

**STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES**

NDA #: 21-318

Drug: Forteo (teriparatide)¹

Sponsor: Eli Lilly and Company

Indication: Treatment of osteoporosis in postmenopausal women and men

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¹ Teriparatide is also referred to as LY333334 in documents presented by the sponsor. In this review, the drug name will be abbreviated by PTH.

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Keywords: clinical studies, NDA review, endpoint analysis/LOCF, post-hoc analyses/prospective analyses

Introduction

The sponsor has presented the results of four Phase 3 clinical trials (Table 1) to demonstrate the efficacy and safety of teriparatide (PTH) for the treatment of osteoporosis in men and women. Two doses of PTH were studied (20 Fg and 40 Fg) but only the 20 Fg dose is proposed for marketing. The 20 Fg dose of PTH is studied in Trials B3D-MC-GHAC and B3D-MC-GHAJ; the other two studies (B3D-MC-GHAF and B3D-MC-GHAH) were of the 40 Fg dose only. Therefore, the focus of this review is Trials B3D-MC-GHAC and B3D-MC-GHAJ.

Table 1. Brief Summary of Double-Blind, Randomized, Parallel, Controlled Clinical Trials

Study Number (# of sites)	Population	Treatment Arms (Rand. N)	Duration of Treatment	Primary Endpoint
B3D-MC-GHAC (99 USA)	Females W/vert. frac. \$5 yrs PMP	PTH 20 (541) PTH 40 (552) PLA (544)	16-23 months (3 yrs planned)	New vertebral fractures
B3D-MC-GHAJ (37 USA)	Males Low BMD	PTH 20 (151) PTH 40 (139) PLA (147)	8-14 months (2 yrs planned)	Vertebral BMD
B3D-MC-GHAF (11 USA)	Females Low BMD \$5 yrs PMP	PTH 40+HRT (122) PLA+HRT (125) About 50% on HRT pre- study	12-16 months (2 yrs planned)	Vertebral BMD
B3D-MC-GHAH (10 USA, CA. Europe, Mex)	Females Low BMD \$5 yrs PMP	PTH 40 (73) Alendronate 10mg (73)	13-17 months (2 yrs planned)	Vertebral BMD

PMP=postmenopausal

PTH=teriparatide Fg sc injection per day PLA=placebo

HRT=hormone replacement therapy

Due to the limited time available to prepare this document for an advisory committee meeting scheduled for July 27, 2001, Studies GHAF and GHAH will be reviewed in a separate document.

On December 8, 1998 all ongoing clinical trials of PTH were stopped due to the finding of osteosarcoma in a rodent carcinogenicity study. Therefore in all four trials, treatment was discontinued early. In the review of each trial, drug exposure is summarized and efficacy is assessed in the context of the curtailed treatment.

Following the closure of each trial, patients could opt to continue in an observational safety study, Study GHBJ. Due to the time constraints on this review, this trial has not been reviewed in detail here. This reviewer has the following preliminary comments:

- The primary objective of GHBJ was to collect additional safety data
- The secondary objectives were to assess BMD at the lumbar spine and hip
- A subset of the total number of randomized patients were followed
- Several post-hoc analyses of variables not defined in the protocol were performed by the sponsor
- The impact of the use of osteoporosis drugs in a subset of patients on interpretation of the efficacy results is not clear to this reviewer
- X-rays were performed if indicated by clinical symptoms; no x-rays were scheduled as part of the trial protocol

This reviewer believes that conclusions regarding efficacy endpoints (especially vertebral fractures

and back pain) are most likely unsubstantiated by the data.

Reviewer's Methods

Data were submitted with this NDA; however, the database was not well-documented and not organized in a format readily usable by this reviewer. The sponsor did not follow several of the recommendations offered in the guidance for submission of electronic data and did not confer with an FDA statistician before submitting the datasets. Therefore it was necessary to request new datasets from the sponsor. The new datasets provided by the sponsor were used to compute the results presented here.

All graphs and tables in this review were created by this reviewer. Unless otherwise noted, all results were computed by this reviewer. Results that differ from the sponsor's are noted.

The statistical methods used by the sponsor and by this reviewer are included with the results presented.

For both studies, the sponsor defined two substudies by a prespecified algorithm that assigned centers to a substudy based largely on size. The sponsor presented the primary efficacy results for both substudies and for the study overall. Generally the results for the substudies match the results closely for the overall study so only the overall results are presented here.

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Study GHAC (12/96 to 12/98)

Design

Study GHAC is a Phase III, multicenter, double-blind, placebo-controlled, randomized study designed to show that teriparatide (PTH) reduces the incidence of new vertebral fractures (primary endpoint) in postmenopausal women.

The trial was planned to consist of the following four phases:

1. Ca (~1000 mg/day) plus vitamin D (400-1200IU/day) for 2 weeks to 6 months
2. Ca and vitamin D with placebo injection for 2 weeks
3. Ca and vitamin D with randomized treatment injection for 3 years
4. Optional extension of the third phase by about 2 years

The trial was stopped by the sponsor after about 23 months with median time on drug of about 19 months. No patients completed the third phase.

The entry criteria for this trial included the following:

- Postmenopausal women 30-85 years old
- \$1 moderate or \$2 mild atraumatic vertebral fractures
- \$7 evaluable non-fractured vertebrae

In the protocol, the primary and secondary objectives are listed as follows.

Primary objective:

- Show reduction in **proportion of patients with new vertebral fractures** for PTH compared to placebo (note that the protocol states that the combined PTH groups (20 Fg and 40 Fg) and each group separately will be compared to placebo)

Secondary objectives:

- Show increase in **BMD** (lumbar spine and hip for all patients; total body and radius for a subset of patients)
- Show reduction in **rate of new vertebral fractures** (total number of new fractures divided by the total time on study)
- Show reduction in **proportion of patients with new non-vertebral fractures and proportion of patients with new vertebral plus non-vertebral fractures** (in the description of the analysis, it is stated that this variable will be assessed as a rate not as a proportion)
- Show lack of reduction in **height**
- Show effects on histomorphometric measures and **biochemical markers** for subset of patients
- Assess population pharmacokinetics
- Perform a cost-effectiveness analysis
- Perform a quality of life assessment

This reviewer will only focus on the primary objective and the first five secondary objectives listed above.

In addition to the above endpoints, the sponsor analyzed the following endpoints that were NOT pre-specified in the protocol:

- Multiple new vertebral fractures
- Moderate and severe new vertebral fractures
- Number needed to treat to prevent a vertebral fracture

The results for the first 2 endpoints are included in the proposed labeling and reviewed here.

The schedule for assessment of the primary and secondary endpoints is shown below in

Table 2. X-rays were planned for baseline, Month 24 and study endpoint. Only 6 patients reached Month 24 so for most patients x-rays were performed before Month 24. At the time of study closure, all patients still on study were scheduled for a study close-out visit. Assessments were scheduled also for Month 36 but no patients reached Month 36 due to cessation of the trial.

Table 2. Schedule for assessing height, fractures and BMD

MONTH	0	3	6	12	18	24	End
Height	U			U		U	U
Lat. thor. + lumbar spinal x-ray	U					U	U
PA lumbar spine BMD	U	(subset U)	(subset U)	U	U	U	U
Femoral neck BMD	U			U		U	U
Body, hip+ radial BMD (subset of pts.)	U			U		U	U
Biochemical markers (subset of pts.)	U	U	U	U		U	U

Patient Disposition

According to the protocol, the sponsor planned to enroll 492 patients in each treatment group. In actuality, about 50 more patients were enrolled in each group (there is no explanation for this in the NDA). (See [Appendix 1](#) for a graph of number of patients by last month on therapy for more detail.) About 90% of the patients completed 9 months on the study; about 74% completed 18 months (Table 3). At study termination, about 80% of the patients were still on study; the median time on study for those patients was 19 months (minimum of 5 months and maximum of 29 months).

Table 3. Patients by month of drug exposure¹

	PLA	PTH 20	PTH 40
Planned to randomize	492	492	492
Actually randomized	544	541	552
Month 3	526 (97%)	517 (96%)	517 (94%)
Month 6	500 (92%)	492 (91%)	490 (89%)
Month 9	487 (90%)	478 (88%)	472 (86%)
Month 12	478 (88%)	461 (85%)	457 (83%)
Month 15	463 (85%)	452 (84%)	434 (79%)
Month 18	404 (74%)	350 (65%)	335 (61%)
Month 21	110 (20%)	101 (19%)	112 (20%)
Month 24	2 (0.4%)	1 (0.2%)	1 (0.2%)
On study at study termination	447 (82%)	433 (80%)	415 (75%)
Assessed for spinal fractures	448 (82%)	444 (82%)	434 (79%)

At study end, about 94% of the patients still on study had an x-ray. Of the patients who discontinued treatment early; about a had an x-ray upon exit from the study. Overall about 80% of the patients randomized had an x-ray at baseline and endpoint. The median time on study for the patients assessed for spinal fractures was 19 months (minimum of <1 month, maximum of 25

1 The data in this table was created using the last month variable provided in the sponsor's dataset.

months).

The most common reasons for early discontinuation of treatment in all treatment groups were ADE and patient decision (Table 4). About twice as many ADE's were observed in the PTH40 group (11%) as the placebo group (6%). About half of the total ADE's occurred during the first six months of therapy.

Table 4. Study GHAC Reasons for discontinuation of treatment

	PLA (n=544)	PTH 20 (n=541)	PTH 40 (n=552)
ADE	32 (6%)	35 (7%)	59 (11%)
Lack of Efficacy	5 (1%)	0 (0%)	2 (0.4%)
Lost to follow-up	5 (1%)	6 (1%)	8 (1.4%)
Patient decision	32 (6%)	45 (8%)	40 (7%)
Physician decision	2 (0.4%)	2 (0.4%)	5 (0.9%)
Protocol violation	12 (2%)	11 (2%)	8 (1.5%)
Sign. lab value	4 (0.7%)	2 (0.4%)	8 (1.4%)
Death	4 (0.7%)	6 (1.1%)	6 (1.1%)
Other	0 (0%)	0 (0%)	1 (0.2%)
Study ended early	447 (82%)	433 (80%)	415 (75%)

Baseline Demographics

The treatment groups were well-balanced regarding baseline demographics (Table 5). The majority of the patients were 65 years or older (~75%), Caucasian (99%), non-smokers (83%) and naïve to osteoporosis treatment (85%).

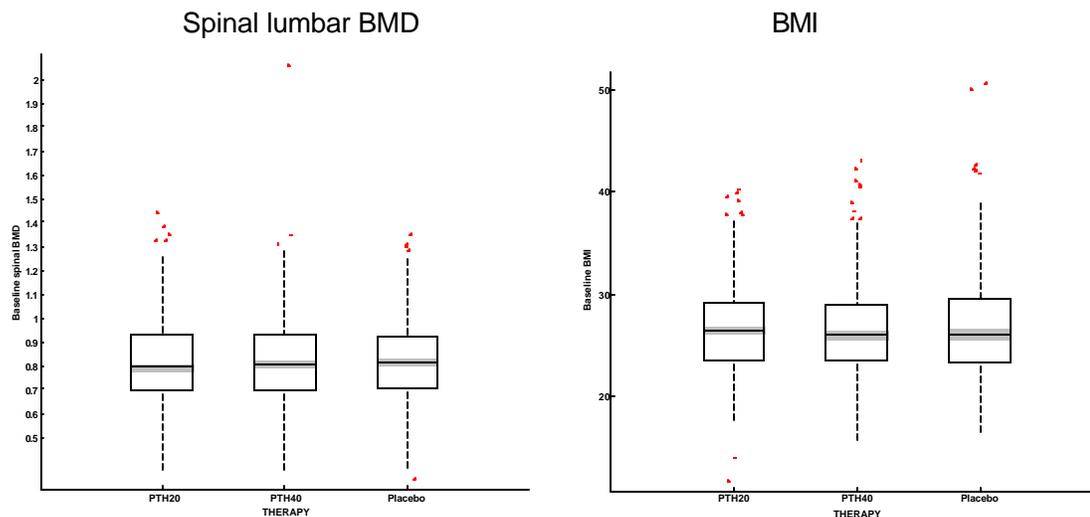
Table 5. Study GHAC Baseline Demographics (Sponsor's Results)

	PLA (n=544)	PTH 20 (n=541)	PTH 40 (n=552)
Age			
Mean (SD)	69 (7)	70 (7)	70 (7)
Range	42-85	45-85	45-85
\$65	70%	75%	77%
BMI Mean (SD)	26 (5)	27 (4)	27 (4)
Caucasian	99%	99%	98%
No Alcohol use	64%	63%	62%
Non-smoker	81%	84%	84%
Years Postmenopausal	21 (9)	21 (9)	22 (8)
No Previous Osteo. Drug Treatment	85%	85%	87%
# vertebral fractures			
Mean (SD)	2.3 (1.8)	2.3 (1.8)	2.3 (1.8)
Median	2	2	2
Range	0-10	0-10	0-9
Spinal BMD Mean (SD)	0.82 (0.2)	0.82 (0.2)	0.82 (0.2)
PTH Mean (SD)	3.7 (1.2)	3.6 (1.2)	3.6 (1.2)

Bone turnover markers (Median)	(n=171)	(n=170)	(n=171)
BSAP	12	11	11
P1CP	116	110	113
NTX	42	45	41
DPD	6.9	6.9	6.5

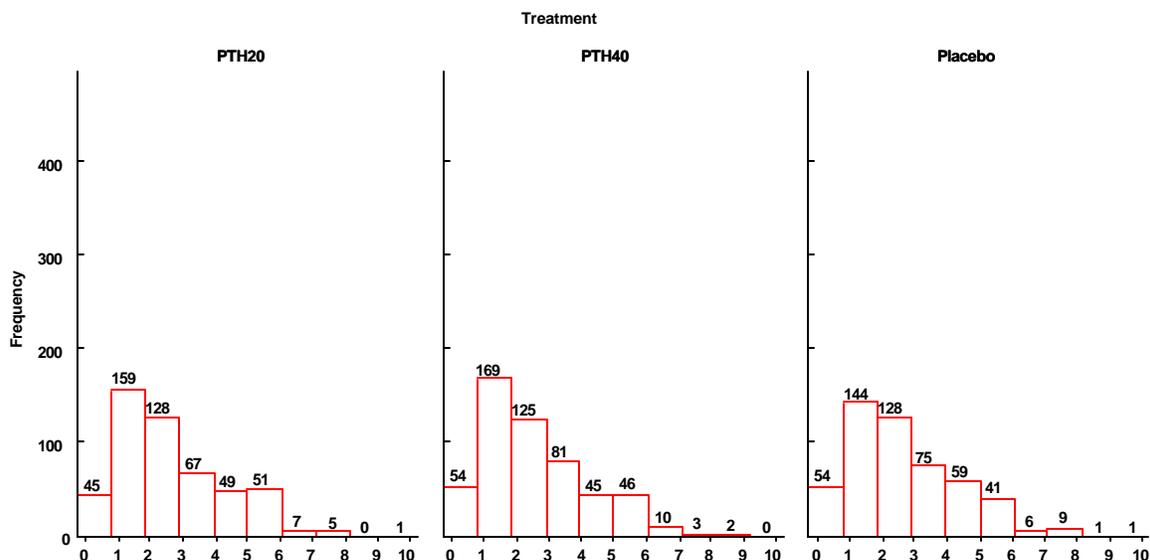
Number of vertebral fractures, spinal lumbar BMD and BMI at baseline are strong prognostics variables so this reviewer looked more carefully at the distribution of these variables. The boxplots (Figure 1) of spinal BMD and BMI show that the distributions for the treatment groups are essentially the same.

Figure 1. Boxplots for baseline spinal BMD and BMI



Histograms (Figure 2) of the number of vertebral fractures at baseline by treatment group show that the majority of patients in all treatment groups had one or two fractures at baseline. The groups are well-balanced with regard to number of vertebral fractures at baseline. Note that about 9% of the patients had no fractures at baseline and therefore did not meet entry criteria.

Figure 2. Histograms of baseline vertebral fractures



The sponsor also presented baseline demographics for the subset of patients (about 80% of the patients) included in the primary efficacy analysis. Those demographics were similar to those shown in Table 5 above.

Efficacy Results

Primary Efficacy Measure: Proportion of Patients with New Vertebral Fractures

New vertebral fractures were assessed for the randomized patients who had both a baseline x-ray and an endpoint x-ray (about 80% of the randomized patients). More than twice as many placebo patients (14%) had new vertebral fractures than PTH20 (5%) or PTH40 (4%) patients with relative risk¹ (RR) of 0.35 and 0.31, respectively. The results for those patients are shown in Table 6 below. The treatment effect for each dose versus placebo is statistically significant with a p-value of .001 (Pearson's chi square test) for each comparison. No significant difference was seen between the two doses.

Table 6. Proportion of patients with new vertebral fractures

Placebo	PTH 20	PTH 40	PLA vs PTH20 RR (95% CI)	PLA vs PTH40 RR (95% CI)
14% (64/448)	5% (22/444)	4% (19/434)	0.35 (0.22, 0.55)*	0.31 (0.19, 0.50)*

The failure of the sponsor to obtain fracture data on about 1/5 of the patients can impact the interpretation of the results since the sample is not a true intent-to-treat sample. Given the strength of the evidence this reviewer did not think that a complex analysis such as a sensitivity analysis or an imputation procedure was warranted. This reviewer, though, does believe that some further examination of the data for the patients not included in the analysis is necessary to

1 In the labeling for actonel and fosamax, the odds ratio not the relative risk is used to obtain estimates of risk reduction. When the incidence of an event is small (as in the case of fracture studies), the odds ratio and relative risk do not differ appreciably.

establish the robustness of the sponsor's results.

Of the 311 patients missing both baseline and endpoint x-rays, 62 had at least one x-ray on therapy but not a baseline x-ray. Of those 62 patients, 52 patients had multiple x-rays on therapy an average of about 1 year apart. An examination of that data by this reviewer showed that 2 placebo, 1 PTH20 and 2 PTH40 had one or more new fractures on their last x-ray. The addition of this data to the data in Table 6 has no effect on the results.

This reviewer did an additional analysis which uses all the data and where one assumes that the patients without fracture data did not have a fracture. All patients, then, are included in the risk group (the denominator). The assumption of no new fractures in these additional patients is not unreasonable given the low incidence of fractures overall and the short exposure times. The relative risks from this analysis were 0.35 for placebo versus PTH20 (same as in Table 6) and 0.29 for placebo versus PTH40 (slightly lower than in Table 6). Including all patients in this way did not change the overall results.

The sponsor recruited approximately 50 more patients in each treatment group than originally planned without explanation. These patients were all randomized during the last month of the study. To check the robustness of the results, this reviewer analyzed the data excluding these additional patients. The relative risk for PTH20 versus placebo was 0.39 while the risk for PTH40 was 0.29; both results are consistent with the results above.

Secondary Efficacy Measures

BMD

BMD of the lumbar spine, total hip, femoral neck¹, whole body ultradistal radius and midshaft radius were measured according to the schedule shown in Table 2. All patients were scheduled for BMD measurements at the lumbar spine and femoral neck; a subset of patients were chosen to have BMD measured for the other 4 sites. Also a subset of patients had lumbar spine measured at Months 3 and 6. Since the study was stopped abruptly, most of the randomized patients did not have BMD measurements at Month 24; about half of the patients had measurements at Month 21. Data for Months 12 and 21 and at endpoint (last-observation-carried-forward, LOCF²) is presented in the table on the following page. Highly significant increases in BMD for both PTH groups over placebo are seen for the lumbar spine, total hip and femoral neck with significant dose response effects seen for each site.

The small differences at endpoint for whole body BMD are significant for each PTH dose versus placebo. For the radius, the BMD results are unfavorable for PTH with no differences seen for the ultradistal site and significant decreases seen for the midshaft site compared to placebo.

A correlation analysis showed strong positive correlations among BMD changes in lumbar spine, hip and femoral neck and with BMD change for whole body for the 40 dose only. Changes at the 2 radial sites were also highly correlated.

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1 Femoral neck BMD was not a pre-specified secondary endpoint according to the protocol. It is included here due to its relationship to total hip BMD (a pre-specified endpoint).

2 LOCF data contains data off treatment collected at the closeout visit.

Table 7 Study GHAC BMD results (Mean (SD)) by site

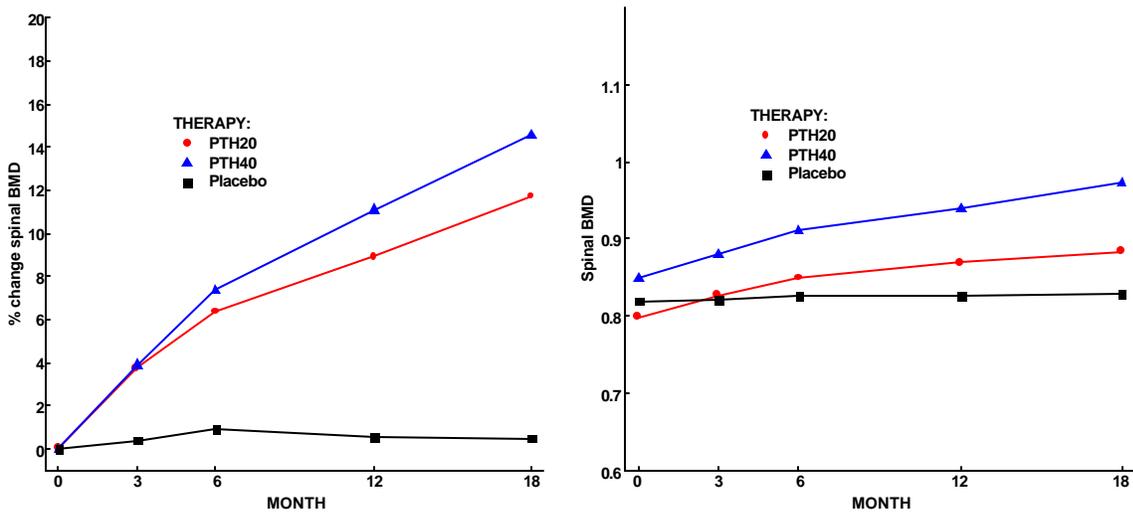
	Placebo (n=544)	PTH 20 (n=541)	PTH 40 (n=552)	PLA vs. PTH20 p-value¹	PLA vs. PTH40 P-value¹
Lumbar spine					
Baseline	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)		
% change					
Month 12	+0.8% (4.9) (n=467)	+8.3% (6.1) (n=466)	+11.9% (6.8) (n=452)	.0001	.0001
Month 21	+1.4% (5.4) (n=250)	+10.2% (6.9) (n=239)	+14.7% (9.6) (n=228)	.0001	.0001
LOCF	+1.1% (5.5) (n=504)	+9.7% (7.4) (n=498)	+13.7% (9.7) (n=497)	.0001	.0001
Total hip					
Baseline	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)		
% change					
Month 12	-0.5% (3.8) (n=213)	+1.7% (4.5) (n=209)	+2.6% (4.1) (n=214)	.0001	.0001
Month 21	-1.1% (4.3) (n=111)	+2.7% (3.4) (n=104)	+3.7% (4.9) (n=106)	.0001	.0001
LOCF	-1.0% (4.2) (n=230)	+2.6% (4.9) (n=222)	+3.6% (5.4) (n=232)	.0001	.0001
Femoral neck					
Baseline	0.6 (0.1)	0.6 (0.1)	0.7 (0.1)		
% change					
Month 12	0% (4.5) (n=442)	+1.5% (4.8) (n=453)	+3.1% (5.6) (n=442)	.0001	.0001
Month 21	-0.9% (5.3) (n=237)	+2.8% (5.9) (n=241)	+5.6% (6.8) (n=225)	.0001	.0001
LOCF	-0.7% (5.4) (n=479)	+2.8% (5.7) (n=479)	+5.1% (6.7) (n=482)	.0001	.0001
Whole body					
Baseline	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)		
% change					
Month 12	-0.4% (3.2) (n=134)	-0.1% (2.6) (n=127)	+0.2% (2.9) (n=117)	.55	.06
Month 21	-0.7% (2.8) (n=66)	+0.1% (2.7) (n=71)	+1.6% (3.2) (n=61)	.16	.0001
LOCF	-0.5% (3.1) (n=140)	+0.6% (2.5) (n=134)	+1.5% (3.3) (n=131)	.008	.0001
Ultradistal radius					
Baseline	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)		
% change					
Month 12	-1.2% (6.9) (n=146)	-0.6% (6.2) (n=143)	+2% (11.8) (n=129)	.62	.14
Month 21	-0.7% (8.8) (n=81)	-1.6% (7.4) (n=84)	-0.9% (9.9) (n=72)	.48	.93
LOCF	-1.6% (8.3) (n=154)	-0.1% (7.2) (n=152)	-1.5% (8.4) (n=145)	.10	.76
Midshaft radius					
Baseline	0.6 (0.1)	0.6 (0.1)	0.6 (0.1)		
% change					
Month 12	-1.1% (2.7) (n=146)	-1.8% (3.4) (n=143)	-3.2% (4.2) (n=129)	.06	.0001

1 Results of analysis of covariance (ANCOVA) with baseline BMD as a covariate.

Month 21	-1.0% (2.9) (n=81)	-2.7% (4.5) (n=84)	-3.6% (5.1) (n=72)	.01	.0002
LOCF	-1.3% (3.3) (n=154)	-2.1% (4.2) (n=152)	-3.2% (4.5) (n=145)	.06	.0001

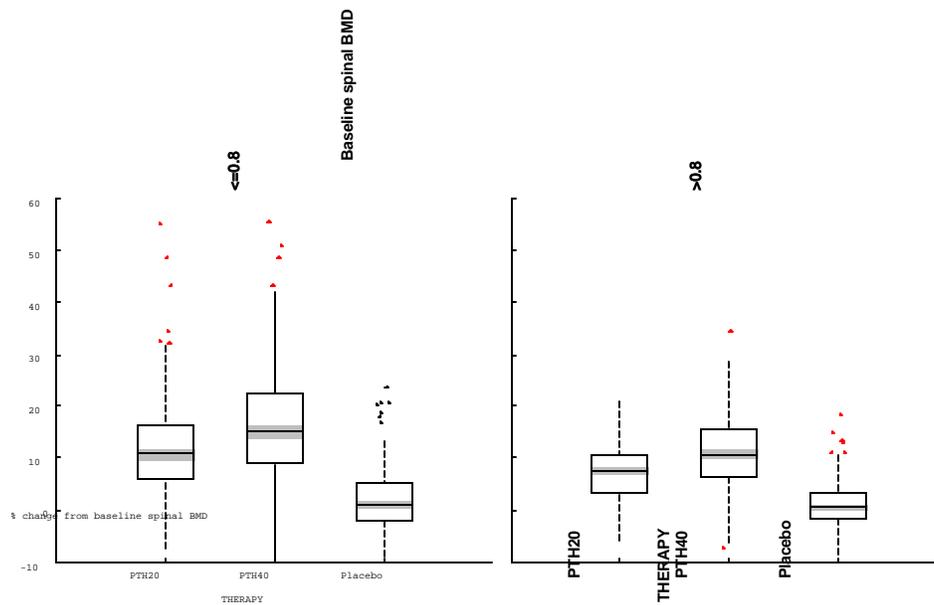
Figure 3 illustrates the % change from baseline (left figure) and the observed BMD (right figure) for lumbar spine for the subset of patients (about a of the patients) who had a BMD assessment at Months 3, 6, 12 and 18. An analysis of covariance with baseline as the covariate yielded significant differences for each dose versus placebo at each timepoint for both variables ($p < .0001$).

Figure 3 Study GHAC BMD % change from baseline and observed values month on study



Analyses by this reviewer showed a significant interaction between treatment and baseline BMD ($p = .0001$). A larger treatment effect was observed for PTH patients with low BMD at baseline; the boxplots below illustrate this point. A small differential effect was seen based on age with older patients generally showing a larger treatment effect (interaction $p = .06$).

Figure 4 Boxplots of spinal BMD % change from baseline (LOCF) by baseline BMD median



Rate of new vertebral fractures

The rate of new vertebral fractures was computed by the sponsor as the total number of fractures observed for a patient divided by the exposure time from randomization to the time of the final x-ray. The sponsor reported **mean** rates of 135.56 for placebo, 49.24 for PTH 20 and 30.30 for PTH 40 as the number of fractures per 1000 person years. This is an unusual way to report the rate in terms of 1000 person years. Essentially what the sponsor has done is computed the mean number of fractures that could be observed for a patient in a 1,000 year period. The method most often used is to count the number of fractures observed and divide that by the sum of exposure standardized to 1000 person years. Those computations are shown in Table 8.

Table 8 Rate of new vertebral fractures

	Placebo (n=448)	PTH 20 (n=444)	PTH 40 (n=434)
Total number of fractures	101	33	22
Total exposure in years	710.17 years	702.43 years	677.86 years
Fracture Rate per 1000 person years	142	46	31

A fracture rate implies that the time of fracture is known. That is clearly not the case here. X-rays were not performed until endpoint so fractures were only detected at the time a patient completed therapy. Alternatively, this reviewer examined the incidence of fractures by time of exposure to see if the results are consistent across these subgroups and to ascertain that early closure of the trial did not greatly impact interpretation of the overall results. The data in Table 9 shows a stronger treatment effect in PTH20 patients treated under 18 months compared to patients treated for more than 18 months; however, the confidence intervals overlap for these groups and are consistent with the overall results. (The results for PTH40 are the same for these subgroups.) This reviewer would conclude that the time of exposure does not play a role in interpretation of the results.

Table 9 Vertebral fracture rates by time on study

	Placebo	PTH 20	PTH 40	PLA vs PTH20 RR (95% CI)	PLA vs PTH40 RR (95% CI)
All Patients	14% (64/448)	5% (22/444)	4% (19/434)	0.35 (0.22, 0.55)*	0.31 (0.19, 0.50)*

Mos. on study #18 >18	15% (29/199) 14% (35/249)	3% (5/194) 7% (17/250)	5% (9/197) 4% (10/237)	0.18 (0.07, 0.45)* 0.48 (0.28, 0.84)*	0.31 (0.15, 0.65)* 0.30 (0.15, 0.59)*
Mos. on study #15 15-18 18-20 >20	21% (6/29) 14% (23/170) 14% (20/143) 14% (15/106)	4% (1/27) 2% (4/167) 6% (10/154) 7% (7/96)	5% (2/38) 4% (7/159) 7% (10/134) 0% (0/103)	0.18 (0.02, 1.39) 0.18 (0.06, 0.50)* 0.46 (0.23, 0.96)* 0.52 (0.22, 1.21)	0.25 (0.06, 1.17) 0.32 (0.14, 0.74)* 0.53 (0.26, 1.1) NA (zero cell)

Proportion of patients with new non-vertebral fractures

In the study report, the sponsor reported the results for both traumatic and non-traumatic non-vertebral fractures. According to the protocol, only analyses of non-traumatic non-vertebral fractures were planned¹; the same statistical methods proposed for vertebral fractures were planned for the analysis of non-vertebral fractures.

A total of 58 patients had non-traumatic (fragility) non-vertebral fractures on therapy (Table 10); 7 patients out of the 58 patients with non-vertebral fractures had two fractures (3 placebo, 1 PTH20 and 3 PTH40 patients).

Table 10 Study GHAC Percent (N) of patients with non-vertebral fragility fractures

	Placebo N=544	PTH 20 N=541	PTH 40 N=552
Non-vertebral	5.5% (30)	2.5% (14)	2.5% (14)
Non-vertebral site	1.3% (7)	0.4% (2)	0.5% (3)
Wrist	0.9% (5)	0.6% (3)	0.4% (2)
Ribs	0.7% (4)	0.2% (1)	0.7% (4)
Ankle/foot	0.4% (2)	0.4% (2)	0.4% (2)
Humerus	0.7% (4)	0.2% (1)	0.5% (3)
Hip	0.6% (3)	0% (0)	0% (0)
Pelvis	1.5% (8)	1.1% (6)	0.5% (3)
Other			

Each PTH dose (2.5%) had significantly fewer non-vertebral non-traumatic fractures than placebo (5.0%, $p < .02$, Pearson's chi square test) with nearly identical results:

Placebo Versus PTH20	RR 0.47 (0.25, 0.88)
Placebo Versus PTH40	RR 0.46 (0.25, 0.86)

The results by site are not individually convincing due to the small number of fractures observed and the lack of statistically significant differences at any site.

The sponsor also analyzed the time to a new non-vertebral fracture; this was not a pre-specified analysis. The results of a log rank test were borderline significant ($p = .042$), at best. Adjustments for secondary endpoints and post-hoc analyses would render this comparison non-significant.

The non-vertebral fracture results are supportive of the vertebral results (though this reviewer found no relationship between having a vertebral fracture and having a non-vertebral fracture) but are not convincing alone. Only 3 more fractures in the PTH groups would change the results to non-significant which speaks to the lack of strength of the results. Also any adjustments for secondary endpoints will render the results for this endpoint as non-significant. **The labeling should only contain a brief mention of the overall non-vertebral fracture results; the results do not warrant placing a figure of the by site results or a graph of the Kaplan-Meier estimates as proposed by the sponsor.**

Change in Height

A mean loss in height was seen for all three treatment groups; a comparison of each treatment group to placebo yielded varying results. An analysis of variance on change from baseline showed no treatment effect for either dose of PTH compared to placebo (Table 11,

¹ Section 3.9.1.2. states that vertebral and non-vertebral fractures due to automobile accidents or trauma more severe than a fall from standing height will be excluded from the analyses.

p>.20). A test for normality on the change from baseline was significant indicating that the data is not normally distributed (about 15% of the changes equaled zero). An analysis of the ranks of the change from baseline yielded a significant p-value for PTH20 versus placebo (p=.02) but not for PTH40 versus placebo (p=.72). This lack of consistent results for the two dose levels speaks to the lack of integrity of the height data and/or the spuriousness of the results.

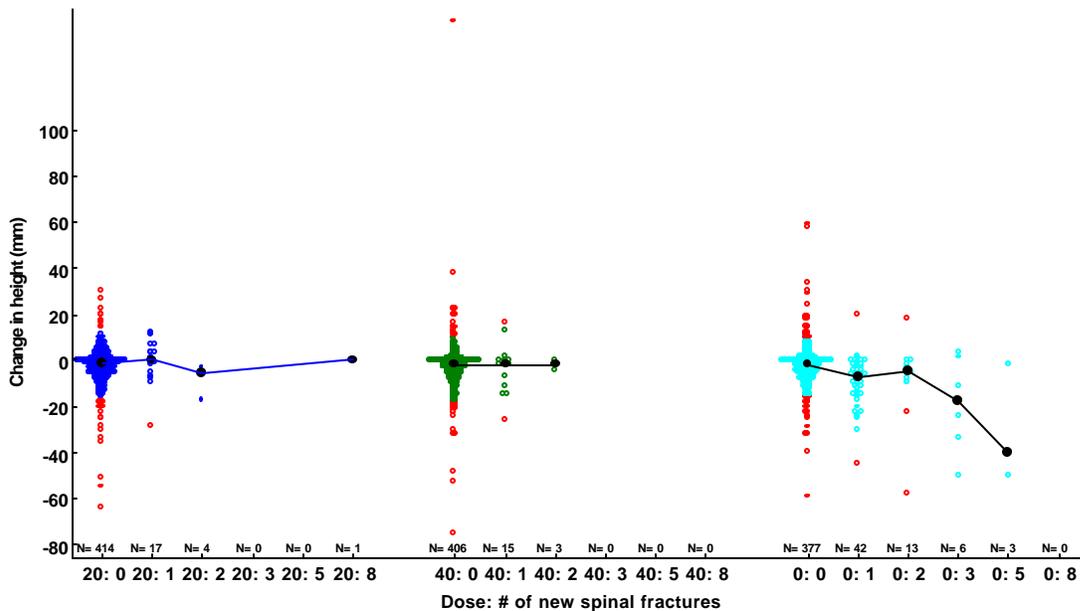
Table 11 Study GHAC Change in height

	Placebo	PTH 20	PTH 40
Baseline mm	1574 (63)	1569 (65)	1573 (68)
Change Mean mm	-3.6 (10.6)	-2.8 (8.7)	-3.2 (11.4)
Median	-2.0	-1.0	-2.0
P-value PTH vs PLA			
ANOVA on change		.22	.48
ANOVA on ranks		.02	.72

A plot of the data (Figure 5) shows that a number of patients (24%) had an increase in height which suggests substantial variability in the measurement tool. The small treatment difference of about 1mm seems irrelevant given the potential measurement error as well as its clinical significance.

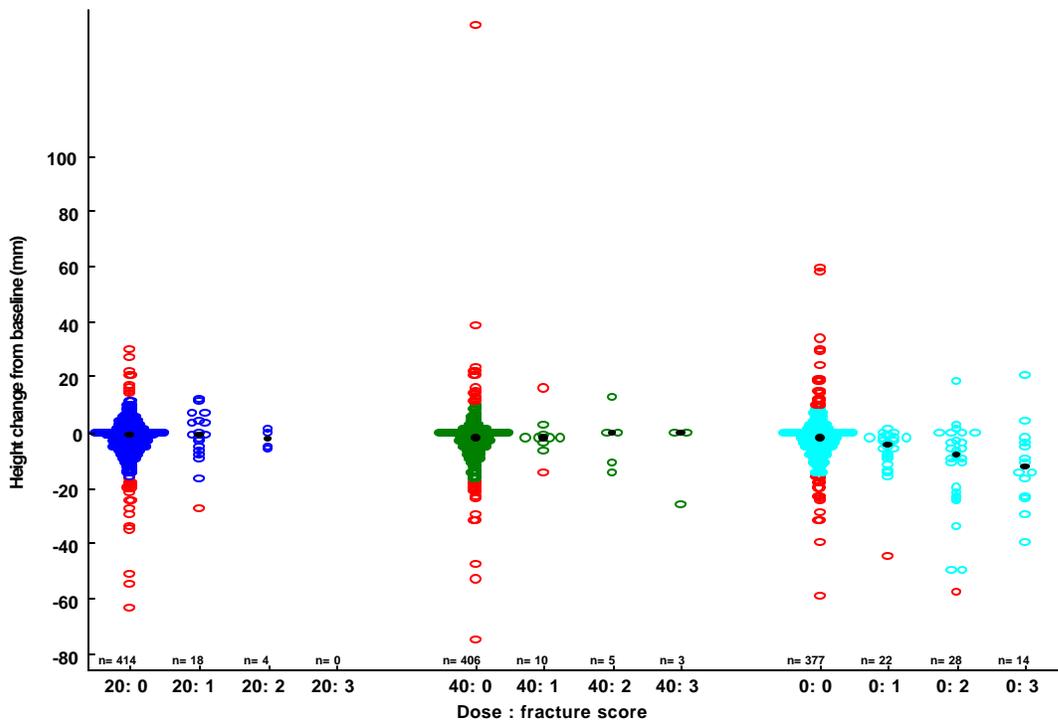
Figure 5 also illustrates the relationship between change in height and having a fracture. The plot of the medians for the placebo patients suggests a relationship between number of new fractures and change in height. However, a correlation analysis of the placebo data showed a very low correlation between presence of a new fracture and change in height with only 6% of the variation in height explained by fractures (analyses of the PTH data yielded very small correlation coefficients of less than .05). This data further illustrates the lack of beneficial effect of PTH on height.

Figure 5 Change in height (mm) by dose and number of new spinal fractures
(Each point on the graph represents a single patient)



In addition, this reviewer looked at the relationship of severity of fracture (Genant score) and change in height (Figure 6). In the placebo group, there appears to be a greater height loss with greater severity of fracture. Again though, the correlation between severity and height loss is weak.

Figure 6 Change in height (mm) by dose and maximum Genant score
(Each point on the graph represents a single patient)

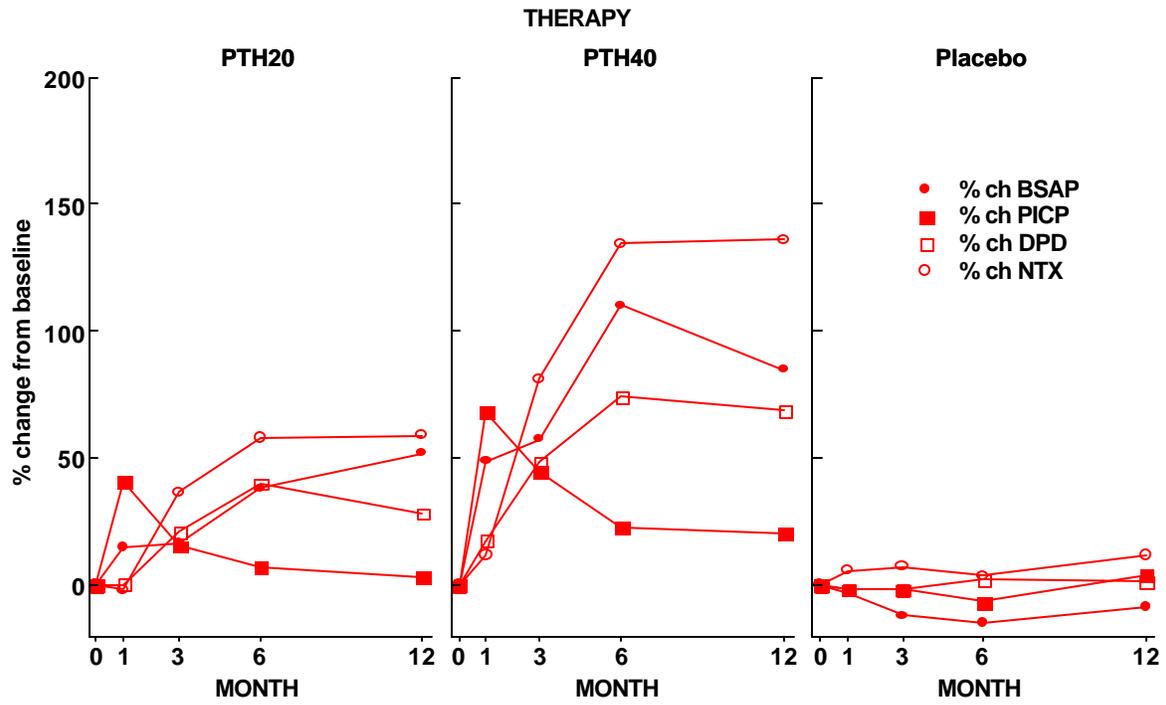


Biochemical Markers

Two markers of bone formation (serum bone-specific alkaline phosphatase (BSAP) and procollagen 1 carboxy-terminal propeptide (P1CP)) and two markers of bone resorption (urinary deoxypyridine (DPD) and urinary N-telopeptide (NTX)) were measured on about a of the patients. The baseline values for these markers are included in [Table 5](#).

In Figure 7 on the following page, all four markers are plotted in a single graph for each treatment group; solid symbols represent measures of bone formation and open symbols represent measures of bone resorption. In the PTH groups, all markers increase during the first month; these increases are statistically significantly greater than placebo for BSAP and P1CP. P1CP subsequently decreases with no differences from placebo seen by Month 12. Measures of resorption (DPD and NTX) continue to increase until about Month 6 where the response appears to stabilize; changes in the resorption markers are statistically significantly greater than placebo at Months 3 (for NTX only), 6 and 12 (P<.001).

Figure 7 % change from baseline (medians) in biochemical markers for each treatment group



Additional efficacy measures not defined in the protocol

The following three variables not defined in the protocol were analyzed by the sponsor.

- Multiple new vertebral fractures
- Moderate and severe new vertebral fractures
- Number needed to treat to prevent a new vertebral fracture
- Back pain

The first three variables are directly related to the primary efficacy variable and therefore may offer further insight into the efficacy of PTH. However, since these variables were not prespecified, the analyses should be considered exploratory. Post-hoc selection of variables introduces bias since variables may be chosen based on their ability to produce positive results. The results would need to be observed in a second study in order to be considered confirmatory. Nevertheless the results of these variables are reviewed here with an emphasis on the first two variables both of which are included in the sponsor's proposed labeling.

Back pain was collected as a safety endpoint but was reported by the sponsor as a efficacy endpoint with claims that PTH reduces back pain. The following is the only reference to back pain in the protocol:

“Since incident vertebral fractures are assessed for the primary efficacy criteria, they should not be reported as clinical adverse events if detected on scheduled or unscheduled x-ray films. The clinical syndrome of acute back pain accompanied by a new vertebral deformity at the location of the pain should be reported as a clinical adverse event of 'back pain'.”

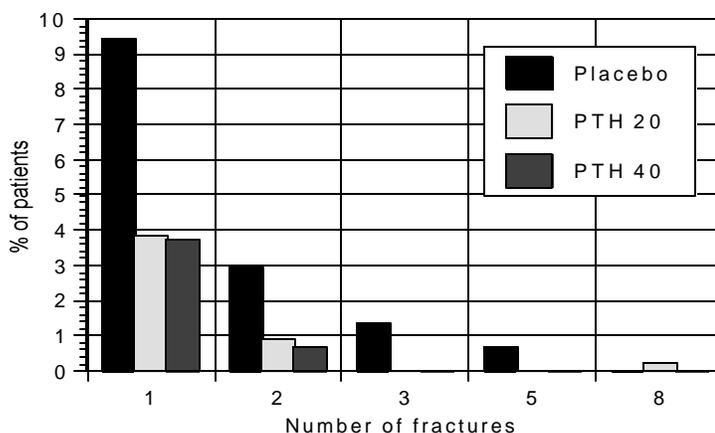
So investigators were alerted to the reporting of back pain in the presence of a vertebral fracture. The fact that the sponsor found an association between fractures and back pain may be related in some part to how this data was collected. Regardless, it is clear that back pain was not intended to be assessed as an efficacy endpoint and therefore no a priori hypotheses were defined to measure the effect of PTH on back pain. Data about back pain may be included with the reporting of ADE's but should not be presented as an efficacy endpoint. Back pain is not reviewed here as a efficacy endpoint.

This reviewer requested data from the sponsor on worsening fractures. The protocol stated that pre-existing fractures would be rated at baseline and endpoint (see the top of page 20 for an excerpt from the protocol describing this) but not analyzed. Since the proportion of patients with new and worsening fractures has been analyzed for other osteoporosis drugs and was available for this application, this reviewer requested results for this endpoint and they are presented here.

Multiple new vertebral fractures

A small number of patients (~5%) in each treatment group had more than one vertebral fracture at the end of the study (Figure 8 and Table 12).

Figure 8 % of patients by number of new vertebral fractures and by treatment group



Statistically significantly more placebo patients (5%) had multiple fractures than PTH patients (1%) (Table 12). The relative risk for multiple fractures was 0.23 indicating a risk reduction of about 77% for PTH20 compared to placebo.

Table 12 Study GHAC Patients with multiple fractures

	Placebo	PTH 20	PTH 40	PLA vs PTH20 RR (95% CI)	PLA vs PTH40 RR (95% CI)
All Patients	5% (22/448)	1% (5/444)	1% (3/434)	0.23 (0.09, 0.60)*	0.14 (0.04, 0.47)*
By Baseline Fractures					
0-1	1% (2/182)	0% (0/187)	0% (0/184)	Zero cell	Zero cell
>1	8% (20/266)	2% (5/257)	1% (3/250)	0.26 (0.10, 0.68)*	0.16 (0.05, 0.53)*
By Baseline vert. BMD med.					
#0.8	8% (17/204)	2% (5/229)	0% (0/213)	0.26 (0.10, 0.70)*	Zero cell
>0.8	2% (5/237)	0% (0/210)	1% (2/212)	Zero cell	0.45 (0.09, 2.28)

Most of the multiple fractures occurred in high risk patients (more than one baseline fracture or spinal BMD of .8 or less) (Table 12); the benefit of PTH was also the greatest in these subgroups.

Severity of new vertebral fractures

Severity of new vertebral fractures was not a pre-specified endpoint in this trial; vertebrae were graded on severity in order to identify new or worsening fractures. The protocol states the following under Section 3.9.1.2. Efficacy Criteria:

*“An **incident vertebral fracture** will be assessed using a semiquantitative approach by which an experienced radiologist grades all vertebrae by visual inspection from normal (grade 0) to severely deformed (grade 3) (Genant et al. 1993). The semiquantitative method defines an incident vertebral fracture as a deterioration of at least one grade. A deterioration of a preexisting fracture will be considered an incident fracture if the decrease in vertebral height is at least one grade in the semiquantitative assessment.” Page 41 of Volume 218*

All vertebrae were graded at baseline and at endpoint. According to the study report (not the protocol), only vertebrae graded as zero at baseline were considered in the analysis of new fractures. Worsening fractures were not considered as suggested by the paragraph above.

Each new vertebral fracture was rated as mild (1), moderate (2) or severe (3) (Table 13). There was no statistical plan for analyzing this data.

Table 13 Distribution of scores for all fractures by treatment group

	Placebo	PTH20	PTH40
Total Fractures	101	33	22
Mild (1)	44 (44%)	25 (76%)	12 (55%)
Moderate (2)	43 (43%)	8 (24%)	7 (32%)
Severe (3)	14 (14%)	0 (0%)	3 (14%)

The sponsor analyzed this data in two ways; 1) comparison of proportion of patients with new moderate or severe fractures and 2) comparison of proportion of patients with new severe fractures. The sponsor’s results are shown in Table 14 below. The treatment differences between placebo and PTH are highly significant ($p < .0001$, Pearson’s chi square test).

Table 14 Sponsor’s analysis of vertebral score data

	Placebo	PTH 20	PTH 40	PLA vs PTH20 RR (95% CI)	PLA vs PTH40 RR (95% CI)
Pts. w/ new moderate or severe fractures	9% (42/448)	0.9% (4/444)	2% (9/434)	0.10 (0.04, 0.27)*	0.22 (0.11, 0.45)*
Pts. w/ new severe fractures	3% (14/448)	0% (0/444)	0.7% (3/434)	Zero cell	0.22 (0.06, 0.76)*

This reviewer performed two additional analyses of the score data. For the first analysis, this reviewer summed the scores on all vertebrae and computed the mean score for each patient at baseline (about 0.275 overall) and endpoint. Using ANCOVA with baseline mean score as a covariate, this reviewer found a significant increase in this mean score for placebo patients (+0.03) compared to PTH20 or PTH40 (+0.01 for each). This analysis accounts for the status of all vertebrae and so the treatment comparisons indicate a change in overall vertebral status.

For a second analysis, this reviewer computed the highest score for an individual patient (Table 15). This analysis showed a statistically significant difference between each treatment group

and placebo ($p < .0001$, Wilcoxon test). Stratifying on number of baseline fractures revealed similar results.

Table 15 Percent of patients by highest vertebral score observed

	Placebo	PTH20	PTH40
Highest Score for Patient	(n=448)	(n=444)	(n=434)
0	86%	95%	96%
1 (Mild)	5%	4%	2%
2 (Moderate)	6%	1%	1%
3 (Severe)	3%	0%	0.7%

Regardless of the statistical method used, this reviewer concluded that patients treated with PTH had less severe fractures than patients treated with placebo.

New and worsening vertebral fractures

New and worsening vertebral fractures was not a pre-specified endpoint in this trial, however, like the other variables listed in this section, data was collected for this variable. This reviewer decided to look at this outcome because it has been reported for other osteoporosis drugs.

The sponsor provided the results shown in Table 16. For worsening fractures alone, the treatment groups are statistically significantly different. For new and worsening fractures, each PTH dose is significantly different from placebo ($p < .001$, Pearson's chi square test).

Table 16 Sponsor's results for new and worsening fractures

	Placebo	PTH20	PTH40
worsening fractures	4.5% (18/448)	3.0% (12/444)	2.0% (8/434)
new +worsening fractures	16.5% (74/448)	6.5% (29/444)	5.8% (25/434)

Subgroup analyses

According to the protocol, the primary efficacy measure (proportion of patients with new vertebral fractures) may be analyzed by the following subgroups measured at **baseline**:

- **Number of vertebral fractures**
- Bone turnover rate (not defined)
- **BMD**
- **BMI**
- Number of years postmenopausal
- Smoking status
- Race
- **Age**
- Prior use of concomitant medications

Analyses based on the bolded subgroups above and the subgroups listed below were provided in the sponsor's study report:

- **Baseline biochemical markers (serum BSAP, serum P1CP, NTX and urinary free deoxyypyridinoline)**
- **Baseline weight**
- **Baseline endogenous PTH**
- **Dose reduction (yes/no)**

- **Serum Ca elevation (yes/no)**

This reviewer examined subgroups defined by the list below. Other subgroups suggested by the sponsor had insufficient patients in a subgroup to do a reasonable analysis.

- Baseline number of vertebral fractures
- Baseline vertebral BMD
- Baseline PTH
- Baseline BMI
- Number of years postmenopausal
- Age
- Months on study

It is clear from Table 17 that the results for new vertebral fractures are consistent across many subgroups; these results speak to the strength of the fracture data.

Table 17. Subgroup results for new vertebral fractures
Subgroups are defined by the median of the subgroup variable

	Placebo	PTH 20	PTH 40	PLA vs PTH20 RR (95% CI)	PLA vs PTH40 RR (95% CI)
All Patients	14% (64/448)	5% (22/444)	4% (19/434)	0.35 (0.22, 0.55)*	0.31 (0.19, 0.50)*
Baseline Fractures					
0-1	6% (11/182)	3% (5/187)	2% (4/184)	0.44 (0.16, 1.25)	0.36 (0.12, 1.11)
>1	20% (53/266)	7% (17/257)	6% (15/250)	0.33 (0.20, 0.56)*	0.30 (0.17, 0.52)*
Years post-menopausal					
#20	13% (25/199)	4% (8/198)	4% (7/190)	0.32 (0.15, 0.70)*	0.29 (0.13, 0.66)*
>20	15% (29/198)	7% (13/198)	6% (11/194)	0.45 (0.24, 0.84)*	0.39 (0.20, 0.75)*
Baseline BMI					
#26	20% (42/215)	5% (11/202)	5% (10/215)	0.28 (0.15, 0.53)*	0.24 (0.12, 0.46)*
>26	10% (22/226)	4% (10/232)	4% (8/211)	0.44 (0.22, 0.91)*	0.39 (0.18, 0.86)*
Baseline vert. BMD					
#0.8	19% (38/204)	6% (14/229)	4% (9/213)	0.33 (0.18, 0.59)*	0.23 (0.11, 0.46)*
>0.8	9% (22/237)	4% (8/210)	4% (8/212)	0.41 (0.19, 0.90)*	0.41 (0.19, .89)*
Baseline PTH					
#3.5	14% (31/219)	6% (14/220)	4% (8/219)	0.45 (0.25, 0.82)*	0.26 (0.12, 0.55)*
>3.5	15% (33/214)	4% (8/212)	5% (11/206)	0.25 (0.12, 0.52)*	0.35 (0.18, 0.67)*

Age <70 \$70	14% (33/241) 15% (31/207)	4% (9/227) 6% (13/217)	2% (5/213) 6% (14/221)	0.29 (0.14, 0.59)* 0.40 (0.22, 0.74)*	0.17 (0.07, 0.43)* 0.42 (0.23, 0.77)*
Mos. on study #18 >18	15% (29/199) 14% (35/249)	3% (5/194) 7% (17/250)	5% (9/197) 4% (10/237)	0.18 (0.07, 0.45)* 0.48 (0.28, 0.84)*	0.31 (0.15, 0.65)* 0.30 (0.15, 0.59)*
Mos. on study #15 15-18 18-20 >20	21% (6/29) 14% (23/170) 14% (20/143) 14% (15/106)	4% (1/27) 2% (4/167) 6% (10/154) 7% (7/96)	5% (2/38) 4% (7/159) 7% (10/134) 0% (0/103)	0.18 (0.02, 1.39) 0.18 (0.06, 0.50)* 0.46 (0.23, 0.96)* 0.52 (0.22, 1.21)	0.25 (0.06, 1.17) 0.32 (0.14, 0.74)* 0.53 (0.26, 1.1) NA (zero cell)

*p<.05

Reviewer's comments on Study GHAC

Study GHAC is a Phase III study designed to show that PTH reduces the incidence of new vertebral fractures compared to placebo in post-menopausal women with osteoporosis. About 80% of the randomized patients contributed data to the analysis of the primary endpoint.

The proportion of patients with new vertebral fractures was reduced from 14% for placebo patients to 5% for patients treated with PTH20 ([Table 6](#)); no significant further lowering was seen by increasing the dose to 40 Fg. The results were robust to alternative analytical methods and across several subgroups ([Table 16](#)).

Analyses of pre-specified secondary efficacy measures revealed the following:

- BMD for PTH patients was significantly increased in a dose response manner at the lumbar spine, total hip, femoral neck¹ and whole body compared to placebo ([Table 7](#)). The magnitude of these changes for PTH was related to the baseline BMD. No improvements in BMD were seen at the ultradistal and midshaft radius; in fact, there was a significant decrease in midshaft radius BMD for PTH40 compared to placebo.
- The incidence of fractures was unrelated to the time of exposure ([Table 9](#)).
- About half as many non-vertebral fragility fractures were observed in the PTH groups (2.5%) as the placebo group (5.5%), p<.02. From a statistical perspective, these results are not convincingly in favor of PTH due to the small number of fractures observed and since any adjustment for multiple endpoints would render the results as non-significant.
- A small mean decrease in height (about 3 mm) was observed in all treatment groups with about 15% of the patients showing no changes ([Table 11](#)). Comparisons of each PTH group to placebo produced varying results and suggests to this reviewer that PTH does not have a notable effect on change in height.
- Dose-related increases in biochemical markers (P1CP, BSAP, DPD and NTX) were observed after one month of therapy and sustained for 12 months for 3 of the markers (BSAP, DPD and

1 Femoral neck BMD was not a pre-specified endpoint in this trial. However, the results were presented by the sponsor and are reviewed here due to the relationship to total hip BMD.

NTX) [Figure 7](#).

Two variables, defined by the sponsor in the study report but not defined a priori in the protocol were proportion of patients with multiple new vertebral fractures and severity of new vertebral fractures. Both of these variables showed statistically significant results for PTH compared to placebo. The results should be considered exploratory since these endpoints were not defined in the protocol (see page 18 for more details).

Back pain was reported by the sponsor as an efficacy endpoint but back pain data was collected as an ADE; no hypothesis with regard to back pain was prospectively defined. Therefore, back pain was not reviewed here; see Dr. Stadel's safety review for back pain data.

In conclusion, PTH was shown to be highly efficacious at lowering the proportion of patients developing new vertebral fractures and increasing BMD at several sites.

Study GHAJ (10/97 to 12/98)

Design

Study GHAJ is a Phase III, multicenter, double-blind, placebo-controlled, randomized study designed to show that teriparatide (PTH) increases spinal BMD (primary endpoint) in men with primary osteoporosis.

The trial was planned to consist of the following two phases:

1. Ca (~1000 mg/day) plus vitamin D (400-1200IU/day) for up to 2 months
2. Ca and vitamin D with randomized treatment injection for 2 years

The trial was stopped by the sponsor after about 15 months with median time on drug of about 10 months. At the time of trial cessation, medication was stopped and a closeout visit was scheduled for all patients still on study. For most patients, the closeout visit took place within about 7 weeks of stopping medication. All end-of-study measurements were performed at the closeout visit.

The entry criteria for this trial included the following:

- Men 30-85 years old with primary osteoporosis
- spinal BMD t-score#-2

In the protocol, the primary and secondary objectives are listed as follows.

Primary objective:

- Show increase in **BMD** lumbar spine

Secondary objectives:

- Show increase in **BMD** at the hip, total body and radius
- Show lack of reduction in **height**
- Show effects on **biochemical markers**
- Assess population pharmacokinetics
- Perform a cost-effectiveness analysis
- Perform a quality of life assessment

The last three objectives are not reviewed here.

The schedule for assessment of the primary and secondary endpoints is shown below in Table 18. No patients in this trial had an assessment at Month 18 or 24.

Table 18. GHAJ schedule for assessing endpoints

MONTH	0	1	3	6	12	18	24	End
Height	U				U		U	U
Lat. thor. + lumbar spinal x-ray	U							
PA lumbar spine BMD	U		U	U	U	U	U	U
Hip	U				U		U	U
Body + radial BMD (subset of pts.)	U				U		U	U
Biochemical markers	U	U	U	U	U		U	U

Patient Disposition

A total of 437 patients were randomized to treatment at 34 centers in 11 countries (Table 19). According to the protocol, the plan was to enroll a total of 279 patients. The sponsor explains in their study report that over-enrollment occurred due to a long screening period and high enrollment at the end of screening.

Table 19 shows the number of patients completing Months 3, 6 and 12. More placebo patients than PTH patients have data at each timepoint.

	PLA	PTH 20	PTH 40
Planned to rand.	93	93	93
Actually rand.	147	151	139
Month 3	139 (95%)	137 (91%)	122 (88%)
Month 6	138 (94%)	131 (87%)	112 (81%)
Month 12	42 (37%)	40 (26%)	36 (26%)
% on study at end	130 (88%)	123 (82%)	103 (74%)

A more detailed presentation of the completion data is given in [Appendix 2](#) where the number of patients by month is depicted. The median time on therapy was about 10 months in all treatment groups. Less than a of the patients had a 12-month visit.

More patients on PTH discontinued treatment for an ADE or due to patient decision than placebo patients (Table 20). The ADE and patient-decision dropouts occurred throughout the trial. As a result of the differential dropout rates, there were more placebo patients (88%) on study than PTH patients (PTH20:82%, PTH40:74%) when the study was terminated.

	PLA (n=147)	PTH 20 (n=151)	PTH 40 (n=139)
ADE	7 (5%)	14 (9%)	18 (13%)
Lack of Efficacy	2 (1.4%)	0 (0%)	0 (0%)
Lost to follow-up	2 (1.4%)	0 (0%)	1 (1%)
Patient decision	4 (3%)	8 (5%)	13 (9%)
Physician decision	1 (1%)	0 (0%)	0 (0%)
Protocol violation	1 (1%)	2 (1.3%)	2 (1.4%)
Sign lab value	0 (0%)	2 (1.3%)	1 (1%)
Death	0 (0%)	2 (1.3%)	0 (0%)
Other	0 (0%)	0 (0%)	1 (1%)
Study ended early	130 (88%)	123 (82%)	103 (74%)

Baseline Demographics

The treatment groups were generally comparable with regard to baseline demographics (Table 21). The only significant difference between each of the PTH groups and placebo was for previous non-vertebral fractures with more fractures seen for PTH20 (66%) than placebo (54%), $p < .03$. The mean age was 59 years with a little more than a of the patients 65 or older. Nearly all the patients were Caucasian. The majority of patients (~85%) had not been previously treated with osteoporosis drugs. Baseline mean spinal BMD and mean PTH were similar to the women in GHAC.

Table 21. Study GHAJ Baseline Demographics (Sponsor's Results)

	PLA (n=147)	PTH 20 (n=151)	PTH 40 (n=139)
Age			
Mean (SD)	59 (13)	59 (13)	58 (13)
Range	28-85	32-84	31-84
≥65	37%	39%	34%
BMI Mean (SD)	25 (4)	25 (4)	25 (4)
Caucasian	100%	99%	99%
No Alcohol use	30%	25%	35%
Non-smoker	68%	70%	73%
Osteoporosis Type			
Idiopathic	50%	52%	51%
Hypogonadal	50%	48%	49%
No Previous Osteo. Drug Treatment	88%	85%	82%
Previous non-vertebral fracture	54%	66%	57%
Spinal BMD Mean (SD)	0.85 (0.1)	0.89 (0.2)	0.87 (0.1)
PTH Mean (SD)	3.7 (1.2)	3.6 (1.2)	3.6 (1.2)
Bone turnover markers Median (SD)			
BSAP	12 (0.4)	10 (0.6)	10 (0.9)
P1CP	120 (3)	119 (2)	118 (5)
NTX	35 (1)	34 (1)	31 (1)
DPD	4.4 (0.2)	4.4 (0.1)	4.3 (0.1)

Efficacy Results

As seen in [Table 18](#), BMD was measured at the spine at Months 3, 6 and 12 while BMD at other sites was measured only at Month 12. Since only 27% of randomized PTH patients and 30% of placebo patients had a Month 12 visit, most of the data for BMD at secondary sites is from the study closeout visit.

The sponsor in their study report has mis-characterized the closeout visit as Visit 6 – the Month 12 visit - and incorrectly argues that since most patients have Month 12 data (when actually ~70% do not) that a Month 12 LOCF analysis is preferable to a last observation on study analysis (a “true” endpoint analysis). The so-called Month 12 LOCF analysis then excludes data past Month 12.

This reviewer thinks that one should not include closeout data for only patients who do not reach Month 12 and exclude closeout data for patients who have data past Month 12. In fact, one would anticipate that the latter patients should show more effect due to increased exposure (as can be seen from the GHAC graph in [Appendix 3](#)). This reviewer does not think there is a reasonable argument for doing a Month 12 LOCF analysis and, therefore, those data are not

presented here (the sponsor's Month 12 LOCF are included in the medical officer's review).

In addition to a Month 12 LOCF analysis, the sponsor presented an overall LOCF analysis. For this analysis, the last observation (the only observation for most patients) is used. For most patients, the last observation is the closeout visit when about 90% of the patients are off therapy. Note that this analysis is the one specified in the protocol as the primary analysis.

This reviewer has computed and analyzed endpoint data in two ways. First, this reviewer used the patient's last observation on therapy. For lumbar spine most of the patients are included in this analysis. For the secondary BMD sites, less than a of the randomized patients contribute data. For a second analysis (identical to the sponsor's overall LOCF analysis), this reviewer used the patient's last observation on study; this analysis then contains data for a large number of patients off drug. For the secondary BMD sites, the last observation is the only observation for most patients. Both analyses may underestimate the treatment effect; the first due to the short amount of time on therapy at the time of the BMD measurement and the second due to the time off therapy at the time of the BMD measurement. So time of exposure to drug and time off drug at time of last observation both complicate interpretation of the data. These factors are examined as they relate to efficacy by this reviewer in the following sections.

Primary Efficacy Measure: Lumbar spine BMD

Lumbar spine BMD was measured at baseline, Months 3, 6 and 12 and at closeout of the study. About 86% of the patients had 6-month data while only 27% had 12-month data.

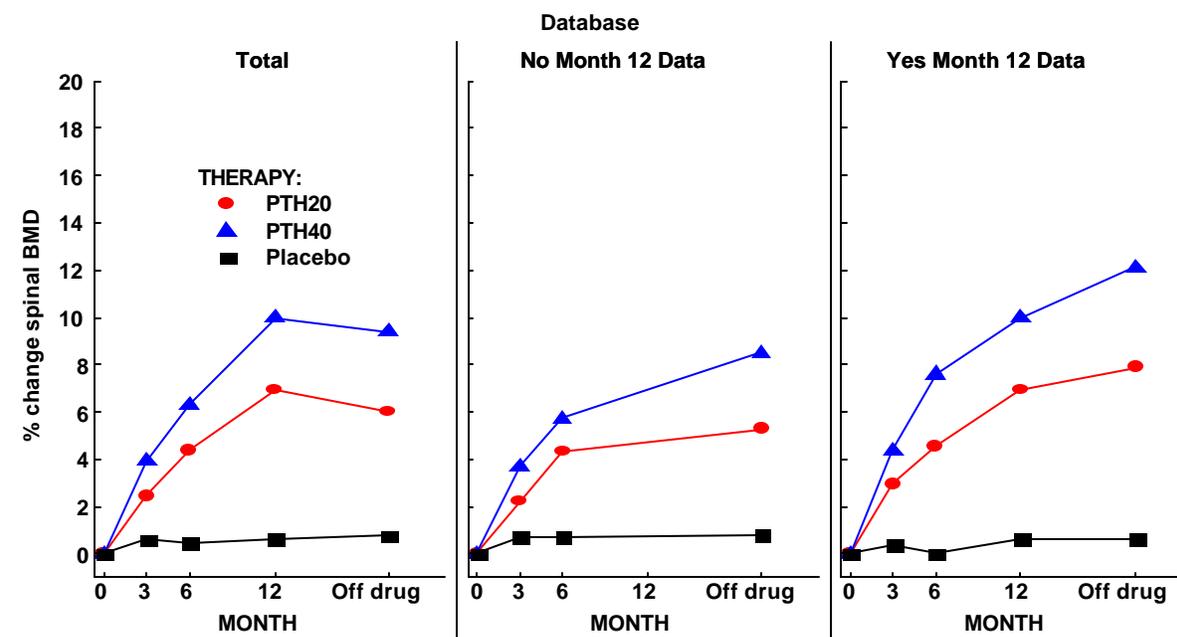
The results of each timepoint as well as for the two endpoint analyses (Table 22) show strong dose-related treatment effects for PTH20 and PTH40 versus placebo ($p < .0001$, ANCOVA with baseline as a covariate).

Table 22 Study GHAI Lumbar spine BMD results (Mean (SD))

	PLA (n=147)	PTH 20 (n=151)	PTH 40 (n=139)	PLA vs. PTH20 p-value	PLA vs. PTH40 P-value
Lumbar spine					
Baseline	0.9 (0.1)	0.9 (0.2)	0.9 (0.1)		
% change					
Month 3	+0.6% (3.3) (n=139)	+2.4% (3.2) (n=136)	+3.9% (3.7) (n=122)	.0001	.0001
Month 6	+0.5% (4.2) (n=138)	+4.3% (3.4) (n=128)	+6.3% (5.5) (n=111)	.0001	.0001
Month 12	+0.7% (4.7) (n=42)	+6.9% (4.6) (n=40)	+10.0% (5.8) (n=36)	.0001	.0001
LOCF (on therapy)	+0.7% (4.2) (n=139)	+5.0% (4.1) (n=136)	+6.9% (5.7) (n=123)	.0001	.0001
Endpoint (last observation)	+0.5% (3.9) (n=143)	+5.9% (4.5) (n=141)	+9.0% (6.5) (n=129)	.0001	.0001

Almost no change in BMD is seen in the placebo group over time while in the PTH groups, BMD increases by about 2% over baseline after each additional 3 months. This is clearly illustrated in Figure 9. Also, the BMD is fairly stable after drug is removed (median time off of about one month).

Figure 9 Study GHAJ Lumbar spine BMD by month and off drug at study closeout
 For 3 databases: all patients, patients with no Month 12 data and patients with Month 12 data



This reviewer also looked at the relationship between exposure time and response ([Appendix 3](#)) and between time off drug and response ([Appendix 4](#)). The graphs in these appendices illustrate two points; 1) patients with longer exposure times show larger effects for both PTH groups (this is consistent with the data illustrated in Figure 9) and 2) the length of time off does not appear to have an effect on magnitude of response at endpoint.

Secondary Efficacy Measures

BMD

BMD was measured at 5 sites for the hip (total hip, femoral neck, trochanter, intertrochanter and Ward's triangle) and at the ultradistal and midshaft radius and for the whole body. These secondary BMD sites were scheduled for assessment at baseline, Month 12 and Month 24. Due to the cessation of the trial prematurely, only 27% of the patients had a Month 12 visit. When the trial was stopped, all patients were scheduled for a closeout visit and BMD measurements were made. Nearly all patients were off treatment at the time of these final BMD measurements; the median time off treatment was 37 days, 80% of the patients were off treatment less than 7 weeks.

BMD data for the secondary sites, then, is available at Month 12 on therapy for a small number of patients and at closeout for all patients (including patients who discontinued early). The last observation at closeout is referred to as endpoint in the following tables. The BMD results for those two timepoints are presented in Tables 23 (hip sites) and Table 24 on the following pages.

The BMD data for the 5 hip sites is summarized in Table 23. For PTH20, significant treatment effects are seen for the femoral neck at endpoint and at the intertrochanter for patients with on-therapy data. Any adjustment for multiple comparisons would render these comparisons non-significant. For PTH40, significant treatment effects were seen at all hip sites except trochanter.

A graph of treatment response by month and treatment group total hip and femoral neck ([Appendix 5](#) and [Appendix 6](#), respectively) show no clear increase in response with increased drug exposure for PTH20. For PTH40, however, there does appear to be a larger effect with more exposure at both the total hip and femoral neck

Overall the hip BMD data is positive for PTH40 but not for PTH20.

Table 23 Study GHAJ BMD results (Mean (SD)) for hip sites

	PLA (n=147)	PTH 20 (n=151)	PTH 40 (n=139)	PLA vs. PTH20 p-value	PLA vs. PTH40 P-value
Total hip					
Baseline	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)		
% change					
On Therapy	+0.9% (2.6) (n=48)	+2.0% (3.0) (n=46)	+3.0% (3.7) (n=39)	.08	.003
Endpoint	+0.5% (2.7) (n=137)	+1.2% (2.9) (n=136)	+2.3% (4.4) (n=125)	.09	.0001
Femoral neck					
Baseline	0.7 (0.1)	0.7 (0.09)	0.7 (0.1)		
% change					
On Therapy	+0.9% (4.0) (n=48)	+2.0% (3.3) (n=46)	+3.1% (5.5) (n=39)	.15	.02
Endpoint	+0.3% (4.1) (n=137)	+1.5% (4.0) (n=136)	+2.9% (6.3) (n=125)	.02	.0001
Trochanter					
Baseline	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)		
% change					
On Therapy	+1.7% (3.3) (n=48)	+2.2% (4.5) (n=46)	+2.3% (3.7) (n=39)	.46	.45
Endpoint	+1.1% (3.3) (n=137)	+1.3% (4.2) (n=136)	+2.1% (5.3) (n=125)	.58	.06
Intertrochanter					
Baseline	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)		
% change					
On Therapy	+0.9% (2.6) (n=48)	+2.2% (2.8) (n=46)	+3.4% (4.0) (n=39)	.04	.0003
Endpoint	+0.6% (2.9) (n=137)	+1.2% (3.1) (n=136)	+2.3% (4.4) (n=125)	.13	.0001
Wards triangle					
Baseline	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)		
% change					
On Therapy	+1.5% (6.9) (n=48)	+3.2% (6.3) (n=46)	+6.2% (9.7) (n=39)	.28	.008
Endpoint	+1.1% (9.2) (n=137)	+2.8% (7.3) (n=136)	+6.6% (12.9) (n=125)	.13	.0001

Significant treatment effects were seen for the whole body for PTH40 but not for PTH20 (Table 24). A graph of treatment response by month and treatment group ([Appendix 7](#)) shows no increased response for either PTH group with increased drug exposure.

No beneficial effects are seen at the radius for either dose; in fact, a significant decrease in BMD at the midshaft radius is seen for PTH40 compared to placebo. These findings are consistent with what was seen for the women in GHAC.

Table 24 Study GHAJ BMD results (Mean (SD)) for whole body and radius

	PLA (n=147)	PTH 20 (n=151)	PTH 40 (n=139)	PLA vs. PTH20 p-value	PLA vs. PTH40 P-value
Whole body					
Baseline	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)		
% change					
On Therapy	+0.2% (2.2) (n=35)	+0.8% (2.2) (n=32)	+0.2% (2.7) (n=34)	.28	.97
Endpoint	-0.4% (2.7) (n=87)	+0.4% (2.9) (n=84)	+0.5% (2.4) (n=83)	.08	.04
Ultradistal radius					
Baseline	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)		
% change					
On Therapy	-0.1% (3.6) (n=37)	-0.2% (3.1) (n=33)	+0.4% (7.7) (n=35)	.94	.44
Endpoint	-0.3% (3.2) (n=94)	-0.5% (3.2) (n=89)	+0.2% (5.8) (n=85)	.93	.65
Midshaft radius					
Baseline	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)		
% change					
On Therapy	-0.1% (2.2) (n=37)	-0.3% (2.0) (n=33)	-1.2 (2.7) (n=35)	.97	.05
Endpoint	-0.1% (1.9) (n=94)	-0.5% (2.4) (n=89)	-0.6% (2.4) (n=85)	.40	.23

Change in Height

A small loss (median of 1 mm or less) in height was seen for all three treatment groups; a comparison of each treatment group to placebo showed no treatment differences (Table 25).

Table 25 Study GHAJ Change in height

	Placebo (n=139)	PTH 20 (n=137)	PTH 40 (n=133)
Baseline (mm)	1736 (75)	1739 (73)	1732 (74)
Change (mm)			
Mean (SD)	-1.9 (6.5)	-2.2 (7.1)	-3.2 (7.8)
Median	-1.0	-0.7	-1.0
P-value ¹ PTH vs PLA		.69	.32

Biochemical Markers

Two markers of bone formation (serum bone-specific alkaline phosphatase (BSAP) and

1 Results of Wilcoxon rank sum test.

procollagen 1 carboxy-terminal propeptide (P1CP)) and two markers of bone resorption (urinary deoxypyridine (DPD) and urinary N-telopeptide (NTX)) were measured on all patients. The baseline values for these markers are included in [Table 21](#).

This reviewer has plotted the marker data in two ways; 1) in Figure 10, the data for all patients is plotted up to Month 6, the timepoint achieved by about 90% of the patients 2) in Figure 11, the data for patients with Month 12 data (about one-third of the patients) are shown at each month and also at the closeout visit.

The pattern of response for the men is like the responses seen for the women. In the PTH groups, all markers increase during the first month; these increases are statistically significantly greater than placebo for all markers but NTX for PTH20. P1CP subsequently decreases with no differences from placebo seen by Month 6 for PTH20 and by Month 12 for PTH40. BSAP, DPD and NTX continue to increase with significant treatment effects at each timepoint ($P < .001$).

Figure 10 % change from baseline (medians) in biochemical markers for all patients up to Month 6

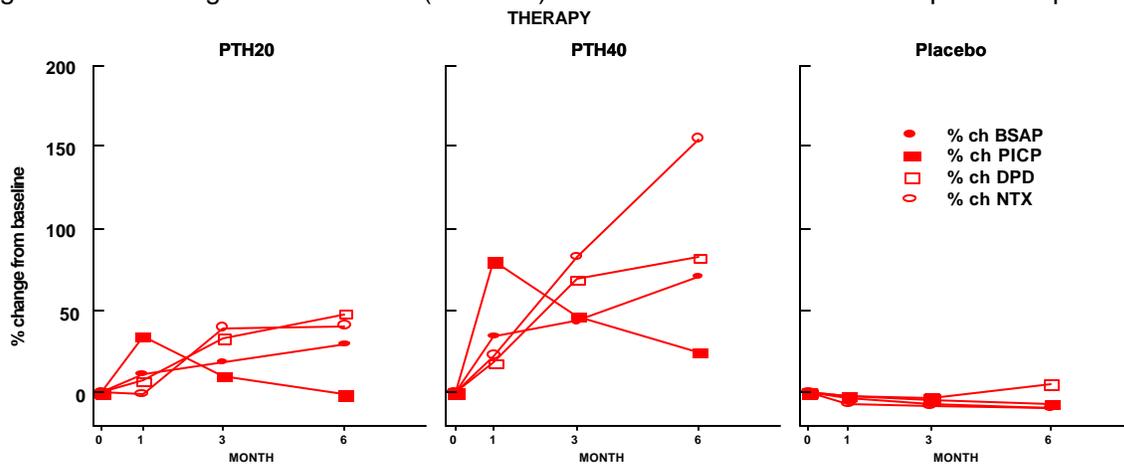
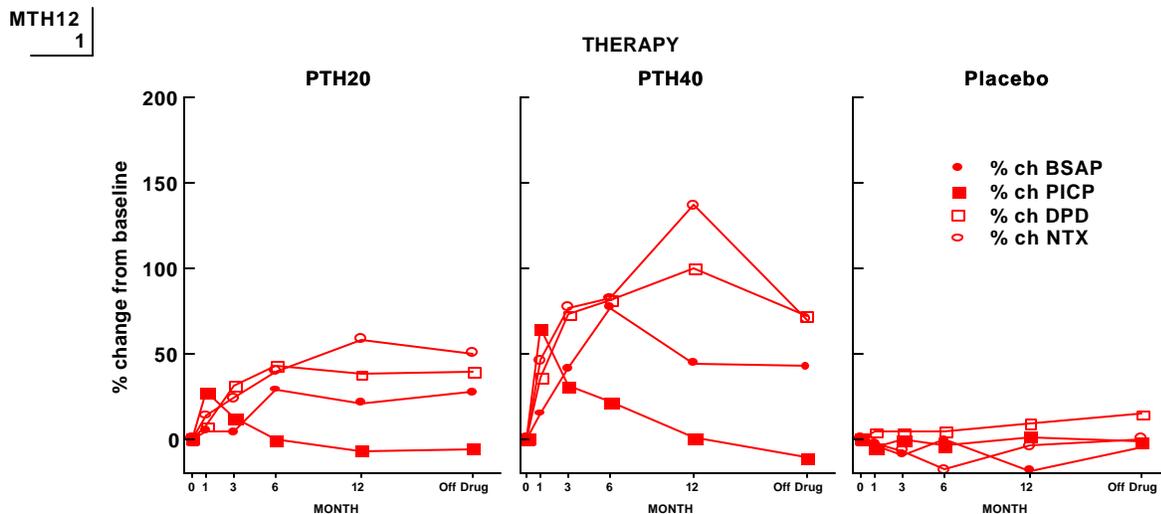


Figure 11 % change from baseline (medians) in biochemical markers for patients with Month 12 data by month on study and for the last observation off drug (closeout visit)



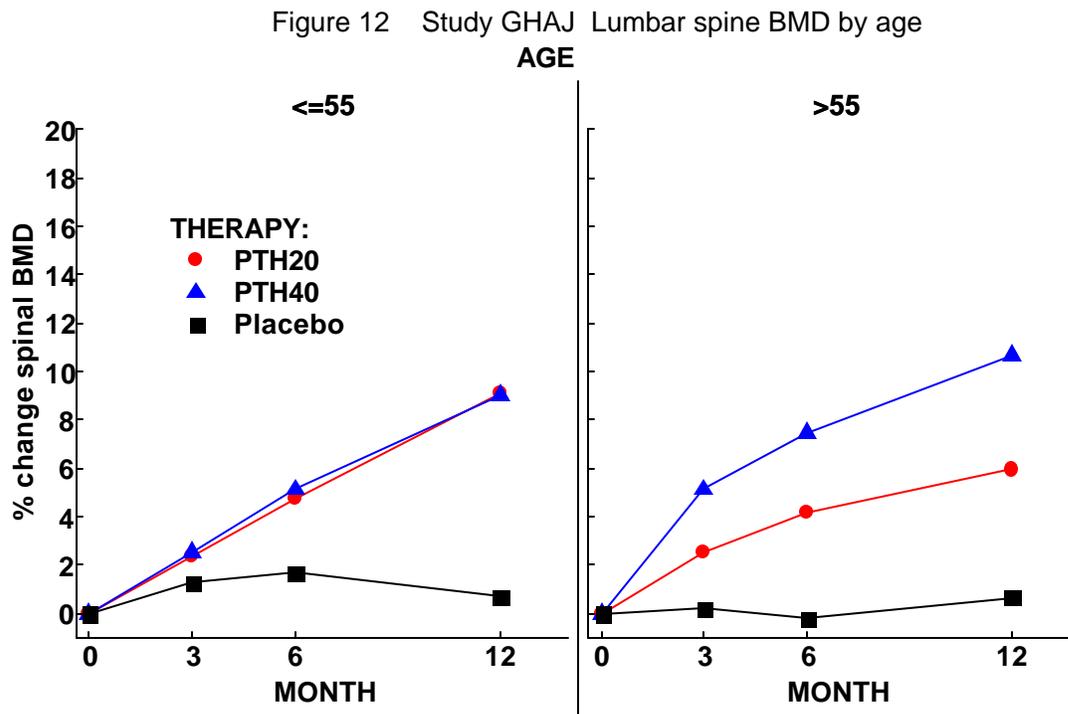
Subgroup analyses

According to the protocol, analyses may be performed by the following subgroups measured at baseline:

- Idiopathic versus hypogonadal osteoporosis
- Biochemical markers
- BMD
- BMI
- Age
- Free testosterone
- History of previous non-vertebral fracture

This reviewer examined the lumbar spine BMD data by these subgroups. For all subgroups except age, this reviewer found no differential treatment effects. A slightly higher magnitude of effect was seen for both treatment groups for patients with lower BMD at baseline (as seen for the women).

A significant interaction for age by treatment was found by this reviewer ($p=.04^1$). This was true using median age of 60 as a cutpoint and lower values for age as well. Figure 12 illustrates the source of the interaction; younger patients show a smaller treatment effect than older patients and the same effect for PTH20 and PTH40. This interaction was not confounded by any of the other subgroup variables.



1 P-value is a result of analysis of variance of % change from baseline of the lumbar spine at endpoint (last observation for all patients)

Reviewer's comments on Study GHAJ

Study GHAJ is a Phase III study designed to show that PTH increases lumbar spine BMD compared to placebo in men with primary osteoporosis. The trial duration was intended to be 24 months but due to early stopping of the trial no patients were able to complete 24 months. The median time on study was 10.5 months; about a of the patients had a Month 12 visit. Upon cessation of the trial, patients were scheduled for a closeout visit. The closeout visit took place within 7 weeks of the last dose of medication for 80% of the patients.

The primary efficacy variable, lumbar spine BMD % change from baseline, was measured at Months 0, 3, 6, and 12 and at closeout. About 86% of the patients had data at 6 months; 27% at 12 months. This reviewer analyzed the data at each of the scheduled visits and also did an LOCF analysis of the on-therapy BMD data and an endpoint analysis. The endpoint analysis was an analysis of the last observation for each patient; for nearly all patients the last observation was collected at the closeout visit when the patient was off therapy. The results of all analyses of lumbar spine BMD show highly significant dose-related treatment effects for PTH compared to placebo ($p < .0001$, [Table 22](#)). Subgroup analyses showed the results are consistent across subgroups based on several baseline characteristics. This reviewer found a significant treatment by age interaction with younger patients showing a smaller effect overall than older patients and showing no dose-response effects. A second study would be needed to explore the significance of this finding.

In addition to lumbar spine, BMD was measured at 8 sites (total hip, femoral neck, trochanter, intertrochanter, Ward's triangle, ultradistal radius, midshaft radius and whole body). The only sites pre-specified in the protocol were hip (no specifics), whole body and radius (forearm). The lack of detail in the protocol with regard to the hip sites complicates interpretation of the results since results could be reported selectively (as done in the sponsor's proposed label). Nevertheless, this reviewer does not think this is an important issue here since the BMD results are not favorable to PTH20. The hip results ([Table 23](#)) show a strong effect for PTH40 at most of the hip sites; the PTH20 results are variable and unconvincing from a statistical perspective. At both radial sites, the BMD results show no positive effects for PTH ([Table 24](#)). There was a borderline significant treatment effect for PTH40 for the whole body. Overall only PTH40 shows a significant effect on BMD compared to placebo at the secondary sites.

All three treatment groups had a small loss in height (median of about 1 mm) with no differences seen between the groups.

The pattern of response of the biochemical markers (P1CP, BSAP, DPD and NTX) was the same as was seen for the women (compare [Figure 7](#) and [Figure 11](#)). Dose-related increases were observed after one month of therapy for all markers and sustained for 12 months for 3 of the markers (BSAP, DPD and NTX).

In conclusion, this trial demonstrated that PTH20 significantly increases BMD at the lumbar spine but not at other sites. PTH40, though, shows significant increases in BMD at the hip sites as well as the lumbar spine.

Reviewer's overall summary and conclusions

The sponsor has presented the results of two Phase III clinical trials; one in women (GHAC) and one in men (GHAJ) to demonstrate the efficacy of PTH for the treatment of osteoporosis (Table 26). Two doses of PTH were studied (20 Fg and 40 Fg) but only the 20 Fg dose is proposed for marketing.

On December 8, 1998 all ongoing clinical trials of PTH were stopped due to the finding of osteosarcoma in a rodent carcinogenicity study. At the time of study closure about 80% of the randomized patients were still on study in both GHAC and GHAJ. Median time completed on study for patients in GHAC was 19 months and in GHAJ, 10.5 months. (See Appendices 1 and 2 for a graph of the number of patients completing each month.)

Table 26. Brief Summary of Double-Blind, Randomized, Parallel, Controlled Clinical Trials

Study Number (# of sites)	Population	Treatment Arms (Rand. N)	Median Time on study	Primary Endpoint
B3D-MC-GHAC (99 USA)	Females W/vert. frac. \$5 yrs PMP	PTH 20 (541) PTH 40 (552) PLA (544)	19 months (3 yrs planned)	New vertebral fractures
B3D-MC-GHAJ (37 USA)	Males Low BMD	PTH 20 (151) PTH 40 (139) PLA (147)	10.5 months (2 yrs planned)	Lumbar spine BMD

In Study GHAC, the primary efficacy variable was proportion of patients having a new vertebral fracture. Non-vertebral fragility fractures were analyzed as a secondary endpoint. The results for both endpoints are shown in the table below. The results for new vertebral fractures show a strong treatment effect for PTH20 and PTH40 compared to placebo reducing the number of fractures by more than half. These results are robust to additional analyses performed by this reviewer which accounted for the 20% of randomized patients not assessed for fractures.

Table 27. Study GHAC Fracture Results

	Placebo	PTH 20	PTH 40	PLA vs PTH20 RR (p-value)	PLA vs PTH40 RR (p-value)
New Vertebral Fractures	14% (64/448)	5% (22/444)	4% (19/434)	0.35 (p<.001)	0.31 (p<.001)
New Non-Vertebral Fractures	5.5% (30/544)	2.5% (14/541)	2.5% (14/552)	0.47 (p<.02)	0.46 (p<.02)

The results for new non-vertebral fractures are not as convincing statistically since adjustments for multiple comparisons for the numerous analyses of secondary endpoints would render the difference non-significant. This reviewer would suggest reporting these results in the label with confidence intervals not p-values.

Several variables related to fracture incidence but not named as efficacy endpoints in the GHAC protocol were analyzed by the sponsor. The results of these variables, given in pages 19 to 22 of this review, are consistent with the primary efficacy variable with statistically significant results favoring PTH over placebo. Due to the post-hoc nature of these analyses, this reviewer feels they should be replicated before being presented in labeling.

BMD was measured at multiple bone sites in both studies. In Study GHAJ, lumbar spine BMD was the primary efficacy variable. The % change from baseline results for lumbar spine in Study GHAC and Study GHAJ both show highly significant increases for PTH compared to placebo

(Table 28). Similar results are seen in both studies at Month 12; at endpoint, larger treatment effects are seen in GHAC than GHAJ, most likely due to the longer exposure in GHAC.

Table 28 Study GHAC and Study GHAJ **Lumbar spine BMD** results (Mean (SD))

	Placebo	PTH 20	PTH 40	PLA vs. PTH20 p-value ¹	PLA vs. PTH40 P-value ¹
Study GHAC					
Baseline	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)		
% change					
Month 12	+0.8% (4.9) (n=467)	+8.3% (6.1) (n=466)	+11.9% (6.8) (n=452)	.0001	.0001
Endpoint	+1.1% (5.5) (n=504)	+9.7% (7.4) (n=498)	+13.7% (9.7) (n=497)	.0001	.0001
Study GHAJ					
Baseline	0.9 (0.1)	0.9 (0.2)	0.9 (0.1)		
% change					
Month 12	+0.7% (4.7) (n=42)	+6.9% (4.6) (n=40)	+10.0% (5.8) (n=36)	.0001	.0001
Endpoint	+0.5% (3.9) (n=143)	+5.9% (4.5) (n=141)	+9.0% (6.5) (n=129)	.0001	.0001

In Study GHAC, BMD for PTH patients was significantly increased in a dose response manner at the total hip, femoral neck² and whole body compared to placebo. In Study GHAJ, only PTH40 showed convincingly positive results for BMD at the hip sites and whole body.

No improvements in BMD were seen at the ultradistal and midshaft radius for men or women; there was a significant decrease in midshaft radial BMD for PTH40 compared to placebo.

The changes in BMD at all sites were clearly dose-related in both studies. No dose response relationship was evident for any other pre-specified endpoints. The lack of dose response for fractures in Study GHAC could be due to the short duration of the trial (under 2 years) and the few number of fractures observed. An analysis of worsening fractures (not a pre-defined endpoint) suggests that the incidence of fractures may be dose-related (see Table 16 on page 21).

Change in height was a secondary endpoint in both studies. All treatment groups lost height during the study (1-3mm) with no statistically significant differences among the groups.

Dose-related increases in biochemical markers (P1CP, BSAP, DPD and NTX) were observed after one month of therapy and sustained for 12 months for 3 of the markers (BSAP, DPD and NTX) in both studies.

In conclusion, the results for the primary efficacy variables in GHAC and GHAJ show that PTH is effective in the treatment of osteoporosis in men and women.

Joy D. Mele, M.S.
Mathematical Statistician

Concur:

1 Results of analysis of covariance (ANCOVA) with baseline BMD as a covariate.

2 Femoral neck BMD was not a pre-specified endpoint in Study GHAC.

Todd Sahlroot, Ph.D.
Team Leader

Ed Nevius, Ph.D.
Director of DOB2

cc:

Archival NDA#21-318

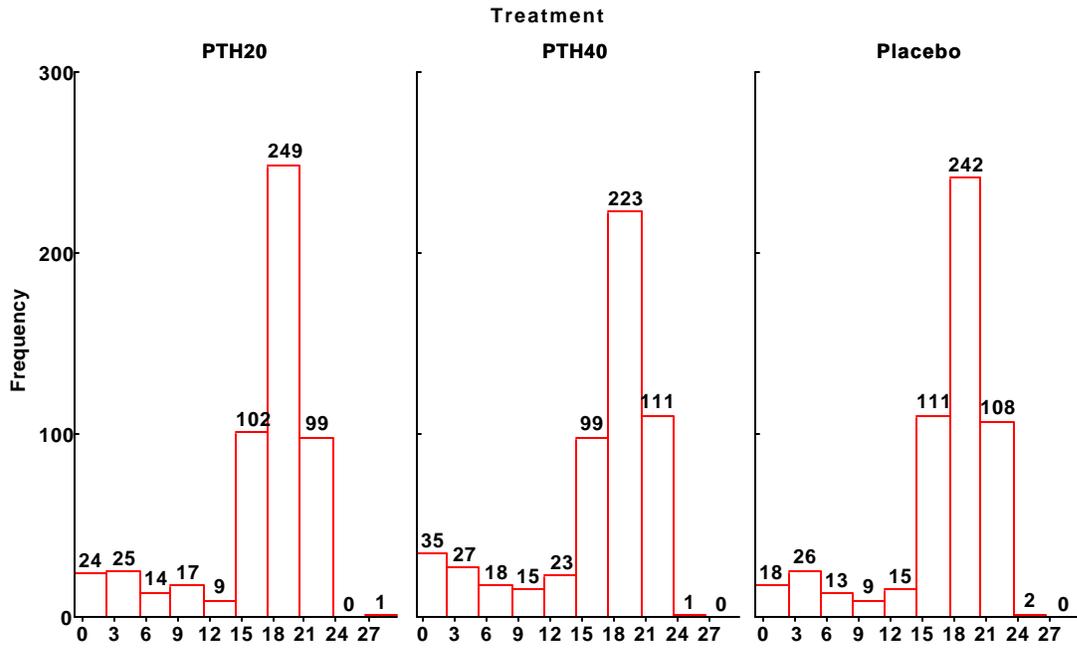
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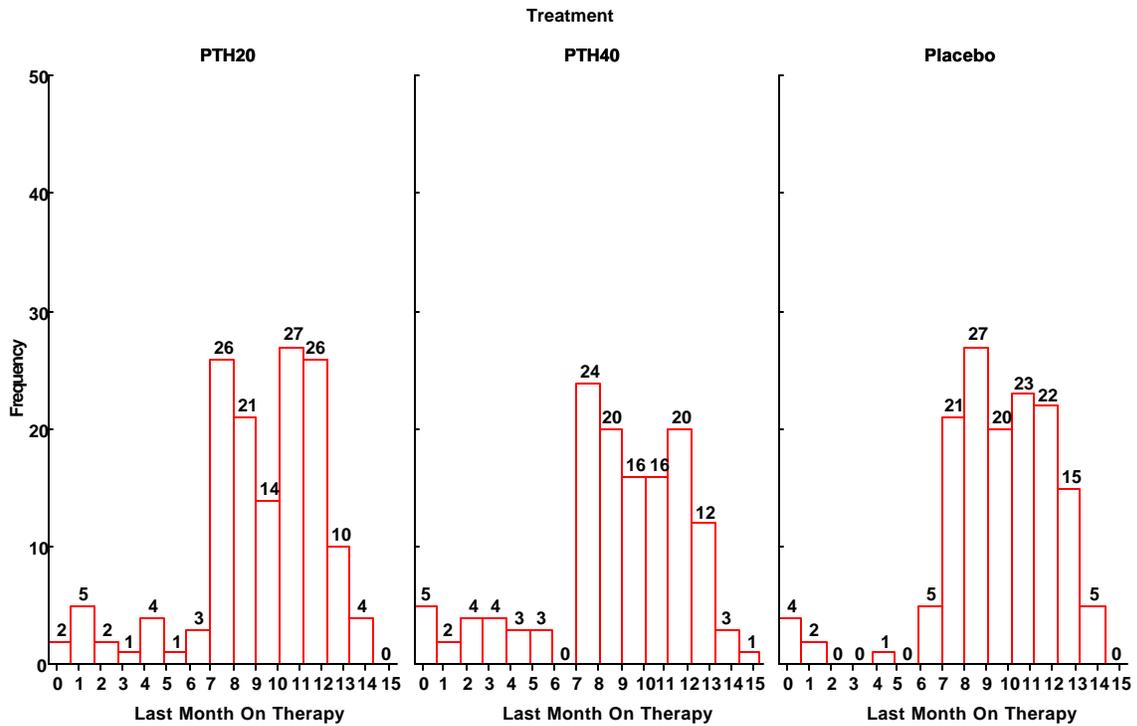
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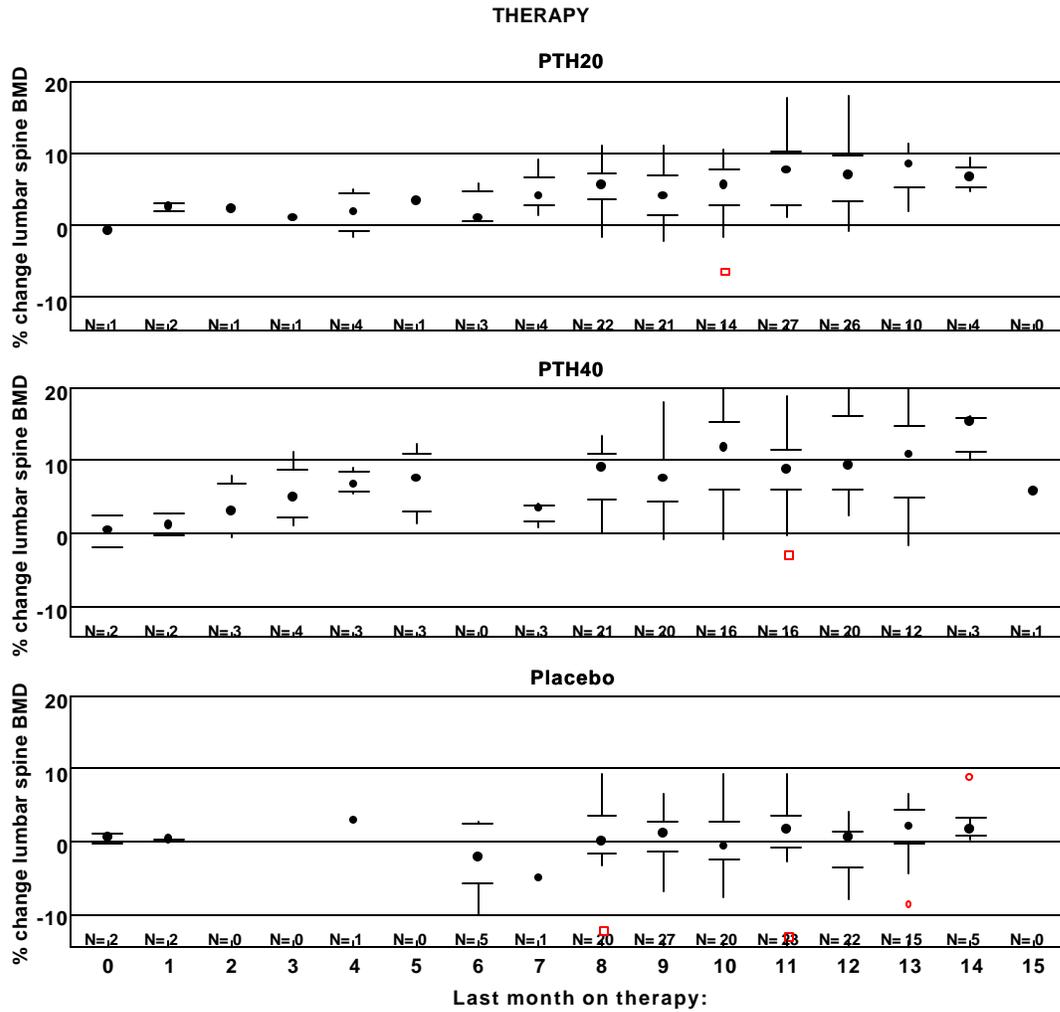
Appendix 1 Study GHAC patients by last month on therapy



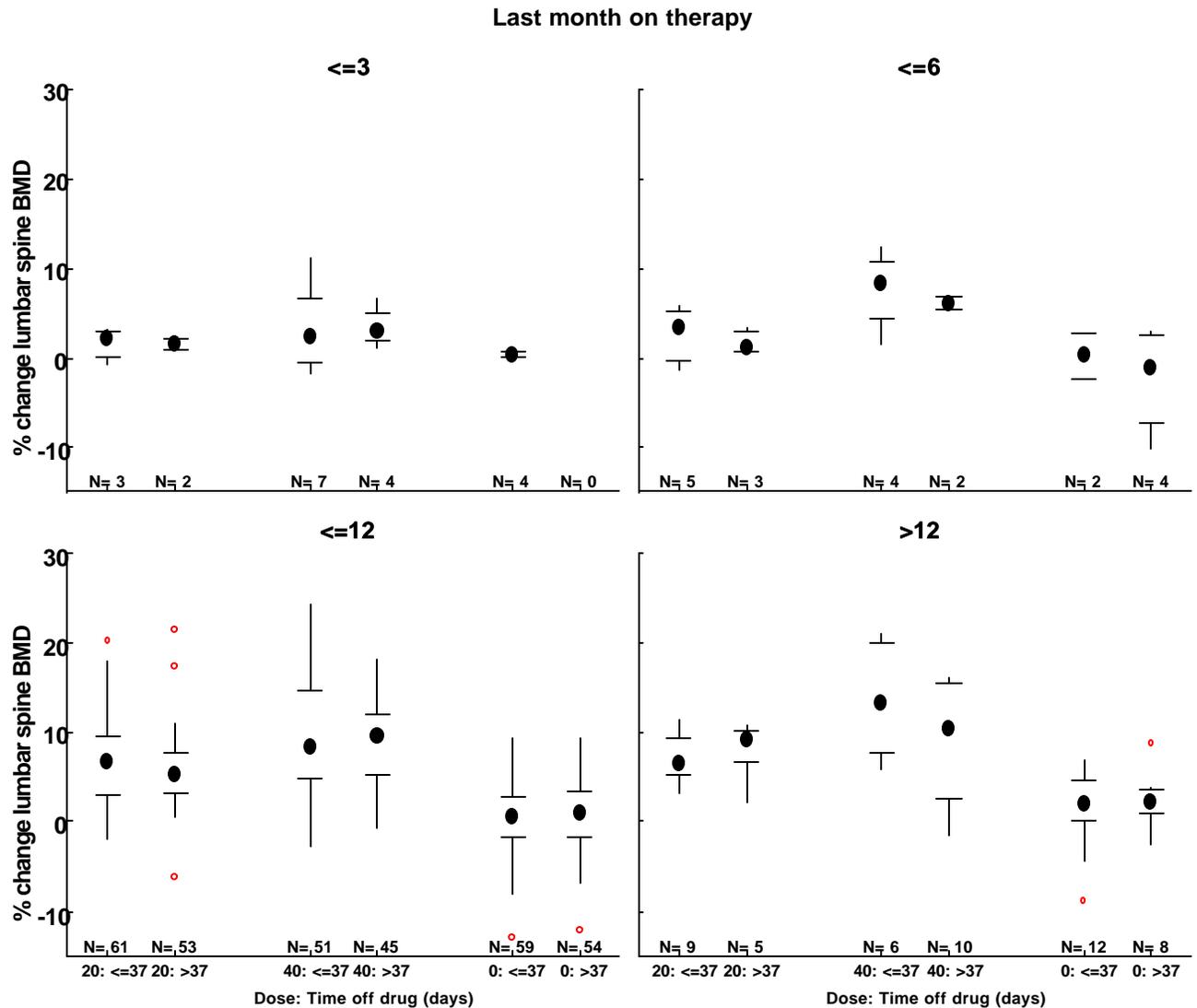
Appendix 2 Study GHAJ patients by last month on therapy



Appendix 3 Study GHAJ Boxplots of % change from baseline for lumbar spine BMD by treatment and by last month on therapy

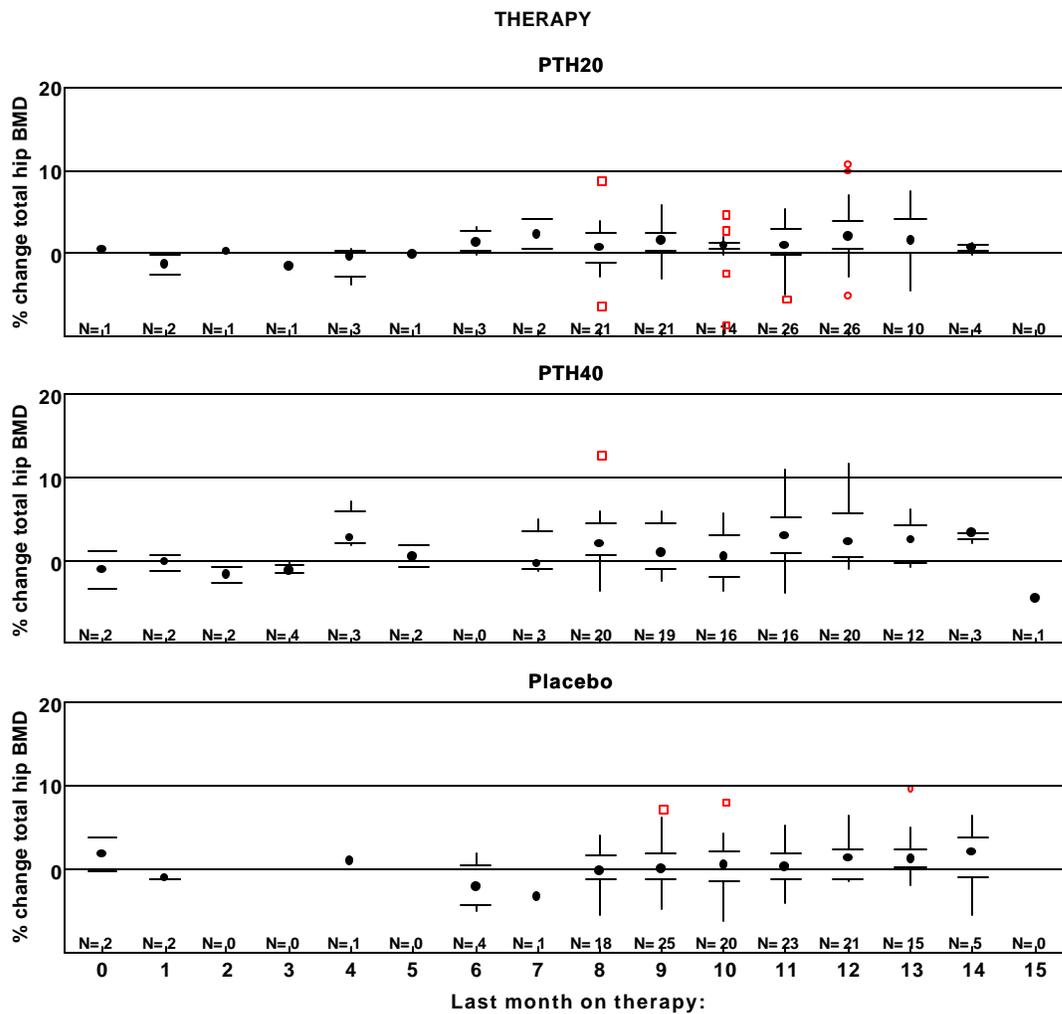


Appendix 4 Study GHAJ Boxplots of % change from baseline for lumbar spine BMD at endpoint by treatment, by last month on therapy and by time off therapy (cutoff is median of 37 days; time off is time from last dose to closeout visit)

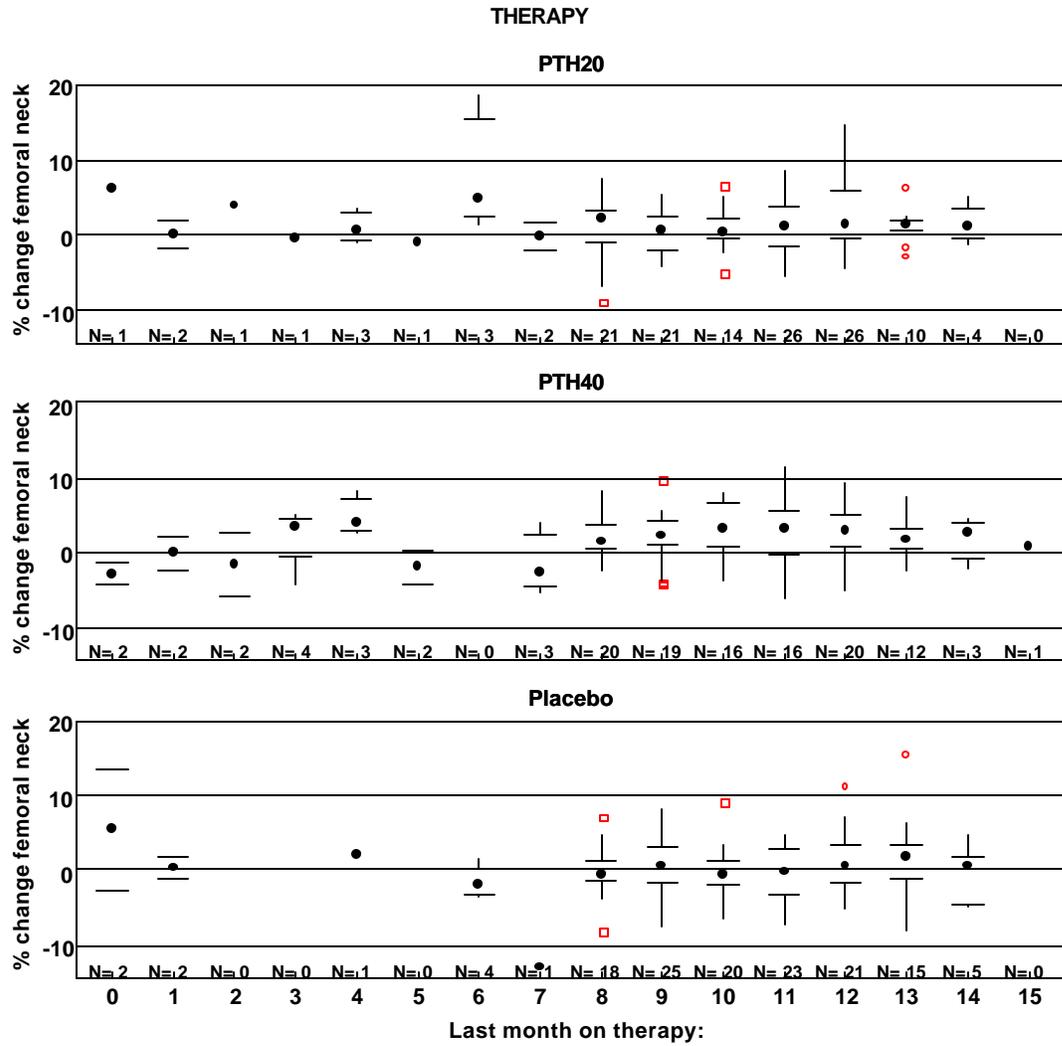


Note that each pair of boxplots represents a single dose level with the order from left to right of 20, 40, and 0. For each pair of boxplots, the box to the left represents data for patients with 37 or fewer days from last dose to closeout visit and the box to the right represents data for patients with more than 37 days from last dose to closeout visit.

Appendix 5 Study GHAJ Boxplots of % change from baseline for total hip BMD by treatment and by last month on therapy



Appendix 6 Study GHAJ Boxplots of % change from baseline femoral neck BMD by treatment and by last month on therapy



Appendix 7 Study GH AJ Boxplots of % change from baseline for whole body BMD by treatment and by last month on therapy

