral apposition rate
Ct.MS/BS	Intracortical mineralizing surface (bone surface based)
Ct.Po.Ar	Total area of cortical porosity
Ct.Po.N	Total Number of Cortical Porosity per mm2
Ct.Th	Average Thickness of Inner and
Ec.BFR/BS	Endocortical bone formation rate
Ec.MAR	Endocortical bone mineral apposition rate:
Ec.MS/BS	Endocortical mineralizing surface (bone surface based)
Ec.MAR	Endocortical bone mineral apposition rate
Ec.OS/BS	Osteoid surface/bone surface
Ec.O.Th	Endocortical osteoid thickness
ES/BS	Eroded surface / bone surfac
FGF23	Fibroblast growth factor 23
hPTH	Synthetic human parathyroid hormone 1-34
Ic.BFR/BS	Intracortical bone formation rate
Ic.MS/BS	Intracortical mineralizing surface (bone surface based)
MAR	Bone mineral apposition rate
NC/NL	Nephrocalcinosis and Nephrolithiasis

O.Th	Osteoid Thickness
OS/BS	Osteoid surface / bone surface
PTH	Parathyroid hormone
Tb.BV/TV	Trabecular bone volume
Tb.N	Trabecular number
Tb.Sp	Trabecular Separation
Tb.Th	Trabecular thickness

1. PURPOSE OF THIS DOCUMENT

Several journal publications are expected from the study. This is an abbreviated statistical analysis plan with this document's primary focus on the statistical methods that will be used for the main publication. The safety analyses for this study have already been reported to the DSMB and will not be discussed further except to note that the tables and listings generated for the DSMB will be provided.

2. PROTOCOL SUMMARY

2.1 Study Objectives

The primary objective of this study is to evaluate the skeletal effects of hormone replacement therapy with synthetic human parathyroid 1-34 hormone (hPTH) in hypoparathyroidism

2.2 Overall Study Design and Plan

Copied from the protocol:

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.

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 (± 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 μg/kg/dose subcutaneously twice a day (study month 0). 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 Appendices to the protocol.

2.3 Study Population

Copied from the protocol:

This study will enroll up to 69 subjects with physician-diagnosed hypoparathyroidism. 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. GENERAL ANALYSIS AND REPORTING CONVENTIONS

- Categorical variables will be summarized using counts (n) and percents (%) and will be presented in the form n (%).
- Standard deviations and confidence limits will be reported at 1 more significant digit than the mean.
- Order statistics including median, min and max will be reported to the same level of precision as the original observations. If any values are calculated to have more significant digits then the value should be rounded so that it is the same level of precision as the original data.
- Following SAS default rules, the median will be reported as the average of the two middle numbers if the dataset contains even numbers.
- No preliminary rounding should be performed; rounding should only occur after analysis. To round, consider digit to right of last significant digit: if < 5 then round down, if >=5 then round up.
- All analysis will be performed using the SAS System version 9.4.

4. ANALYSIS POPULATIONS

There are 3 Study Cohorts for purposes of analysis**:**

Cohort 1: subjects who received hPTH under the original protocol;

Cohort 2: subjects who received conventional care in the original protocol and who re-enrolled into the current protocol and who were treated with hPTH;

Cohort 3: new subjects who initially enrolled into the current protocol.

Subjects in cohort 1 will be analyzed separately from the other subjects; only safety analyses will be conducted on this cohort. Subjects in cohorts 2 and 3 will be combined, and efficacy and safety analyses will be conducted on this group. However, the timing of the baseline biopsy relative to the on-treatment biopsy differs in cohorts 2 and 3. For cohort 2 there was a much longer period of time between the baseline biopsy and their 1, 2, or 4 year on hPTH biopsy, in that the baseline period also include their entire period being on conventional care. Whereas for cohort 3, baseline biopsies were taken immediately prior to beginning hPTH. Because of this difference, all efficacy analyses will be repeated on subjects in cohort 3 alone.

Safety Population: The Safety Population will consist of all enrolled subjects (all cohorts) who have started any study treatment including, but not limited to, conventional care. This population will be used for safety data summaries.

Bone Biopsy Population: The Bone Biopsy Population will consist of all subjects who have completed both their baseline and randomized 1, 2, or 4 year bone biopsies. This will include subjects from cohorts 2 and 3.

Secondary Efficacy Population: This population consists of all subjects who received at least one dose of hPTH and had at least one post-baseline non-biopsy efficacy assessment. This will include subjects from cohorts 2 and 3.

5. STUDY PATIENTS

5.1 Disposition of Patients

Subject disposition will be summarized for the total set of enrolled (ie, consented) subjects by study cohort. The subject disposition table will include:

- Number of enrolled subjects,
- Number of subjects in the safety, bone biopsy, and in the secondary efficacy populations
- Number and percentage of subjects completing the study and the number of those terminating early, and
- Number and percentage of subjects terminating early by reason for early termination.

For the presentation of the early terminations and reasons for early terminations, subjects will be counted under the last study visit completed prior to early termination.

5.2 Protocol Deviations

For cohorts 2 and 3, protocol deviations reported on the current protocol will be summarized by deviation type in a table and subject listing (as previously provided to the DSMB).

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Subject demographics at baseline will be summarized descriptively for each analysis population and cohort combination with appropriate descriptive statistics (number and percentages for categorical variables and mean, standard deviation, median, minimum and maximum for continuous variables). Demographic data will include: sex, ethnicity, race, age, weight, height, and body mass index (BMI).

7. EFFICACY EVALUATION

7.1 Handling of Dropouts or Missing Data

Missing data will not be initially imputed for the primary efficacy analyses. However, if the pattern of missing data in the primary efficacy analyses suggests the possibility of causing bias then as a secondary analysis, the primary analysis will be repeated using imputed values as described in section 7.4.3 below.

7.2 Efficacy Analysis

7.2.1 Primary Study Endpoints

The primary endpoints are changes in static and dynamic bone histomorphometry after 1 year, 2 years, and 4 years of hPTH therapy. These changes will be determined from antibiotic-labeled biopsies taken before and during hPTH therapy. The original protocol called for analyzing 7 bone markers of static and dynamic bone histomorphometry but the SAP has changed these to 8 bone markers of bone structure and bone remodeling. Analyses will be done on z-scores, when normative data are available. These are listed as follows:

7.2.1.1 Bone Structure

1. Cn.BV/TV: cancellous bone volume
2. Ct.Po.N: total number of cortical porosity per mm^2

7.2.1.2 Cancellous Bone Remodeling

1. Cn.BFR/BS: Cancellous bone formation rate
2. Cn.MS/BS: Cancellous mineralizing surface (bone surface based)

7.2.1.3 Endocortical Bone Remodeling

1. Ec.BFR/BS: Endocortical bone formation rat.
2. Ec.MS/BS: Endocortical mineralizing surface (bone surface based)

7.2.1.4 Intracortical Bone Remodeling

1. Ic.BFR/BS: Intracortical bone formation rate
2. Ic.MS/BS: Intracortical mineralizing surface (bone surface based)

7.2.2 Secondary Study Endpoints

7.2.2.1 Static and dynamic bone histomorphometry (After 1, 2, and 4 years of hPTH) in secondary bone biomarkers

Analyses relating to bone endpoints listed below will be done on z-scores, when normative data are available.

1. Bone Structure
    a. Tb.Th: Trabecular Thickness
    b. Tb.N: Trabecular Number
    c. Tb.Sp: Trabecular Separation
    d. Ct.Th: Average Thickness of Inner and Outer Cortices
    e. Ct.Ar: Total Area of Inner and Outer Cortices
    f. Ct.Po.Ar: Total Area of Cortical Porosity
2. Cancellous Bone Remodeling
    a. Cn.O.Th: Osteoid Thickness
    b. MAR: Bone Mineral Apposition Rate
    c. OS/BS: Osteoid Surface / Bone Surface
    d. ES/BS: Eroded Surface / Bone Surface
    e. AjAR: Adjusted Apposition Rate
3. Endocortical bone remodeling
    a. Ec.O.Th: Osteoid Thickness
    b. Ec.MAR: Bone Mineral Apposition Rate
    c. Ec.OS/BS: Osteoid Surface/Bone Surface
    d. ES/BS: Eroded Surface / Bone Surface

e. AjAR: Adjusted Apposition Rate

4. Intracortical bone remodeling

    a. O.Th: Osteoid Thickness

    b. MAR: Bone Mineral Apposition Rate

    c. OS/BS: Osteoid Surface / Bone Surface

    d. ES/BS: Eroded Surface / Bone Surface

    e. AjAR: Adjusted Apposition Rate

7.2.2.2 Changes in bone mineralization density (BMD) 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:

Analyses will be done on z-scores, when normative data are available.

1. Spectral calcium-mean
2. Calcium-peak
3. Calcium-width
4. Calcium low
5. Calcium high

7.2.2.3 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:

1. Biochemical markers of bone metabolism: osteocalcin, bone-specific alkaline phosphatase, collagen cross-linked N-telopeptide.
2. Serum and urine calcium; 1,25-OH2-Vitamin D
3. Bone mineralization density assessed by DXA and quantitative CT including both raw and z-scores (based upon sex and age). These will include measures at the following anatomical sites

    a. AP Spine

    b. Lateral Spine

c. Femoral Neck

d. Total Hip

e. 1/3 Radius

f. Whole Body

The quantitative CT is limited to only the spine.

4. Nephrocalcinosis and Nephrolithiasis by ultrasound and CT

5. Fatigue Symptom Inventory

6. 6-Minute Walk Test

7. SF-36 Health Survey

7.3 Tertiary Outcome Measures

7.3.1 Changes in blood chemistries

Blood parameters include serum albumin, calcium, phosphorus, magnesium, sodium, potassium, chloride, total CO2, creatinine glucose, and urea nitrogen.

7.3.2 Changes in fibrobast growth factor 23

This was assessed via fibroblast growth factor 23 (FGF23) analysis of the blood.

7.3.3 Changes in renal mineral handling and PTH sensitivity

Parameters for analysis include urine cAMP, creatinine, phosphorus, calcium, and pH.

7.4 Analysis Methods

All study endpoints used in analyses will be summarized in tables. Continuous endpoints will be summarized over time using n, mean ± se, median, min, max. Endpoints requiring log-transformation will also be summarized over time using geometric means with their 95% confidence limits. Ordinal endpoints will be summarized using medians, min, max, and their 10^{th} and 90^{th} percentiles. Categorical endpoints will be summarized using number and percent in each category.

All efficacy analyses related to the bone biopsies will be performed on the Bone Biopsy Population. All efficacy analyses other than the bone biopsy related endpoints will be performed on the Secondary Efficacy Population.

For subjects who enter menopause during the study, any of their efficacy endpoints collected during or post-menopause will be excluded from the efficacy analyses, and will have such endpoints reported separately in the subject listings.

Unless otherwise stated, all statistical inference will be based on an alpha level of 0.05 with adjustments for multiple comparisons when needed as described below. Analyses will be made using SAS (SAS Institute, Cary, North Carolina), version 9.4 or later.

7.4.1 Primary Efficacy Analyses

Separate primary analyses will be performed for each of the eight primary bone structure and bone remodeling biopsy endpoints listed in section 7.2.1. Since the study was terminated early and is thus under-powered, no corrections for multiplicity will be made in the analyses of the 8 primary efficacy endpoints. For each of these primary bone biopsy endpoints, the primary analysis will test for differences with respect to the time of the biopsy (baseline, 1, 2, and 4 year). These endpoints will be analyzed using repeated measures mixed models with the bone biopsy endpoint as the dependent variable, the baseline value of the bone biopsy endpoint and study cohort as covariates, biopsy time (baseline, 1 year, 2 year, and 4 year) as the repeated measure, and subject as the random variable. The repeated measures will include a time-dependent covariate to adjust the baseline biopsy of Cohort 2 for the time delay between the baseline biopsy and the start of hPTH treatment. This covariate will adjust Cohort 2 for any possible further progression of disease occurring between the baseline biopsy measures and the start of hPTH therapy. An indicator variable in the statistical model will set the effects of this time-dependent covariate to zero for Cohort 3 and for the post-baseline biopsies of Cohort 2.

Pairwise contrasts between the bone biopsy times will be performed within the repeated measures analyses to compare the effects of the biopsy times on the bone biopsy endpoints. Because the sample size for 2-year and 4-year biopsies are reduced in size due to withdrawal and the early termination of the study, the 2-, and 4-year biopsies may be combined into one group provided their effects are qualitatively similar (i.e. the estimates of their effects are in the same direction). If the 2- and 4-year biopsies are qualitatively different then the 4-year biopsies may be dropped from the analysis due to its small sample size. The post hoc pairwise comparisons among the

biopsy time-points will be corrected for multiple comparisons using Fisher's protected LSD with Bonferroni corrections when the overall effect of biopsy year is not statistically significant.

Residual analysis will be used to confirm that model assumptions are reasonable. Log-transformations of the bone biopsy endpoints will be made if indicated by the residual analysis. The repeated measures will be fit using both a compound symmetry and an unstructured covariance structure. The better covariance structure will be selected as the model with the better Schwarz's Bayesian criterion. If the residual analyses of the statistical models indicate a failure to meet the assumptions of the repeated measures statistical models then other methods of statistical analysis including nonparametric analysis may be considered.

7.4.2 Secondary Efficacy Analyses

7.4.2.1 Covariate adjustments for dose on the primary efficacy analysis models of the bone biopsy endpoints

The bone biopsy repeated measures analyses described in the primary analyses will be explored further by repeating the same analysis but with hPTH dose as an additional covariate. Four measures of dose will be tested as covariates: 1) average dose over the last 6 months prior to the bone biopsy or weaning whichever comes earlier; 2) average dose per kg body weight over the last 6 months prior to the bone biopsy or weaning whichever comes earlier; 3) total daily dose across the whole study up to the time of the bone biopsy or weaning whichever comes earlier; and, 4) total dose per kg of body weight across the whole study up to the time of the bone biopsy or weaning whichever comes earlier . The effects of these dose measures on the bone biopsy results will be modeled separately fitting both linear and quadratic (curvilinear) effects for the dose variable. The best covariate models will be selected based upon examination of the residuals and comparison of the Schwarz-Bayesian criterion.

The relationships between dose and bone biopsy endpoint will be graphically illustrated using scatterplots of the bone biopsy endpoint over dose with appropriate regression lines.

7.4.2.2 Sensitivity analyses of female menopause status in the primary bone biopsy efficacy models

Sensitivity analyses will be performed to test the effects menopause status in females on our best primary efficacy bone biopsy repeated measures models (with or without dose covariates, sections 7.4.1 and 7.4.2.1). Menopause status will be tested as a covariate in the statistical models (excluding males). The covariate for menopausal status will be parameterized into a categorical variable with 2 levels: 1) pre-menopausal female; and 2) menopausal or post-

menopausal female. If the data is rich enough, further exploratory analyses may test for interactions between dose, and menopausal status. Best models will be selected based upon residual analysis and the Schwarz-Bayesian criterion. Results will be summarized in tables.

7.4.2.3 Changes in bone mineralization density based on back-scattered electron imaging of bone-biopsies

Parameters derived from the back-scattered electron imaging of the bone biopsies include the spectral calcium mean, peak, width, low, and high. These spectral calcium parameters will be analyzed separately using repeated measures mixed models with the spectral calcium parameter as the dependent variable, the baseline value of the biopsy endpoint and study cohort as covariates, biopsy time (baseline, 1 year, 2 year, and 4 year) as the repeated measure, and subject as the random variable. Because there are only a few subjects with the 4 year biopsy, the 2 and 4 year biopsies may be collapsed into one biopsy group for analysis purposes if the 2 and 4 year biopsies appear to have similar effect sizes and variances. If the 2- and 4-year biopsies are qualitatively different then the 4-year biopsy endpoints may be dropped from the analysis due to their small sample sizes. Pairwise contrasts will be performed within the repeated measures analyses to compare the effects of the biopsy times on the bone biopsy endpoints.

Since these spectral calcium parameters are secondary endpoints, these analyses are considered more exploratory and thus no adjustments will be made for performing multiple secondary analyses. However, post hoc pairwise comparisons within each repeated measures analysis will be controlled for multiple comparisons using Fisher's protected LSD followed by Bonferroni correction if the overall effect is not significant.

Results will be summarized in a table. The effects of hPTH treatment on the spectral calcium endpoint will be illustrated in figures of the mean ± se (or geometric means with 95% confidence limits) over biopsy time.

7.4.2.4 Repeated measures analyses of the non-biopsy secondary endpoints

The secondary non-biopsy secondary endpoints are listed in section 7.2.2.

Unlike the biopsy endpoints, the secondary non-biopsy secondary endpoints had measurements at baseline and then every 6 months over the 5 years of the study as compared to biopsies at baseline, 1, 2, and 4 years of hPTH treatment. As a complication, subjects were on hPTH therapy for various lengths of time due to study withdrawal and early study termination. Thus, the effects of study month are not the same for each subject with some subjects on hPTH therapy and some

subjects off hPTH therapy for the later study months. Thus, the 6-month time-points will be reduced to the following experimental time-points: baseline visit, 6-month study visit, end of hPTH therapy, and post-hPTH follow-up visit.

The effect of hPTH therapy over the experimental time-points (baseline, 6-month study visit, last hPTH treatment, and post-hPTH follow-up) on each of the non-biopsy endpoint parameters will be analyzed using repeated measures mixed models with the non-biopsy endpoint as the dependent variable, the baseline value of the non-biopsy endpoint, and study cohort as covariates, the experimental time-point as the repeated measure, and subject as the random factor. If dose is found to improve model fits in the bone-biopsy repeated measures analyses (section 7.4.2.1) then the effect of dose will be added as a covariate to these secondary repeated measures. Pairwise post hoc comparisons will be made to test for endpoints differences among the experimental time-points (baseline, 6-month study visit, last hPTH treatment, and post-hPTH follow-up). The significance of these post hoc pairwise comparisons will be corrected for multiple comparisons using Fisher's protected LSD. When the repeated measures overall effects of study time-point are not significant, Bonferroni corrections will be used to adjust the pairwise contrasts for muiltiplicity.

Residual analysis will be used to confirm that repeated measures model assumptions are reasonable. Log-transformations of the bone biopsy endpoints will be made if indicated by the residual analysis. The repeated measures will be fit using both a compound symmetry and an unstructured covariance structure. The better covariance structure will be selected as the model with the better Schwarz- Bayesian criterion.

7.4.2.5 Summary of the effects of hPTH weaning on serum calcium, phosphorus, calcitriol, and biomarkers of bone turnover.

The effects of weaning subjects off hPTH will be summarized descriptively by the study PI.

Mixed models repeated measures analysis will test treatment effects on 10 outcome measures: serum calcium, serum phosphorus, 3 bone turnover markers (Osteocalcin, n-Telopeptide, and Alkaline Phosphatase), and 5 DEXA Bone Mass Density (BMD) parameters. The DEXA bone mass density measures included: AP spine BMD, femoral neck BMD, total hip BMD, Forearm BMD, and whole body BMD. Treatment effects will be summarized at three study time-points: Baseline (immediately at start of hPTH treatment), Treatment (immediately prior to Weaning, i.e. end of hPTH treatment), and Follow-up. The repeated measures analyses will be performed using each of these 10 outcome measures as the dependent variables, with random effects for subject,

and repeated fixed effects for 3 study time-points within a subject These outcome measures will be log-transformed if necessary to normalize the data. Two covariance structures will be tested (compound symmetry and unstructured) and the covariance structure with the smallest Bayesian Information Criterion (BIC) and the best residual distributional properties will be used. Pairwise post hoc contrasts will be made to compare the effects of treatment at the study time-points. These post hoc pairwise contrasts will be corrected for multiple comparisons using Fisher's protected LSD will Bonferroni corrections when the overall effect of time is not significant.

Rho will provide figures with panel columns for the subject and the panel rows for the time course (baseline, during hPTH, through the start of weaning to the post-hPTH follow-up) of oral elemental calcium and calcitriol dosing, plasma calcium, and PTH dose.

7.4.2.6 Summary of hPTH therapy on nephrocalcinosis and nephrolithiasis by ultra sound and CT

The rate of new, stable, and progressing nephrocalcinosis and nephrolithiasis (NC/NL) in study subjects will be summarized.

7.4.3 Other Efficacy Analyses

If there is a high study withdrawal rate before the second biopsy for reasons other than the final termination of the study then patterns associated with subject withdrawal will be analyzed with respect the primary bone biopsy endpoints. If the patterns associated with early withdrawal suggest a possible source of bias, then a sensitivity analysis on the primary efficacy analyses using multiple imputation (Proc MI in SAS) will be employed.

The tertiary outcomes include changes in blood chemistries, FGF23, renal mineral handling, and PTH sensitivity will be analyzed using repeated measures if the outcome is continuous or using contingency tables for categorical outcomes. Results will be summarized in tables. Figures will be provided upon request.

8. SAFETY EVALUATION

Safety evaluation will include all tables and listings previously provided for the DSMB. Additional safety tables and listing will be provided if requested by the study PI.

9. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

The study was discontinued early, due to pharmacy issues. Upon termination of new enrollment in June of 2015, subjects began to be slowly weaned off of hPTH. Of the 32 planned, newly enrolled subjects, only 19 were actually enrolled and treated and of these, 8 subjects provided their on-treatment biopsy. This early termination provides less power to detect significant differences in endpoints. We will evaluate the possibility of combining the 2- and 4- year biopsy groups to address this issue (see section 7.4.1 for details).

The primary bone biopsy endpoints have changed. The original primary endpoints included: 1) mineralized perimeter; 2) bone formation rate; 3) cortical width; 4) cortical area; 5) osteoid width; 6) osteoid perimeter; and 7) mineral apposition rate. These primary bone biopsy endpoints have been replaced with the eight primary endpoints listed in section 7.2.1. In the analysis of the pilot study of the first 5 patients as well as other relevant pilot studies, we learned that these are the more informative indices.

The primary and secondary analyses will be performed using repeated measures mixed models rather than the paired t-tests, ANOVA, and ANCOVA analyses as stated in the protocol.

Although the protocol specifies imputation analyses for all secondary endpoints collected every 6 months over the 5-year study period, for purposes of efficiency the sensitivity analyses using multiple imputation (Proc MI in SAS) of missing values will be initially limited to the primary efficacy bone biopsy endpoints. After reviewing patterns of missing-ness in the secondary endpoints, additional sensitivity analyses involving multiple imputations may be performed at the request of the PI.

10. LIST OF PLANNED TABLES

Subject listings associated with the tables below will be provided. Experimental time refers to the baseline, last hPTH treatment, and post-hPTH follow-up visits. Additional tables (eg, those based on the results of sensitivity analysis) will be provided. Other displays, as requested by the PI may be provided as well.

Table Type	**Table**
Disposition	Summary of Subject Disposition
Demographics	Summary of Study Enrollment by Demographic Characteristics
hPTH Therapy	Summary of the Duration of hPTH Therapy
Primary Efficacy	Summary Statistics of Primary Bone Biopsy Endpoints by Biopsy Year. (Separate tables for Cohorts 2, 3, and Cohort 2 combined with Cohort 3)
	Repeated Measures Analysis of Primary Efficacy Analysis (Separate tables for Cohorts 2, 3, and Cohort 2 combined with Cohort 3)
Secondary Efficacy	Summary of Bone Mineralization Density Assessed by Back-Scattered Electron Imaging by Years of hPTH therapy
	Summary of Biochemical Markers of Bone Metabolism by Experimental Time Including the Statistical Significance of Changes.
	Summary of Blood and Urine Chemistries by Experimental Time Including the Statistical Significance of Changes.
	Summary of Bone Mineralization Density Assessed by DXA and Quantitative CT by Experimental Time Including the Statistical Significance of Changes.
	Summary of Nephrocalcinosis and Nephrolithiasis by Time on Study Drug
	Summary of Fatigue Symptom Inventory and 6-Minute Walk Test by Experimental Time Including the Statistical Significance of Changes.
	Summary of SF-36 Health Survey by Experimental Time Including the Statistical Significance of Changes.
Adverse Events *(as provided to DSMB)*	Summary of Adverse Events Occurring While on hPTH 1-34 or After Withdrawal from hPTH 1-34
	Summary of Adverse Events Occurring on or after hPTH 1-34
	Summary of Adverse Events Occurring While on Conventional Care
	Summary of Adverse Events for Subjects on Conventional Care
	Summary of Adverse Events Occurring While on hPTH 1-34 or After Withdrawal from hPTH 1-34: Current PI
	Summary of Adverse Events Occurring While on hPTH 1-34 or After Withdrawal from hPTH 1-34: Prior to Current PI
	Summary of Adverse Events Occurring While on Conventional Care: Current PI
	Summary of Adverse Events Occurring While on Conventional Care: Prior to Current PI

	Summary of Adverse Events Occurring While on hPTH 1-34 or After Withdrawal from hPTH 1-34; Related (Unlikely, Possible, Probable, or Definite) to hPTH 1-34
	Summary of Adverse Events Occurring While on hPTH 1-34 or After Withdrawal from hPTH 1-34
	Summary of Adverse Events Occurring on or after hPTH 1-34
	Summary of Adverse Events Occurring While on Conventional Care
	Summary of Adverse Events for Subjects on Conventional Care
	Summary of Adverse Events Occurring While on hPTH 1-34 or After Withdrawal from hPTH 1-34: Current PI
	Summary of Adverse Events Occurring While on hPTH 1-34 or After Withdrawal from hPTH 1-34: Prior to Current PI
	Summary of Adverse Events Occurring While on Conventional Care: Current PI
	Summary of Adverse Events Occurring While on Conventional Care: Prior to Current PI
	Summary of Adverse Events Occurring While on Conventional Care: Events During the Reporting Period
	Summary of Adverse Events Occurring While on hPTH 1-34 or After Withdrawal from hPTH 1-34: Current PI
	Summary of Adverse Events Occurring While on hPTH 1-34 or After Withdrawal from hPTH 1-34: Prior to Current PI
	Summary of Adverse Events Occurring While on Conventional Care: Current PI
	Summary of Adverse Events Occurring While on Conventional Care: Prior to Current PI
	Summary of Exposure to hPTH at Time of First On-Treatment Event within a Subject and SOC/Preferred Term Includes Only Events Occurring for ≥ 3 Subjects Within a Category
Protocol Deviations *(as provided to DSMB)*	Summary of Protocol Deviations