

The sponsor attempted to analyze the effects of race on LY333334 pk. However, at least 98% of the study populations were Caucasian; thus the possible effects of race on pk could not be determined from the available database.

As noted above, systemic exposure to LY333334 was consistently lower in men than in women, across several clinical pharmacology studies. A composite analysis of gender effects showed that C_{max} and AUC_{0-t} were 16% and 19% lower in men than in women, respectively ($p < 0.05$). The cause of the difference is unknown. However, there were no differences in baseline endogenous PTH (1-84) levels according to gender, in several of the clinical trials, including GHAC and GHAJ. Comparing pk parameters in the two osteoporotic populations in trials GHAC and GHAJ, the men had significantly lower systemic exposure than women. In men, the median C_{max} was 25% lower, and the median $AUC_{0-\infty}$ was 30% lower, than in women.

Despite the gender-related differences in systemic exposure, there were no such differences in safety/tolerability profiles in any of the clinical trials, including GHAC and GHAJ. Gender-related differences in efficacy have been mentioned above and are discussed in greater detail in the review of the male osteoporosis trial, GHAJ.

There was no specific program to assess the effects of hepatic insufficiency on pk of LY333334, because the drug is not metabolized by hepatocytes. However, the sponsor analyzed the relationship between alterations in hepatic function and the disposition of the peptide. There was no relationship between LY333334 disposition and serum bilirubin, ALT, AST, or GGTP levels in studies GHAC and GHAJ.

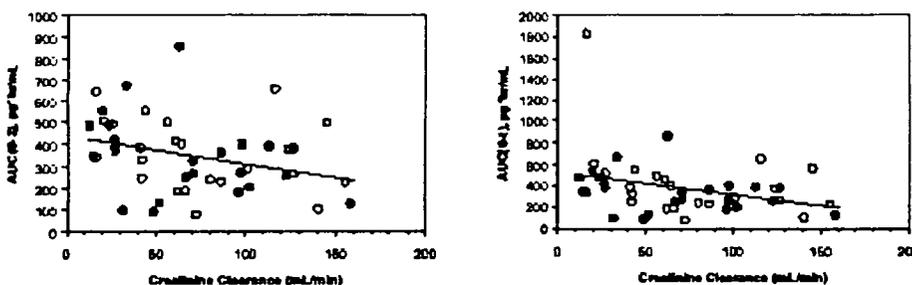
The effects of reduced hepatic blood flow were estimated indirectly by analyzing the adverse events reported by the 48 patients with congestive heart failure in the Phase 3 study GHAC. The sponsor believes that a reduction in hepatic blood flow in this subgroup of patients may have reduced the clearance of LY333334. However, since the major determinant of systemic exposure is the rate of absorption of the peptide from the s.c. injection site, the sponsor also believes that such a reduction would insignificantly affect the systemic exposure. The results of this analysis disclosed no increase in adverse events in this sub-population of patients with congestive heart failure.

The sponsor also studied the effects of renal insufficiency on the pk of LY333334 by assessing the disposition of a single 40 μ g dose of the peptide (with and without co-administration of furosemide) in patients with mild to severe renal insufficiency. Pharmacokinetic parameters observed in these patients were compared those following the same dose of LY333334 in normal subjects. The sponsor found no significant differences in any pk parameters between subjects with mild to moderate renal insufficiency and normals. The C_{max} , AUC_{0-3} ,

and AUC_{0-t} did not differ between healthy individuals and patients with creatinine clearance ≤ 30 mL/min (severe renal insufficiency). However, patients with severe renal impairment had statistically significant increases in $AUC_{0-\infty}$ (about 89% higher, $p < 0.02$) over values in healthy subjects. The sponsor re-analyzed the data for this parameter ($AUC_{0-\infty}$) using log-transformation, because a few of the patients had sustained concentrations of LY333334 in the terminal segments of the time curves. This created inhomogeneity of variance. Re-analysis of the log-transformed data disclosed no statistically significant differences, in any pk parameters, between normal subjects and those with severe renal impairment.

Comments: It appears that there were some outliers, but these values occurred both in normal individuals and in those with impaired renal function. The sponsor also notes that endogenous PTH 1-84 cross-reacts to some extent in their LY333334 assay. If the endogenous peptide levels are elevated in renal failure patients, this could falsely increase the measured LY333334 concentrations, particularly in the terminal segments of the concentration-time curves when levels of the latter peptide are low. It is likely that this accounts for the lack of statistical significance in the between-group comparisons of AUC_{0-3} and AUC_{0-t} .

Although there was a small overall increase in AUC_{0-3} and AUC_{0-t} with decreasing renal function (down to 13 ml/min), these increases are unlikely to be of clinical significance. To illustrate the individual data points, I have reproduced the sponsor's data depicting the relationships between creatinine clearance and both AUC_{0-3} and AUC_{0-t} below:



Open circles = LY333334 alone; closed circles = LY333334 + furosemide.

The sponsor also assessed the effect of renal impairment on LY333334 pk in population pk studies that were conducted as part of the large efficacy trials. Creatinine clearance had no effect on pk of the peptide in women in study GHAC. In men, the clearance of LY333334 was inversely proportional to the

measured creatinine clearance. However, the resultant increase in systemic exposure was small in men with renal failure.

Drug interactions:

No specific drug interaction studies were performed. LY333334 is cleaved by a high capacity enzyme system in Kupffer cells; and the enzymatic function of these cells is unlikely to be affected by co-administered drugs (unlike the drug-metabolizing enzymes within hepatocytes). In addition, as observed above, the sponsor believes that a change in clearance would not have a major effect on systemic exposure to LY333334, since absorption from the site of administration is the critical factor in determining duration of peptide exposure.

Comments: This is probably true, given the above considerations and the fact that 4 hours after administration of 20 µg of LY333334, the peptide cannot be detected in serum. In addition, LY333334 is administered once daily. Future studies should include evaluation of possible interactions with digitalis. These studies should be conducted in phase 4, if LY333334 is approved.

Population pharmacokinetics:

Population pk studies were performed on a subset of women in GHAC and on all the men in GHAJ. These were the two pivotal phase 3 studies.

For GHAC, pk sampling was performed in 37 of the 99 study sites. Of the 1637 women randomized into the trial, 616 participated in the pk studies (approximately 200 in each of the three arms: 20 µg, 40 µg, and PBO). For GHAJ, all 437 randomized subjects participated in the sub-study (about 150 patients in each of the 3 treatment arms). Serum LY333334 concentrations were evaluated at 1, 3, 6, and 12 months after beginning treatment. In addition, study GHAC included a sampling at 18 months.

The results of these studies were entirely consistent with the outcomes of the earlier (traditional) pk studies. Following a 20 µg dose, blood levels of the peptide rose to a maximum concentration of 160 pg/ml in women and 120 pg/ml in men, both maxima occurring 30 min. after injection. LY333334 levels were below limits of detection (50 pg/ml) by 3 hours in both men and women. The $AUC_{0-\infty}$ was 295.5 pg hr/ml in women and 208.6 pg hr/ml in men.

Comments: As mentioned above, the peak levels of immunoreactive LY333334 were about 4-5 times the upper limit of normal for endogenous PTH, on a molar basis. According to the sponsor, the rapid disappearance of LY333334 from serum, and the slight suppression of endogenous PTH for a few hours following exposure to LY333334, result in overall 24-hour PTH exposure that is less than that of individuals who maintain PTH levels

at the upper limits of normal (65 pg/ml by IRMA), and certainly less than in patients with mild primary hyperparathyroidism.

In my opinion, there are insufficient data to support this statement. It should be noted that the sponsor employed an immunoradiometric assay that has a lower limit of detection of 50 pg of PTH (1-34)/ml. This assay, which is not sensitive by current standards, is inadequate for optimal evaluation of the terminal segments of concentration-time curves. It is important to note that 50 pg of PTH (1-34) = about 123 pg of PTH (1-84), which is about twice the upper limit of normal. This level of sensitivity would be insufficient for the diagnosis of mild hyperparathyroidism, and the assay would be unacceptable in modern clinical practice. There are data from one study (GHAA) showing a small reduction in endogenous PTH (1-84) levels in patients treated with LY333334 in doses $\geq 30 \mu\text{g/day}$ for 6 weeks. I have found no systematic, timed pk studies that demonstrate this suppression in the NDA submission. In summary, I remain unconvinced that the total 24-hour exposure to biologically active PTH peptides in LY333334-treated individuals is less than that in normals. In the absence of hypercalcemia or hypercalciuria, the clinical implications of this are not apparent. However, we should not accept statements regarding total daily exposure to PTH peptides that are made in support of safety claims that are not directly related to calcitropic actions of the drug (e.g., potential for bone tumor induction).

Body weight: Over the range 39.5 kg to 120.0 kg in women (study GHAC) and 47.6 kg to 128.9 kg in men (study GHAJ), body weight did not influence apparent systemic clearance of LY333334. However, V/F (the apparent volume of distribution) increased with body weight in both women and men. When normalized for body weight, V/F remained at about 1.7 L/kg throughout the weight range. The peak concentrations of LY333334 tended to increase as body weight declined, but there was no appreciable change in total systemic exposure with decreasing body weight. There was no relationship between high serum LY333334 levels and episodes of clinically relevant hypercalcemia or hypercalciuria. Nor was there a relationship between high serum levels of the peptide and serious AEs. In addition, there were no statistically significant differences in BMD or bone biomarker responses based on body weight or BMI. Therefore, the small changes in peak concentrations and volume of distribution of the drug that are associated with changes in body weight have not been shown to be clinically important. Dose adjustments based on body weight in the studies range are not necessary.

Injection site: In the pivotal trials, approximately 60% of the patients chose the abdominal wall and the rest chose the thigh as the site of injection. There was an increase in volume of distribution of 21% in women and 30% in men following injection of the peptide into the thigh, resulting in a lower peak concentration but no difference in total systemic exposure. There were no apparent differences

with respect to AEs, serum and urine calcium levels, or lumbar spine BMD or biomarker responses, based on injection site.

In addition to the above investigations, there was no relationship between high serum concentrations of LY333334 (concentrations > the 95th percentiles for the 20 and 40 µg doses) and episodes of serious "drug-related" AEs, hypercalcemia, or hypercalciuria.

Pharmacodynamics

The principal pharmacodynamic parameter was the serum calcium response to graded doses of LY333334 over time. These studies addressed a major safety concern and were crucial in establishing a non-hypercalcemic dose of the drug. In Phase 2 studies, the time course of the serum calcium response was studied across a broad dose range (In studies GHAB, GHBA, and GHBI, the doses of LY333334 were 0, 5, 15, 20, 30, 40, 60, 75, 80, and 100 µg.).

Subjects in GHBA and GHBI were supplemented with approximately 1000 mg/day calcium and 500 IU/day vitamin D. These individuals received 0, 20, 40, and 80 µg of LY333334. In these studies, the serum calcium responses to any dose of drug did not differ from those that followed placebo injections. In study GHAB (in which there was no calcium or vitamin D supplementation), there was some evidence for a dose-related increase in serum total and ionized calcium, but the response was not uniformly proportional to the dose. In this study, the greatest responses were seen following the 75 µg dose; these exceeded those following the 100 µg dose. The largest maximal average increase was 0.189 mM in the 75 µg group and occurred 6 hours post-dose. The peak concentrations of both total and ionized calcium even in this group remained in the mid-normal ranges for both parameters.

Serum calcium levels appeared to decline from the 6-hour peak at the final (12-hour) time point, but did not return to baseline. In subsequent studies (phase 3), serum calcium levels were unchanged from baseline 24 hours post-dose. The calcium increases following a 30 µg dose were slightly less than those following 75 µg.

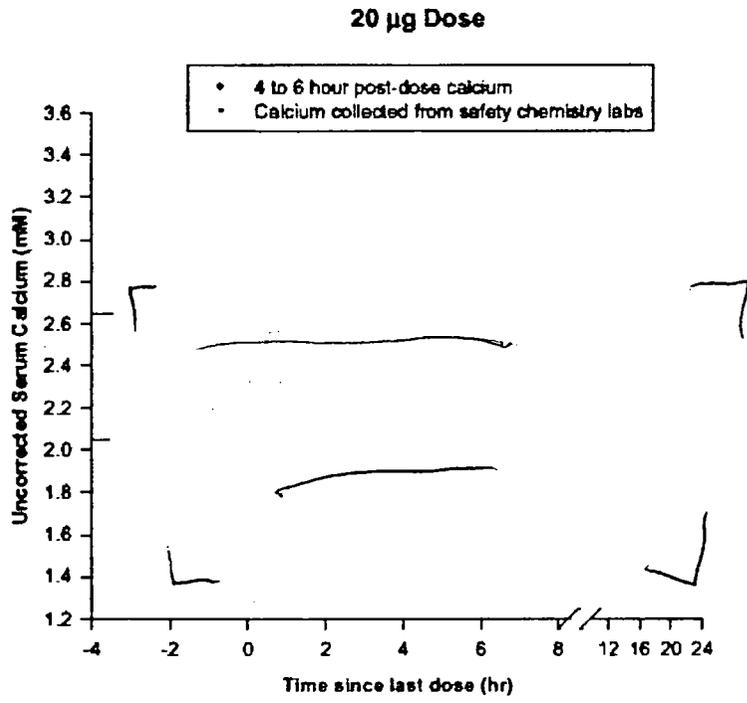
The calcium responses to a single dose of 20 µg (the indicated therapeutic dose) were not included in these early pharmacodynamic studies. However, based on the calcium responses to a wide range of LY333334 doses (both greater and less than 20 µg), the sponsor predicted that, following a single dose of 20 µg, maximal serum calcium levels should be reached by 5-6 hours and should return to baseline well before 24 hours. The maximal levels of calcium should generally fall into the normal range.

These predictions were generally borne out in the phase 3 trials. In GHAC and GHAJ, following long-term exposure to LY333334 (data were obtained at 3, 6,

12, 18, and 24 months), there was no statistically significant change in the 24-hour post-dose serum calcium, compared to baseline. The mean values were well within the mid-normal range for all 3 arms of this study.

However, in the phase 3 postmenopausal osteoporosis trial, GHAC, there was a significant, dose-dependent, and transient increase in the peak post-LY333334 serum calcium concentration. This peak occurred approximately 4 hours after each dose of the drug. In this sub-study, the sponsor recorded every serum calcium observation for which the time of drug dosing and blood sampling were known. The data are displayed in the sponsor's figure below. Since this graph incorporates data from all visits, several serum calcium observations from each patient have been included. Note that there is a higher density of observations in the 4- to 6-hour post-dose interval, because sampling at this time was part of the study protocol. The other time points represent serum calcium values derived from the safety laboratory tests, which were assessed without regard to time of dosing. The highest calcium level attained was about 3.0 mM, and levels above 2.8 mM occurred in about 13 instances among hundreds of samples. There were no elevations of serum calcium noted after 12 hours and only one noted after 7 hours.

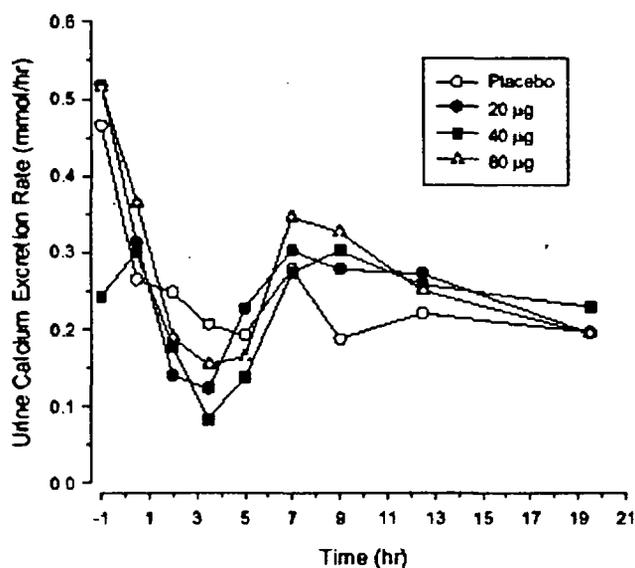
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The sponsor presents a similar graph for patients taking 40 µg/day in GHAC. The results are similar to the data in the 20 µg group, except that there are more data points above the normal range at 4-6 hours post-dose. All recorded data points were in the normal range by 7 hours post-dose. Of interest, there were approximately points (out of several hundred) in the range in the 40 µg group. Acute elevations of serum calcium to these levels would be of some concern. However, the indicated therapeutic dose is 20 µg/day, and elevations of calcium to this degree were not reported in patients receiving the 20 µg dose in the clinical trials. The possible relationship of acute calcium elevations to symptoms is discussed below.

Urine calcium:

Based on the known actions of PTH on the kidney, LY333334 administration was expected to reduce renal calcium excretion acutely. The sponsor investigated the time course of urinary calcium excretion in studies GHBA and GHBI. Urinary calcium was measured hourly for 24 hours following doses of 0, 20, 40, and 80 µg of LY333334. The data are shown in the sponsor's figure below:



Comments: The sponsor claims, on the basis of these data, that the acute pharmacodynamic effect of LY333334 on renal calcium excretion is similar to the known action of PTH on this parameter. The above graph shows an acute drop in renal calcium excretion following each dose of the drug. However, the placebo group (open circles) demonstrated renal calcium responses that were indistinguishable from those of the treatment groups. The reason for this is not known, but may relate to the timing of administration of calcium and vitamin D. The data fail to demonstrate any action of LY333334 on renal calcium excretion.

According to the sponsor, there was no statistically significant difference in the summed 24-hour urinary calcium excreted by subjects receiving any of these doses of LY333334, compared to placebo.

No pharmacodynamic studies of urine calcium responses to LY333334 were performed in phase 3 studies. However, 24-hour urine calcium excretion studies were included in the phase 3 program. These are discussed in the reviews of the individual phase 3 trials.

Serum and urinary phosphorus responses to LY333334: PTH reduces the serum phosphorus level by increasing renal phosphate excretion. There were minor, transient changes in serum and urinary phosphorus in response to LY333334 in the phase 2 studies. No pharmacodynamic studies of serum and urine phosphorus responses to LY333334 were performed in phase 3 studies.

Vitamin D metabolism:

PTH activates renal 1α -hydroxylase, an enzyme that is required for the formation of 1,25-dihydroxyvitamin D. Both the phase 2 and phase 3 studies demonstrated the expected changes in levels of this compound. In study GHAB, concentrations of 1,25-dihydroxyvitamin D rose in a parallel manner in response to single injections of LY333334, in doses ranging from 5 to 75 μ g. Maximum levels of 1,25-dihydroxyvitamin D were observed 6 hours after injection. The maximum response was an increase of 90% over baseline in response to 75 μ g of LY333334. The return towards baseline was slow, and average levels remained above baseline at the 12-hour time point.

Of greater clinical relevance, the sponsor measured the serum 25-hydroxy- and 1,25-dihydroxyvitamin D levels following long-term administration of LY333334 in the phase 3 trials. Following 12 months of treatment with 20 μ g LY333334/day in GHAC, the serum 25-hydroxyvitamin D concentration was reduced by 19% and the 1,25-dihydroxyvitamin D level was increased by 19%.

Comments: The increase in 1,25-dihydroxyvitamin D may reflect the action of LY333334. It is not clear that the reduction in concentrations of the precursor molecule reflect increased conversion to the active form of the vitamin, because the molar concentrations of the two moieties differ by three log orders.

Similarly, in GHAJ, 12 months' administration of LY333334 20 μ g/day resulted in an increase of 14% in concentrations of 1,25-dihydroxy-vitamin D. The smaller changes in men may reflect lower systemic exposure to the drug.

Comments: Increases in serum concentrations of 1,25-dihydroxyvitamin D of this magnitude might possibly enhance intestinal calcium absorption; this would improve overall calcium balance in osteoporotic patients. Examination of 24-hour urine calcium excretion rates following long-term exposure to the drug would indicate whether these increases in levels of biologically active vitamin D were associated with hypercalciuria.

Pharmacodynamic drug-disease and drug-drug interaction studies

Chronic renal insufficiency:

The sponsor examined the serum and urine calcium response to a single dose of 40- μ g dose in subjects with normal renal function and subjects with CLCr 72 to 13 ml/min (mild to severe renal insufficiency). Neither group had a significant serum calcium response to LY333334 and there were no episodes of hypercalcemia. The ionized calcium response to LY333334 was significantly less in subjects with renal impairment. There was no increase in renal calcium excretion. The results of this study suggest that subjects with chronic renal

insufficiency are not at an increased risk of developing hypercalcemia or hypercalciuria in response to 40 µg of LY333334. The long-term efficacy of LY333334 in subjects with severe renal insufficiency has not been studied, although patients with mild to moderate impairment were included in the phase 3 studies.

Comments: It should be noted that patients with renal insufficiency tend to have secondary hyperparathyroidism, and the effects of adding intermittent injections of exogenous PTH to a high background level of the hormone are not known.

Diuretics:

Diuretics can affect the renal handling of calcium, and many patients in the population with osteoporosis receive diuretic therapy. The sponsor examined the effects of co-administered hydrochlorothiazide and of furosemide.

Hydrochlorothiazide, 25 mg orally, did not result in clinically significant drug interaction. Specifically, the serum calcium response to 40 µg of LY333334 alone did not differ from that which followed LY333334 when co-administered with hydrochlorothiazide. Furthermore, the co-administration of the two drugs resulted in a statistically significant reduction of 24-hour urinary calcium that was only 15% less than that observed with LY333334 alone (study GHBA). The serum and urine phosphorus responses were also similar when LY333334 was administered alone or with hydrochlorothiazide.

LY333334 (40 µg) and rapidly infused i.v. furosemide were co-administered to subjects with normal and impaired renal function (CLCr 13 to 72 ml/min). There were small differences in serum and urine calcium responses between LY333334 alone and in combination with furosemide. These changes were not considered clinically relevant.

GHAA: a six-week pharmacodynamic multiple dose study

GHAA was an important phase 2 study that supported the choice of dose for the pivotal phase 3 trials. GHAA was a study of the effects of 6 weeks of treatment with several daily doses of LY333334, or placebo, on a number of parameters of mineral metabolism, including markers of bone formation and resorption. The treatment period was followed by an additional 6 weeks of observation off drug. An examination of changes in BMD was also performed as an exploratory investigation.

The primary efficacy variables in GHAA were PICP and BSAP. Both are serum markers of two aspects of bone formation. PICP (procollagen I C-terminal propeptide) measures new collagen synthesis in bone. This is one of the earliest biochemical events that occur during new bone formation, and PICP has been

shown to be the most suitable bone formation marker in short-term studies with PTH. BSAP (bone specific alkaline phosphatase) indicates enzyme activity of osteoblasts as they promote the mineralization of new bone matrix⁴. Urine NTX (N-telopeptide), an indicator of osteoclastic bone resorption, was also measured in this study. NTX is a product of bone collagen breakdown. As noted above, bone formation and resorption are usually coupled; and it is difficult to alter one process without affecting the other.

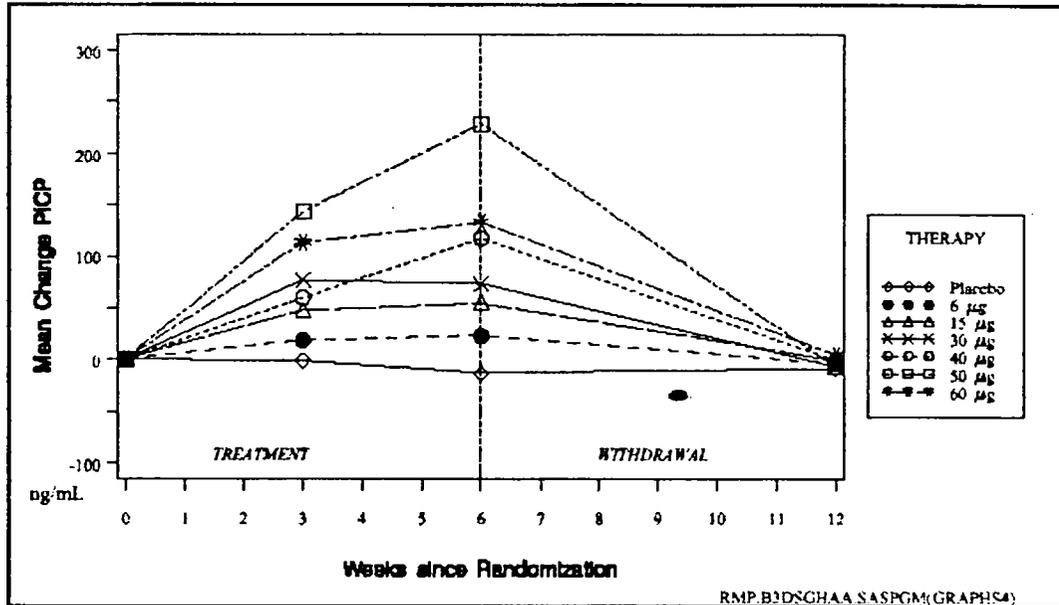
In GHAA, the investigators noted a dose-dependent mean increase from baseline in serum PICP within the LY333334-treated groups at the 15-, 30-, 40-, 50-, and 60- μ g doses, with statistically significant differences from placebo observed at Weeks 3 and 6 in these dose groups. At these time points, the investigators observed a statistically significant linear increase in change from baseline PICP with increasing doses of LY333334 ($p < 0.001$).

LY333334 induced rapid increases in levels of both formation markers. However, due to the greater variability in the BSAP measurements, the response of this marker reached statistical significance (compared to baseline) at 3 weeks only in the 50 μ g/day group. By Week 6, statistically significant increases in serum BSAP were seen in the 15-, 30-, and 50- μ g/day dose groups. There were no increases in formation markers in patients given 6 μ g LY333334/day. In this study, during the 6-week withdrawal phase (Weeks 6-12), PICP returned to baseline in all dose groups; however, serum BSAP levels declined slowly and were still increased over baseline by Week 12.

Data for PICP are presented below:

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⁴ Serum osteocalcin, another marker of osteoblast function, has been employed in other clinical trials. Osteocalcin levels change similarly to BSAP in response to PTH administration.



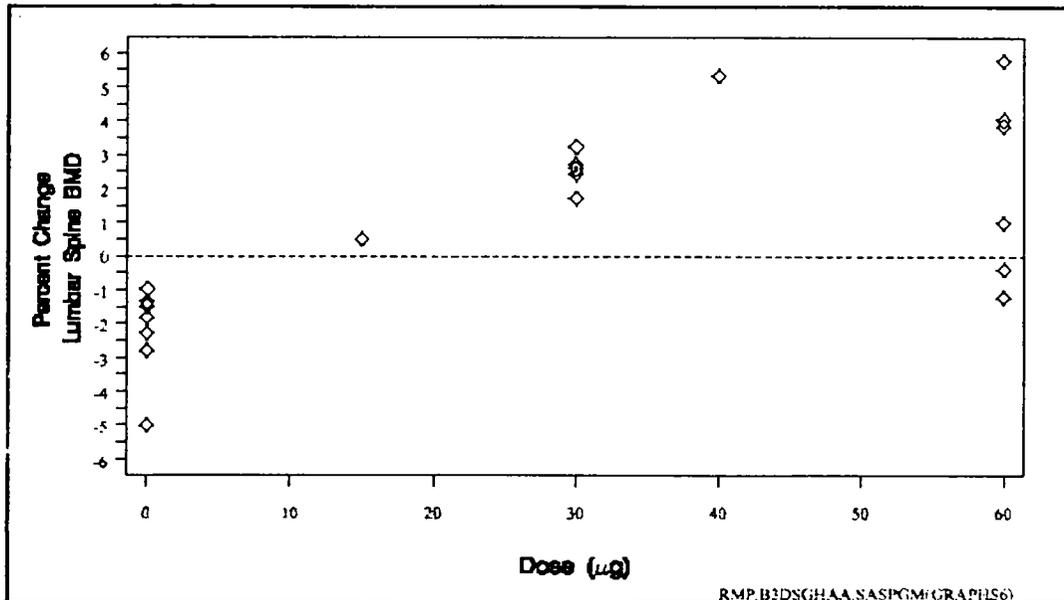
In this study, there was a decrease in mean urine N-telopeptide/ creatinine ratio (NTX/Cr) in both the placebo and 6-µg dose groups, starting at Week 3. In contrast, NTX/Cr increased numerically at Week 6 with doses of LY333334 ranging from 30 to 60 µg/day. The increases from baseline were statistically significant for the 50 and 60 µg/day groups. In addition, a statistically significant increase in NTX/Cr over placebo was observed in the two highest LY333334 dose groups (50 and 60 µg/day) at Weeks 3-12.

Thus for markers of bone formation, particularly for PICP, there was a strong dose-response relationship in the range 15-40 µg/day, beginning at Week 3. Statistically significant increases from baseline were observed in serum levels of PICP and BSAP with doses as low as 15 µg/day. Above 40 µg/day, there appeared to be an overall increase in formation marker response to larger doses, but the variability and small sample sizes limited the interpretation of the changes.

Urine NTX also showed a dose-response relationship that was less pronounced than for bone formation markers. Very little increase was seen in this parameter at any dose at Week 3. At week 6, there was no NTX increase over baseline or placebo at doses < 30 µg/day; only the 2 highest doses, 50 and 60 µg/day, showed statistically significant changes over baseline and over placebo.

Based on these studies, 6 µg/day had no effect on any bone metabolic parameters.

Baseline BMD studies were included in GHAA. Twelve-week follow-up lumbar spine BMD measurements were available for 22 patients in the placebo, 30-, and 60- μg dose groups and 1 patient each in the 15 and 40 μg groups. Despite the short treatment period, there was a statistically significant increase in mean lumbar spine BMD for both 30- and 60- μg dose groups when compared with the placebo group ($p < 0.002$). The data for % change from baseline are shown in the following figure:



Comments: These are probably the first controlled clinical data that demonstrate the BMD response to a short course of PTH. Although there are few data points, there appears to be an early and robust response in all but 2 of the patients treated with $\geq 30 \mu\text{g}/\text{day}$. All 8 placebo-treated patients lost BMD (by about 2% on average) during this period. This seems to be somewhat unusual for a 12-week time course, and it is unclear why this occurred in the placebo group. This response notwithstanding, the increases in the treated patients are impressive and are certainly consistent with the early elevations in bone formation markers in response to LY333334.

Based on overall assessment of adverse clinical and laboratory events, and of efficacy, the sponsor chose doses of 20 and 40 µg/day for the pivotal phase 3 trials of LY333334.

Comments: This was a rational decision and, as it turned out, a wise one. My only comment regarding the dosing schedule is that the sponsor did not investigate the effects of similar doses following less frequent administration. There are published animal studies that demonstrate efficacy of PTH following thrice-weekly administration. I believe that it would be informative to investigate this issue as a phase 4 study.

Population pharmacodynamics:

Population pharmacodynamic studies were based on data derived from the pivotal trials, GHAC and GHAJ. Pharmacodynamic endpoints were responses in lumbar spine BMD and bone biomarkers. The objectives of the population studies were to describe the time course of changes in these response variables, to evaluate the effect of gender on these responses, to identify patient factors that influence responses to the drug, and to evaluate the relationship between early changes in biochemical markers and subsequent increases in lumbar spine BMD.

Time course of changes in pharmacodynamic response variables:

The median observation time was 19 months in women and 11 months in men. Based on data for both males and females, the population-predicted time course of change in spinal BMD fitted a curvilinear model with maximum rate of increase occurring during the first year of treatment. The model predicted a 7.4% increase in BMD at 12 months for a typical patient receiving 20 µg/day and 10.9% increase for patients receiving 40 µg/day. In women, the model predicted increases of 9.9% for patients receiving 20 µg/day and 14.5% for those taking 40 µg. The model did not predict differences between males and females in these responses.

The effects of some covariates differed between genders. For example, the BMD responses increased somewhat with increasing age in women by not in men. The BMD increases over baseline (at 24 months) ranged (Fig. BPS 11.2, not reproduced here) from slightly > 8% in women aged 58 at entry to about 12% in women aged 80. Baseline lumbar spine BMD was a positive predictor of BMD response in men, but not in women.

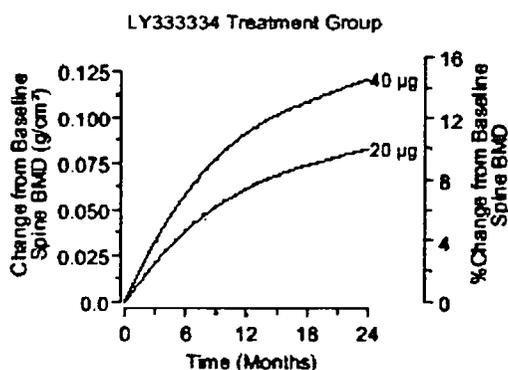
Serum endogenous PTH 1-84 was a predictor of BMD response in women but not in men. Women with low baseline endogenous PTH levels had a greater response to LY333334, compared to those with levels of the hormone that were near 65 pg/ml, the upper limit of normal.

Comments: This might be of importance in future development of LY333334 for indications in which there is some elevation of endogenous PTH, for example, renal failure or glucocorticoid-induced osteoporosis (GCIOP). Long-term studies of the efficacy of intermittent PTH in osteoporotic patients with renal insufficiency have not been done. Patients with GCIOP often have some degree of secondary hyperparathyroidism. There are published data (Lane et al, *JCI*, 1998; *J Bone Miner Res*, 2000; *Osteoporosis Int*, 2000) demonstrating substantial BMD responses to PTH in patients with GCIOP.

However, in postmenopausal osteoporotic women in study GHAC, the BMD increases from baseline to 24 months ranged from about 9% in the group with the highest endogenous baseline PTH levels to 11% in the group with the lowest levels of the hormone. Given the nearly universal and robust responses of lumbar spine BMD in this population, these differences are not likely to be clinically meaningful or informative in predicting responders.

The lumbar spine BMD responses were not influenced by serum free testosterone levels in men. Nor were the responses affected by baseline 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D levels, body weight, BMI, alcohol use, or smoking. The number of previous vertebral or non-vertebral fractures did not influence BMD responses in women. There were insufficient data to evaluate a possible effect of this parameter in men.

Dose: Irrespective of gender, the 40 μg dose produced a 1.5-fold greater increase in lumbar spine BMD, relative to the 20 μg dose (14.5% vs 9.9% increases over baseline at 24 months). The site of injection (abdomen vs thigh) did not influence BMD response to LY333334. The time course of lumbar spine BMD responses to both doses of LY333334 are shown in the next figure. Data were pooled from women and men (GHAC and GHAJ).



Influence of baseline levels of biochemical markers of bone turnover on BMD responses:

IN GHAC and GHAI, patients with high baseline levels of bone biomarkers (BSAP and NTX) had greater BMD responses to LY333334 than those with low levels, suggesting that the anabolic effect of the drug is enhanced in patients who have high turnover rates. However (Fig. BPS 11.6 of NDA), the differences in net increases were not very substantial (from about 8.5% BMD increases in patients with the lowest baseline BSAP or NTX levels to about 11% increases in BMD at two years in those with the highest levels).

Comments: Thus the data and the model would predict that LY333334 will be active in patients with osteoporosis that is associated with low bone turnover. This will be clinically important.

Biochemical bone turnover markers:

In GHAC and GHAI, LY333334, in doses of 20 or 40 µg/day, stimulated markers of bone formation (BSAP and P1CP) in a dose-dependent manner. The pharmacodynamic model showed that after 1 month of treatment, P1CP increased by 41% and 73% above baseline in patients treated with 20 and 40 µg/day, respectively. This was followed by a decline to near baseline levels by 12 months. BSAP levels were elevated early in treatment. In women, the model predicted maximum BSAP increases of 45% and 85% above baseline for the 20 and 40 µg groups, respectively, at 12 months. In men, the corresponding maximal BSAP values were 23% at 12 months and 55% at 5 months. There were also dose-proportional increases in NTX, consistent with the physiological coupling of bone resorption and formation. As with the formation markers, the NTX responses were substantially greater in women than in men, perhaps reflecting the greater systemic exposure in women.

The sponsor summarizes baseline covariates that had statistically significant effects on changes in bone biomarker responses (Table BPS 11.1 of the NDA). Consistent covariates were dose, gender, and endogenous PTH. Age, BMI, and baseline BMD affected biomarker responses inconsistently. The sponsor also presents a detailed population pharmacodynamic analysis of responses of each biomarker to the 20 and 40 µg doses of LY333334. These data will not be reviewed here. Of clinical relevance, the models consistently predict robust responses of biomarkers to both doses of drug, but with greater increases in response to the 40 µg dose.

Relationship between changes in bone biomarkers and BMD responses:

The sponsor performed population pharmacodynamic analyses of the relationship between changes in biochemical markers at 1 and 3 months with the

increases in lumbar spine BMD at 12 months. In this analysis, the biochemical marker concentrations at baseline, 1 month, and 3 months were combined with the patient factors that significantly influenced BMD response to the drug: dose, gender, baseline spine BMD, age, and endogenous PTH 1-84 at baseline.

The change in serum PICP concentration, from baseline to 1 month of treatment, correlated most significantly with increase in lumbar spine BMD at the 12-month time point. The relationship was seen in both dose groups and was more pronounced in women than in men (Fig. BPS 11.11 of the NDA).

Comments: The principal finding of this analysis is entirely in accord with the known mechanism of action of the drug. These data, together with similar results for the other biomarkers, provided further insight into the relationship between individual biochemical responses and increases in BMD.

Overall, the population pharmacodynamic studies helped to elucidate the complex relationships among patient-specific clinical and biochemical factors, LY333334 dose, and resulting BMD increases. However, the BMD responses were very robust; and, as will be discussed in the review of the pivotal trials, nearly universal. It is therefore unlikely that analysis of baseline covariates will influence clinical practice in individual cases of postmenopausal or male osteoporosis. In keeping with this, it is noteworthy that the sponsor identified no factors that could distinguish a patient as a non-responder in advance of treatment. On the other hand, knowledge derived from these studies will be valuable in the future development of LY333334 for other indications.

Comments on Safety/tolerability and choice of dose for the pivotal studies:

The phase 1-2 safety/tolerability data for multiple doses of LY333334 are reviewed in detail in the Integrated Summary of Safety. During these phases of drug development, the major clinical adverse experiences were associated with doses ≥ 40 $\mu\text{g}/\text{day}$. These AE's, principally nausea, headache, and orthostatic hypotension, generally occurred within 4-6 hours of dosing; and it is entirely possible that they resulted from acute elevations of serum calcium levels. Although the sponsor has attempted to correlate clinical AEs with hypercalcemia, the methodology employed is not adequate to resolve this issue. It is important to note that the rapidity of serum calcium increases may be more important than the level achieved, and symptoms can occur at concentrations that are only modestly elevated. In any case, during phase 1-2, no serious or unexpected laboratory or clinical safety concerns emerged in patients receiving 20 μg , and the incidence of adverse events began to increase following administration of 40 μg . The bone biomarker and BMD responses to 40 μg

consistently exceeded those that occurred in response to 20 µg. Although limited data are available, the biomarker and BMD responses to doses in excess of 40 µg were not enhanced further in any consistent manner. Six µg was found to be a no-effect dose. Since the adverse experiences increased substantially in patients given doses > 40 µg/day, the choice of 20 and 40 µg doses for the pivotal phase 3 trials was entirely appropriate. As it turned out, the fracture efficacy resulting from 40 µg/day in women (GHAC) did not exceed that which occurred in the 20 µg treatment group.

Final comments on clinical pharmacology section:

Overall, this part of the development program conclusively established robust and rapid pharmacodynamic responses to LY333334. The responses were predictable on the basis of knowledge of the biological action of intermittently administered PTH. The pharmacokinetic studies yielded results that were entirely consistent with the expected behavior of peptides of this size. Review of the traditional and population-based pharmacokinetic data disclosed no patient characteristics that would necessitate dose modification (see above). These results and predictions notwithstanding, in the male osteoporosis study, GHAJ, the choice of dose determined statistical significance in BMD efficacy at nearly all extra-vertebral sites (see review of GHAJ below).

Analysis of dose effects on biological response variables and well as on clinical and laboratory safety outcomes established 20 and 40 µg as the appropriate doses for testing in the subsequent pivotal trials. It would have been of great interest to test the pharmacodynamic responses to the 20 and 40 µg doses following less frequent administration (e.g., every other day), because this regimen might prove to be more acceptable to patients. I strongly suggest that this study be conducted in phase 4, if the drug is approved.

In the population pharmacodynamic studies, the sponsor examined approximately 30 demographic, clinical, and laboratory parameters from over 1900 men and postmenopausal women and found no effects or interactions that would necessitate modification of LY333334 dosing. The data support the conclusion that the drug can be administered to men and postmenopausal women without regard to age, body weight, BMI, cigarette or alcohol use, or mildly to moderately impaired renal function. Site of injection (abdomen vs thigh) did not affect safety or efficacy.

IV. Review of pivotal phase 3 trials

Description of clinical data sources: The sponsor has submitted four phase 3 controlled clinical trials in support of approval of LY333334 for the treatment of osteoporosis in men and postmenopausal women. The two pivotal trials were GHAC (osteoporosis in postmenopausal women) and GHAJ (osteoporosis in men). These are reviewed in detail below (Section VI). The two supportive phase 3 trials were GHAH (a comparison of effects of LY333334 vs alendronate in postmenopausal women) and GHAF (effects of LY333334 in postmenopausal women receiving HRT). These were also reviewed for efficacy in Section VI, but in much less detail because approval was not dependent on the outcomes of these supportive studies, because no labeling claims are made on the basis of these investigations, and because the only dose of LY333334 in these trials was 40 µg/day. The safety review is based on all patients from all trials of LY333334.

The clinical data were derived from all patients participating in the phase 3 trials. The NDA was submitted both in paper and electronic format. Clinical data were obtained from all the men and women who participated in the trials. In addition, data from the most recent safety updates were reviewed. Individual case report forms were also reviewed, as necessary.

V. Clinical Review Methods: See above.

VI. Review of Efficacy

This section contains detailed reviews of the two pivotal trials (GHAC and GHAJ) that were submitted in support of treatment claims for osteoporosis in postmenopausal women and in men. Reviews of two additional controlled clinical trials are also included in this section. Because of the size of the NDA submission and the number and complexity of the analyses, the reviews will focus primarily on major efficacy claims. I have chosen to review each trial separately, for multiple reasons. These include differences in gender, therapeutic indications, treatment populations, time on trial, susceptibility to adverse events, primary and secondary endpoints pk-pd data, among others. However, following the individual trial reviews, I have included an Integrated Summary of Efficacy across trials. A complete Integrated Review of Safety follows the individual efficacy reviews.

A. Major findings in light of proposed labeling claims

Study GHAC: In patients with postmenopausal osteoporosis, 19 months of treatment with LY333334 20 µg/day, was associated with a 65% relative reduction, and a 9% absolute reduction, in the proportion of patients with new morphometric vertebral fractures. In this same population, there was a 53% relative reduction, and a 3% absolute reduction, in the proportion of patients with new non-vertebral fractures, when all fractures were combined. There were no statistically significant decreases in fractures at individual extra-vertebral sites (e.g., hip, wrist), in association with LY333334 treatment, although the study was not powered to detect such treatment-related differences. There were statistically significant increases in BMD at the lumbar spine and at several extra-vertebral sites, associated with LY333334 treatment. Although the BMD responses to LY333334 40 µg were greater than those associated with 20 µg, the two doses did not differ in fracture efficacy. Thus, GHAC established 20 µg as the dose for this indication.

Study GHAJ: In men with idiopathic osteoporosis or osteoporosis associated with primary hypogonadism, treatment with LY333334 for 11 months resulted in a mean placebo-subtracted difference in BMD at the lumbar spine of 5.35% in the 20 µg group and 8.51% in the 40 µg group. A responder analysis showed that 54.6% of LY333334-treated patients in the 20 µg group had spinal BMD increases of 5% or more, compared to 9.8% in the placebo group. LY333334 20 µg/day was effective in increasing lumbar spine BMD in both hypogonadal and eugonadal patients.

In this same population, treatment with LY333334 20 µg/day resulted in placebo-subtracted increases in BMD of 1.24% at the femoral neck ($p < 0.029$). Although there were positive trends at several other skeletal sites, none achieved statistical significance, using endpoint data. At the lumbar spine, total hip, femoral neck, intertrochanter, and Ward's triangle, the LY333334 40 µg group had substantially and statistically significantly greater increases in BMD, compared to the 20 µg group. In my opinion, osteoporotic men will likely derive greater benefit from a dose that is intermediate between 20 and 40 µg/day. This is most probably due to the lower systemic exposure to the drug in men.

At the lumbar spine, the fracture efficacy (women) and BMD (men and women) responses exceeded those which have been reported for any approved agent. Despite substantial fracture and BMD efficacy at the lumbar spine, treatment with LY333334 20 or 40 µg, had no effect on prevention of height loss in either men or women.

Bone biomarker studies confirmed a rapid anabolic action of the drug in both men and women.

Aside from the unresolved issue of osteosarcomas in rats, there are no major safety issues that cannot be resolved fairly expeditiously in additional studies (see Safety Review).

B. Review of individual studies

B.1 Reviewer's trial #1; Sponsor's trial B3D-MC-GHAC

"Effects of LY333334 in the Treatment of Postmenopausal Women with Osteoporosis"

B.1.1 Design

GHAC was a randomized, double-blind, placebo-controlled, 3-treatment-arm, multi-center (99 US and multinational) trial of the efficacy and safety of LY333334 in the treatment of postmenopausal osteoporosis. The trial population consisted of 1637 postmenopausal women, aged 30-85 years, with at least one moderate or two mild atraumatic vertebral fractures. Patients were randomized 1:1:1 to placebo, LY333334 20 µg/day, and LY333334 40 µg/day. Initially, the patients were prospectively divided into two identical sub-groups in order to form two sub-studies for separate analysis. It was originally intended that GHAC would be analyzed as a whole and that, in addition, each sub-study would be analyzed independently. This was done in order to meet regulatory requirements that existed at the time the study was initiated. This issue is discussed further in the Statistics Section.

The intended treatment duration was 3 years. The design included a calcium + vitamin D run-in phase of 2 weeks to 6 months, an injection run-in phase of 2 weeks, a treatment phase of 3 years, and a randomized extension phase of 2 years. However, the trial was terminated after an average treatment period of 750 days due to findings of osteosarcomas in a long-term study of rats treated with LY333334. At that time, patients had completed the first two phases plus 16-23 months (median time 19.3 months) of placebo-controlled treatment. In agreement with the Division, the data available at close-out were submitted in support of the indication.

B.1.2 Objectives

Primary objective:

As stated by the sponsor, the primary objective of GHAC was *"to demonstrate a reduction in the proportion of patients with new vertebral fractures following 3-year treatment with 20 and 40 µg/day of LY333334 plus calcium and vitamin D compared with calcium and vitamin D alone."*

Secondary objectives:

The sponsor lists 10 secondary objectives. These are (verbatim):

- 1) To establish the safety of chronic administration of LY333334 in postmenopausal women with osteoporosis.
- 2) To establish the effect of long-term treatment with LY333334 plus calcium and vitamin D, compared with calcium and vitamin D alone, on lumbar spine and hip bone mineral density in postmenopausal women with osteoporosis.
- 3) To establish the effect of long-term treatment with LY333334 plus calcium and vitamin D, compared with calcium and vitamin D alone, on total body and radial (forearm) bone mineral density in postmenopausal women with osteoporosis at selected study sites.
- 4) To establish the effect of long-term treatment with LY333334 plus calcium and vitamin D, compared with calcium and vitamin D alone, on the rates of new nonvertebral fractures alone and of new nonvertebral and vertebral fractures combined in postmenopausal women with osteoporosis.
- 5) To assess the effect of long-term treatment with LY333334 plus calcium and vitamin D, compared with calcium and vitamin D alone, on height (via ~~stadiometer~~ or other suitable stadiometer) in postmenopausal women with osteoporosis.
- 6) To determine the histomorphometric effects of long-term therapy with LY333334 plus calcium and vitamin D, compared with calcium and vitamin D alone, on the iliac crest in postmenopausal women with osteoporosis at selected study sites. The histomorphometric effects being evaluated included bone formation and resorption, mineralization, and trabecular structure.
- 7) To assess the effects of LY333334 plus calcium and vitamin D, compared with calcium and vitamin D alone, on biochemical markers of bone formation and resorption (bone-specific alkaline phosphatase [BSAP], serum procollagen I C-terminal propeptide [PICP], urinary N-telopeptide [urinary NTX], and urinary free deoxypyridinoline) in postmenopausal women with osteoporosis at selected study sites.
- 8) To assess population pharmacokinetics of LY333334 at selected study sites.
- 9) To quantify medical resources used by patients during the study so that a cost-effectiveness analysis can be performed.
- 10) To assess the impact of LY333334 on health-related quality of life in postmenopausal women with osteoporosis at study sites where translated and validated instruments were available.

Comments: Meeting the primary objective establishes the drug's efficacy for the treatment of osteoporosis. The list of secondary objectives includes many of the elements of standard osteoporosis treatment trials, plus two new items (9 and 10).

Issues relating to the use and misuse of multiple secondary endpoints in clinical osteoporosis trials recur frequently in drug labeling, in advertising claims, and in the scientific literature. It is necessary to strike a balance between practicality and requirement for new knowledge on the one hand, and formal statistical rigor on the other. The manner in which results are

reported, particularly with regard to the use of p-values, needs to be examined carefully.

The choice of new vertebral fractures as the primary outcome variable was based on the relatively high frequency of their occurrence in the osteoporotic population and the demonstrated reduction in their incidence in several trials of other osteoporosis drugs. In this study, "vertebral fracture" is defined as a radiographic deformity. Most of these "morphometric" fractures are not symptomatic. However, the presence of a vertebral fracture is an indicator of bone fragility and a strong predictor of subsequent fracture. It is noteworthy that the sponsor removed from the study any patient who sustained more than one new moderate vertebral deformity, thus reducing the risk of long-term morbidity in this trial.

B.1.3 Protocol

B.1.3.1 Populations

Inclusion criteria:

- The trial population consisted of ambulatory, postmenopausal women, 30 to 85 years of age at the time of entry into the study.
- Patients were to have been postmenopausal (defined as permanent cessation of ovarian function as a result of natural menopause, surgery, or chemotherapy) for a minimum of 5 years prior to randomization. Women with amenorrhea secondary to other causes (e.g., eating disorders) were not eligible.
- Each patient had a minimum of either one moderate or two mild atraumatic vertebral fractures, and a minimum of seven evaluable non-fractured vertebrae.⁵
- In patients who had fewer than two moderate fractures or had been treated with therapeutic doses of bisphosphonates or fluorides, the BMD at the hip or lumbar spine had to be at least 1.0 standard deviation below the mean for young, healthy women (T-score).
- Baseline serum calcium, PTH(1-84), and urine calcium were within normal limits, and the serum concentration of 25-hydroxyvitamin D was between the lower limit of normal and 3x the upper limit.

⁵ Fractures were evaluated visually using a semiquantitative method (Genant et al. 1993). A "mild" vertebral fracture corresponded to approximately a 20% decrease in anterior, central, or posterior vertebral height (T-4 to L-4) of the average of the adjacent vertebrae; a "moderate" fracture corresponded to approximately a 25-40% decrease in one of these heights. A fracture was atraumatic if it was not caused by injury that was severe enough to cause a fracture in a normal skeleton. Further description of the methodology appears in the following sections.

Exclusion criteria:

- Metabolic bone disease other than postmenopausal osteoporosis.
- Fractures in areas of bone affected by diseases other than osteoporosis.
- Any disease that affects bone metabolism.
- Carcinoma (other than excised superficial lesions).
- Nephrolithiasis, urolithiasis, sprue, inflammatory bowel disease, malabsorption syndrome, any indication of poor intestinal calcium absorption, significantly impaired hepatic or renal function.
- The following treatments were grounds for exclusion, depending on duration of use and dose of the drug: glucocorticoids (including systemic, topical, intra-articular, inhaled, nasal), androgens, bisphosphonates, calcitriol (or agonists), calcitonins, calcium-or aluminum-containing antacids, fluorides (other than fluoridated water or topical dental treatments), estrogens, progestins, coumarins, heparin, anti-convulsants (except benzodiazepines), and any other drug that affects bone metabolism.

B.1.3.1.1 Removal of patients from trial

The sponsor lists a number of causes for removal of patients from assessment or active treatment, or for reduction of dose during treatment. These causes were pre-specified. They include any request by the patient, the physician, the investigator, or the sponsor that the patient be withdrawn; a decision by the investigator or the sponsor to stop the study; the development of an exclusion criterion during the study; or non-compliance. Additionally, if, in the opinion of the investigator, a clinically significant "drug-related" adverse clinical or laboratory event occurred, the study drug could be discontinued.

Reductions in dosage (or discontinuation) of calcium or injectable study drug were pre-specified for increases in serum and/or urinary calcium above normal ranges. In addition, dose reduction or discontinuation was pre-specified in the event of anticipated adverse events (nausea, dizziness, orthostatic hypotension).

Patients could be discontinued from study following accelerated bone loss, which was defined as follows:

For lumbar spine BMD, loss >7% anytime in first year; > 9% anytime in second year. For femoral neck, >9% anytime in first year, >11% anytime during second year.

Blinded BMD readings and notification of investigator in the event of accelerated bone loss were performed according to standard procedures for safety monitoring during osteoporosis trials. Patients who had been in the study for >12

months prior to discontinuation were given the option of receiving LY333334 on an open-label basis for 2 years, at the discretion of the investigator.

If, during the trial, a patient experienced > 1 new moderate vertebral fracture, or a non-vertebral osteoporotic fracture, she could be discontinued from the study. All vertebral fractures were confirmed by the centralized x-ray facility; non-vertebral fractures were documented by x-ray and a written radiology report. As for patients with accelerated BMD loss, those in the study for > 12 months prior to discontinuation were given the option of receiving LY333334, open-label, for 2 years, at the investigator's discretion.

All patients who were discontinued from the study received a standardized clinical and laboratory assessment. The assessment included physical examination, assessment of AEs, a battery of standard chemistry and hematology tests, and laboratory/radiological evaluation of mineral-related parameters (serum and urine calcium, serum 25-hydroxyvitamin D levels, lateral thoracic and lumbar spine x-rays, lumbar spine and hip BMD, and LY333334 antibodies). For a subset of patients who discontinued, the assessment included bone biopsy, serum 1,25-dihydroxyvitamin D levels, bone biomarkers, and total body and radius BMD.

B.1.4 Treatments, concomitant therapy, and schedule of events

B 1.4.1 Treatments

All patients received calcium and vitamin D supplementation (approximately 1000 mg elemental calcium/day and 400-1200 IU vitamin D/day) open-label for a minimum of 1 month prior to randomization. Patients continued this supplementation throughout the course of the study. The supplements were taken at any time of the day.

Comments: Postmenopausal women generally require about 1200 mg of elemental calcium/day to maintain balance of the mineral. This addition to the amount of calcium present in a normal diet should be sufficient. The vitamin D supplementation is adequate.

LY333334 was supplied in a pre-filled _____ PTH injection device. The device contains a cartridge containing 3 ml solution; each ml contained LY333334, 0.5 mg/ml (40 µg/day), 0.25 mg/ml (20 µg/day) or carrier solution (placebo). The devices are stored in a refrigerator (2-8° C).

During the first run-in period, patients were instructed in the use of the _____ PTH injection devices. Following this, patients injected the study drug subcutaneously into the abdomen or outer thigh, rotating injection sites

each day. After an initial period, patients chose the injection site (abdomen or thigh), but alternated daily from side to side within each chosen region.

Patients were randomly assigned to one of the 3 treatment groups. The randomization procedure is provided in the application.

B.1.4.2 Prior and concomitant therapy

Please refer to excluded drugs in Section **B.1.3** above. During the trial, patients were permitted to take intra-vaginal or oral estriol, ophthalmic and otic corticosteroids, topical dental fluoride, fluoridated water. Following randomization, patients were not permitted to receive systemic, topical, nasal, inhaled, or intra-articular corticosteroids.

Total non-dietary calcium intake, including the calcium supplementation mandated by the study protocol and calcium-containing antacid medication, was not to exceed 1200 mg of elemental calcium/day. Aluminum-containing antacids were limited to five doses per week. If a patient received protocol-excluded medication, the investigator was to notify the sponsor, who decided if the patient would be allowed to continue. Concomitant medications were recorded in the clinical report forms.

B.1.4.3 Compliance

Injectable study material was returned to the investigator at each patient visit. The amount of used and unused medication was determined (cartridge counting) and recorded. Patients missing more than 50% of the injectable doses over two consecutive visits, and had participated in the study for more than 1 year following randomization, may have been discontinued from the drug and the study. Those patients with post-baseline data were included in the intent-to-treat analysis.

B.1.4.4 Schedule of events

As indicated above, the original protocol included a calcium + vitamin D run-in phase of 2 weeks to 6 months, an injection run-in phase of 2 weeks, a treatment (either of the 2 doses of LY333334 or placebo) phase of 3 years, and a randomized extension phase of 2 years.

The design is illustrated in the following (sponsor's) figure:

EXAMINATION	PRE-TREATMENT PHASE	TREATMENT PHASE	EARLY DISCONTINUATION#
Adverse event reporting	once	each visit	yes
Sitting BP and HR	once	each visit*	yes
Height, weight	no	Months 0, 12, 24, 36	yes
Dietary Ca assessment	no	Months 0, 36	yes
Serum Ca and albumin (4-6 h post-dose)	yes	each visit*	yes
TSH, PTH 1-84	yes	no	no
25-OH-vitamin D	yes	Months 0, 12, 24, 36	yes
Biochemical markers of bone turnover	no	Months 0, 1, 3, 6, 12, 24, 36	yes
1,25-(OH) ₂ (subset)	no	Months 0, 1,3,6, 12, 24, 36	yes
24-h urine Ca, Cr, P	yes	Months 1, 6, 12, 24, 36	yes
PTH 1-84 post-screening (subset)	no	Months 0, 12, 24, 36	yes
LY333334 antibodies	no	Months 0, 3, 12, 24, 36	yes
Serum LY333334 concentration, subset	no	Months 1, 3, 6, 12, 18, 24, 36	yes
Lateral thoracic and lumbar spine x-rays	yes	Months 0, 24, 36	yes
PA lumbar spine BMD	yes	Months 0, 3, 6, 12, 18, 24, 36	yes
Hip BMD	yes	Months 0, 12, 24, 36	yes
Total body and radial BMD (subset)	no	Months 0, 12, 24, 36	yes
Bone biopsy (subset)	no	Month 0; Month 12 or 24	yes
Misc.(health-related QOL, medical resource utilization)	no	Month 0, then every 3 or 6 months	yes

* excluding telephone contact visits

early discontinuation visits that occurred after December 17, 1998 as a result of the sponsor's termination of the study are referred to as study closeout visits

the NDA. For approximately 10% of the patients, the final scores for the baseline x-ray film were lower than the screening criteria (1 moderate or 2 mild vertebral fractures), reflecting intrinsic inter-rater variability.

I have outlined the relationship between the semiquantitative visual assessment grades and change in vertebral height in the following table:

Grade	Fracture severity	Definition
0	normal	< 20% reduction in anterior, mid, and/or posterior vertebral height
1	mild	20-25% reduction
2	moderate	25-40% reduction
3	severe	>40% reduction

The primary analysis was the proportion of patients with new vertebral fractures as defined by this semiquantitative analysis.

Comments: It is helpful to summarize the analytical methodology by recalling that entry criteria included the presence of one moderate (Grade 2) or two mild (Grade 1) non-traumatic vertebral fractures at baseline, as well as at least 7 evaluable non-fractured vertebrae (i.e., Grade 0). To meet the criterion for a new vertebral fracture required a change in fracture status (for a minimum of 1 vertebral body) from Grade 0 at baseline to Grades 1, 2, or 3 at endpoint. The number and proportion of patients with new moderate or severe fractures (a change from Grade 0 to Grades 2 or 3) were analyzed separately. Worsening fractures would be defined in this system as a change from Grade 1 to 2, 1 to 3, or 2 to 3; however, these were not included in the analysis.

The individual fracture assessment results, obtained from the four x-ray readers who participated in this study, are included in Appendix 16.1.13. Analysis of inter-reader reliability for the digitized images used in this study yielded kappa-scores ranging from _____

Height (a secondary objective) was measured using a _____ stadiometer, or other stadiometer, at baseline, yearly, and at early discontinuation or study closeout visit.

Another secondary outcome variable was the incidence of new non-vertebral fractures alone, and the incidence of new vertebral and non-vertebral fractures combined. Non-vertebral fractures were assessed only when clinically indicated. Fractures were confirmed via a radiologist's written report or by review of the x-rays. New non-vertebral fracture sites were recorded as hip, radius, ankle, humerus, ribs, foot, pelvis, or other. Investigators were also asked to report

whether the fractures were traumatic (defined per protocol as a fracture caused by a "wound or injury that is severe enough to cause a fracture in an otherwise healthy person").

Bone Mineral Density:

In all patients, lumbar spine BMD measurements were performed at baseline, Months 12, 18, 24, and early discontinuation or study closeout. Approximately 1/3 of the patients had additional lumbar spine BMD measurements at Months 3 and 6. At a subset of the study sites, patients (approximately 425) had DXA scans of the radius at baseline and Month 24 and early discontinuation or study closeout. At most of these study sites, the patients also had total body BMD DXA scans at baseline, Months 12 and 24, and early discontinuation or study closeout.

Quality review of all scans was performed at two centers: _____

_____. The scans that were excluded for technical reasons (2 spine, 11 femur, 8 forearm, and 7 total body) are listed in the NDA (Appendix 16.1.14). This section also contains precision, range-of-believability, and outlier quality assurance checks.

All scans used _____ densitometers. Results derived from the different scanners were converted to standardized units and pooled for efficacy analyses (Lu et al. 1997; Steiger 1997). In addition, correction factors generated from DXA phantoms were used by the QA Center to control for differences among densitometers produced by the same manufacturer, as well as longitudinal variations within individual densitometers. Longitudinal quality control and cross-calibration correction data, and all raw BMD data, are included in the NDA (Appendix 16.1.14).

For all skeletal sites, the primary analysis of BMD data was the mean percent change from baseline to endpoint using an ITT approach with LOCF. The data set was derived from all randomized patients with both a baseline and at least one post-baseline value. The patient's last post-randomization value was considered the endpoint result. Additionally, the sponsor analyzed BMD changes from baseline to each visit, including only patients who had data at that visit.

Biochemical markers of bone turnover:

To help elucidate the time course and nature of the effects of LY333334 on the bone remodeling process, the sponsor measured biochemical markers of bone turnover at pre-specified intervals during the trial. The markers of bone formation were BSAP and PICP; markers of resorption were urinary NTX and urinary free deoxyypyridinoline. A brief description of the nature and utility of this set of

biomarkers has been provided above, in **Section III**. Levels of these biomarkers, as well as serum concentrations of 1,25 dihydroxyvitamin D, were measured in a subset of approximately 500 patients at baseline, Months 1, 3, 6, and 12, and Early Discontinuation or study closeout. The sponsor has provided the demographic and other baseline characteristics of this subset of patients in Table GHAC.14.2 of the submission.

The change (and % percent change) in biochemical markers were generally not normally distributed. To evaluate central tendency, the sponsor presents the median and statistical significance from ANOVA with ranked data. Analyses of variance with unranked data are also included in the submission.

Comments: The measurements of incident fractures, BMD, and biochemical markers of bone turnover were all performed according to standardized, well-established methodologies. The sponsor's approach to the treatment of continuous bone marker data that are not normally distributed is appropriate, although other approaches have been successfully applied to this problem.

Patients who participated in GHAC contributed to the overall population pk-pd analysis, reviewed in **Section III** above and independently by biopharmaceutics. A brief review of GHAC-specific population pk-pd data is provided below.

The methodologies for the remaining secondary analyses (QOL, pQCT, and histomorphometry) are presented briefly in the appropriate subsections.

B.1.6 Statistical considerations

Originally, GHAC was to have consisted of two identical sub-studies, to meet regulatory requirements at the time of initiation. The two sub-studies would undergo independent analyses. Plans for prospective allocation of patients into each of the two studies are provided in the submission. GHAC was designed to enroll at least 1476 patients, with approximately 492 assigned to each treatment group. When the study was designed, approximately 295 patients in each group were expected to complete a 3-year double-blind treatment phase.

The primary comparison in GHAC is the between-group difference in the proportions of patients with new vertebral fractures. Based on an anticipated rate of approximately 60 new vertebral fractures per 1000 patient-years in the placebo group, and a 50% reduction in rates for the patients treated with LY333334, each sub-study was to have >75-80% power to detect a significant treatment effect (2-tailed chi-square test of proportions at the 0.05 level) at 3 years, when the data from the two LY333334 dose groups were pooled. Using the same assumptions, the sponsor predicted that the two sub-studies combined would have > 90%

power to detect a significant treatment effect with either dose compared to placebo.

Comments: These predictions were well founded, based on published information and results of other osteoporosis trials (e.g., the Fracture Intervention Trial, which was reported after the start of the LY333334 studies).

B.1.7 Changes in conduct of the study/analyses

The single significant change in conduct of GHAC was the premature termination of the study due to the unexpected finding of osteosarcomas in rats given LY333334 in a long-term carcinogenicity study. The termination led to necessary changes in the analyses of outcomes. On December 8, 1998, the sponsor suspended further administration of the injectable study drug in GHAC (as well as all ongoing clinical trials of LY333334). All patients in GHAC continued their oral medications and returned for all scheduled study visits. A review of the 12-month interim safety data was conducted by the DSMB on December 17, 1998, and no significant issues were identified. At that time, the sponsor instructed the investigators to have all patients complete the Early Discontinuation Visit. As indicated above, early discontinuation visits occurring after December 17, 1998, are referred to as "study closeout visits."

As of December 17, 1998, patients in GHAC had completed 16 to 23 months of the double-blind treatment phase. About 90% of patients completed study closeout visits by February 1, 1999, and the last patient visit occurred on April 12, 1999.

The median interval between drug discontinuation and closeout was 5-6 weeks; consequently, changes were made in the efficacy and safety analyses. Additional, by-visit analyses were performed for all efficacy and safety variables with the exception of fractures and adverse events. The reader is referred to the reviewer's table of scheduled procedures in Section B.1.4.4 above. To assess treatment-related effects while patients were taking the study drug, the sponsor used data obtained from the Month 12 visit for evaluation of BMD of the hip, wrist, and total body, biochemical markers, laboratory safety assessments, and vital signs. This was the last comprehensive efficacy and safety assessment prior to discontinuation of study drug. Similarly, spine BMD data were obtained through Month 18 (the last spine BMD assessment for the majority of the patients prior to discontinuation of study drug). Morphometric vertebral fractures were determined at the Early Discontinuation Visit.

As the sponsor observes, it is unlikely that the time period between study drug discontinuation and the final assessments at closeout had a significant effect on the occurrence and analyses of vertebral fractures. Any effect would tend to underestimate the therapeutic efficacy of the drug. A similar argument could be

made in regard to the BMD measurements, in which the potential effects of the drug would be underestimated.

For analysis of biochemical markers, the Month 12 data are most likely the last that reflect the effects of the drug, since these indices are more labile. Any data obtained after the Month 12 visit to closeout would be more reflective of the effects of drug withdrawal.

Comments: I agree with this assessment, as well as with the sponsor's statement that, in the histomorphometry studies, "structural indices and architecture were probably not significantly affected by the length of time between discontinuation of injectable study drug and the study closeout visit, as the remodeling of bone structure is an inherently slow process." Certainly, structural abnormalities that might result from LY333334 treatment, e.g., woven bone, should persist for 6 weeks following withdrawal of drug. On the other hand, dynamic indices of bone formation and resorption and estimation of bone formation rates may be underestimated by the lag period. As shown by the data, this predication had some validity.

The sponsor maintained a record of clinical adverse events continuously throughout the study. These safety results are expressed as the number of patients who experienced an event *at any time* during the trial. Thus the clinical adverse event analysis reflects the safety of LY333334 over the time of actual exposure.

The other change in protocol was that in May, 1998, the DSMB recommended additional serum calcium monitoring for patients in GHAC.

B.1.8 Results

B.1.8.1 Populations enrolled/analyzed

A total of 9347 postmenopausal women were screened. Of these, 1637 were randomized to one of the 3 study arms (544, 541, and 552 received placebo, 20 µg, or 40 µg of LY333334/day, respectively).

Comments: The sponsor does not provide details concerning the number of patients initially contacted, the source of the patients, or the reasons for exclusion of 82% of those screened. This information is generally lacking from NDAs. In my opinion, such data are needed in order to judge the degree to which the trial population represents individuals in the intended market. In the case of many osteoporosis drugs, this consideration is important mainly from the standpoint of safety, tolerability, and compliance. With regard to evaluation of efficacy of LY333334 in this trial,

these concerns are somewhat mitigated because the endpoints are objective laboratory measures (BMD, fractures, biochemical markers).

B.1.8.2 Discontinuations:

The sponsor lists the reasons for discontinuation from GHAC, by treatment group, in Table GHAC.10.1, reproduced below. As shown in the table, the commonest cause for discontinuation was sponsor's decision to stop the study. There were small, statistically significant between-group differences in discontinuations due to adverse events and in those due to sponsor's decision.

Reasons Discontinued	PLACEBO	PTH20	PTH40	TOTAL	P-VALUES		
	(N=544) n (%)	(N=541) n (%)	(N=552) n (%)	(N=1637) n (%)	P_PCHI	P_MHCHI	_EXACT_
Sponsor's decision	447 (82.2)	433 (80.0)	415 (75.2)	1295 (79.1)	0.014	0.004	0.015
Adverse event	32 (5.9)	35 (6.5)	59 (10.7)	126 (7.7)	0.005	0.003	0.006
Patient decision	32 (5.9)	45 (8.3)	40 (7.2)	117 (7.1)	0.296	0.384	0.296
Exclusion medication	7 (1.3)	6 (1.1)	4 (0.7)	17 (1.0)	0.644	0.358	0.622
Death	4 (0.7)	5 (1.1)	6 (1.1)	16 (1.0)	0.781	0.555	0.818
Significant lab values	4 (0.7)	2 (0.4)	8 (1.4)	14 (0.9)	0.143	0.197	0.165
Protocol entry criteria not met	4 (0.7)	4 (0.7)	3 (0.5)	10 (0.6)	0.655	0.427	0.677
Unable to contact patient (lost to follow-up)	3 (0.5)	2 (0.4)	5 (0.9)	10 (0.6)	0.512	0.450	0.625
Patient moved	2 (0.4)	4 (0.7)	3 (0.5)	9 (0.5)	0.710	0.694	0.719
Physician decision	2 (0.4)	2 (0.4)	5 (0.9)	9 (0.5)	0.381	0.227	0.529
Lack of efficacy, progressive disease	5 (0.9)	0 (0.0)	2 (0.4)	7 (0.4)	0.065	0.160	0.058
Noncompliance	1 (0.2)	1 (0.2)	2 (0.4)	4 (0.2)	0.788	0.545	1.000
Other	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.2)	1.000	0.992	1.000

P-VALUES ARE FROM THE FOLLOWING TESTS:
P_PCHI: PEARSON'S CHI SQUARE TEST
P_MHCHI: MANTEL-HAENSZEL TEST FOR CORRELATION WITH DOSE
EXACT: FISHER'S EXACT TEST
RMP.B1D6GHAC.RASPGM(RD6002CT) PTH-CTG 29APR00
Data from RMP.EAS.B1DM.MOODACEM.SUBMISS

In the 20 µg group, there was no difference in % discontinuations due to an adverse event, compared with placebo. However, in the 40 µg group, there was a statistically significant increase, compared with placebo (p=0.004). Descriptions of the adverse events leading to discontinuation are included in the NDA and are reviewed in **Section VII (Safety)**. Aside from discontinuations due to sponsor's decision to terminate the trial, there were no other statistically significant between-group differences in discontinuation rates. There was a trend toward lower rates of discontinuation due to lack of efficacy (rapid bone loss or occurrence of more than 1 new moderate vertebral or non-vertebral fracture) in the active (LY333334) treatment groups, relative to the placebo group (in which there were 7 patients, 0.4%, who discontinued due to lack of efficacy).

There were 16 deaths during the study. According to the investigators, the deaths were unrelated to study drug. Detailed reviews of these case report forms are provided in **Section VII**.

Comments: Neglecting the patients who discontinued due to the sponsor's decision to terminate the study, the overall rate of discontinuation from all

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causes was about 20%. This represents a reasonably good retention rate (at slightly under two years), one that is consistent with experience from other trials of oral (bisphosphonates, estrogen, raloxifene) or transdermal (estrogen) osteoporosis drugs in the postmenopausal population. There were no meaningful differences in rates of withdrawal among the 3 treatment groups. The relatively small number of patients withdrawn due to lack of efficacy most likely represents the beneficial effects of proper calcium and vitamin D supplementation.

These data do not give the actual exposure times for each treatment group. This information (provided by the sponsor in the Safety analysis) is given in the following table, which shows that about 70% of patients completed more than 17 months and 82% completed more than 15 months.

Number of Patients	Number of Months Completed									Total
	0 to 2	3 to 5	6 to 8	9 to 11	12 to 14	15 to 17	18 to 20	21 to 23	24 to 26	
Macbo	18	23	16	7	15	79	257	127	2	544
PTICU	24	24	14	16	10	76	250	125	0	539
PTH40	34	27	19	15	21	72	235	127	2	552
Total	76	74	49	38	46	227	742	379	4	1635*

B.1.8.3 Protocol violations

Clinically significant protocol violations included any use of excluded concomitant medications at any time during the study, baseline efficacy variables (BMD determinations, x-ray films, biochemical markers, and bone biopsies) that were not performed according to the protocol, and dispensing of the wrong study drug kit. A complete listing of all significant protocol violations appears in Appendix 16.2.3 of the NDA.

A) Excluded/restricted medications: Three hundred eighty-two (23.3%) patients reported taking an excluded or restricted medication at some point in the study. Of these, however, only 20 patients reported using an excluded or restricted medication in violation of allowable protocol limits. These medications were: corticosteroids (10), estrogens (2), anticonvulsants (2), coumarins (2), diuretics (1), bisphosphonates (1), androgens (1), and fluoride (1). Among the 3 treatment groups, there were no statistically significant differences in reported use of excluded medications. A complete listing of patients taking excluded medications appears in Appendix 16.2.3 of the NDA.

B) Baseline efficacy measurements not performed according to protocol:

According to the protocol, the baseline BMD tests were to be performed not more than 30 days prior to randomization; baseline x-ray films were to be obtained < 60 days prior to randomization. If a patient had a baseline BMD assessment or x-ray performed more than 30 or 60 days (respectively) prior to randomization, or more than 1 week after randomization, this was termed a protocol violation.

In addition, biochemical markers and bone biopsies were to be assessed at baseline (randomization) in subsets of patients.

Sixty-seven (4.2%) patients had baseline BMD assessments > 30 days prior to randomization and 77 (4.8%) patients had baseline BMD assessments >1 week after randomization. One hundred eleven (7.1%) patients had baseline x-ray films > 60 days prior to randomization and 17 (1.1%) patients had baseline x-rays > 1 week after randomization. In addition, 17 (3.2%) patients had baseline biochemical markers obtained after randomization and 2 (2%) patients had baseline bone biopsies obtained after randomization.

In the efficacy analysis, the sponsor used all pertinent data collected at or prior to baseline, either inside or outside the appropriate time window, as per the intent-to-treat principle. However, the sponsor excluded from the new vertebral fracture analysis a total of 311 patients who did not have both evaluable baseline and evaluable endpoint x-ray films. There were no statistically significant differences in the number of patients with missing scans or x-rays across treatment groups, and it is unlikely that missing radiological studies influenced the results of the efficacy analysis.

C) Dispensing of wrong study drug kit: Two (0.12%) patients had a reported protocol violation due to incorrect dispensing of study drug kits. Both violations occurred at the same site, and the investigators were instructed as to the correct dispensing procedure, and no further errors occurred.

Comments: A review of the protocol violation data disclosed no reason to suspect that protocol violations of any type could have affected the statistical inferences.

B.1.8.4 Baseline characteristics of the enrolled population

The sponsor provides a detailed list of the baseline demographic and other characteristics, including separate tabulations for subsets of patients who participated in special studies (e.g., the pk, pd, bone biomarker, and histomorphometry study subsets).

Baseline demographic and other characteristics of all enrolled patients are summarized in Table GHAC.11.3. Tables GHAC.14.1, GHAC.14.2, GHAC.14.3, and GHAC.14.4. list the baseline characteristics of patient subsets for the special BMD, pk, pd, and histomorphometry studies.

Comments: A review of baseline characteristics of the trial population disclosed no statistically significant or obviously meaningful differences, among the 3 treatment groups, in any demographic or other variable. In the following table, I have summarized the most relevant baseline characteristics of all randomly assigned patients (population as a whole).

Age (rounded to nearest year)	Mean 69, median 70, range 42-86
Ethnicity/race	98.7% Caucasian
BMI (kg/m²)	Mean 26.62, median 26.13, range 11.72-50.69; 80% < 30, 20% >30
Height (cm)	Mean 157.23, median 157.40, range 136.5-180.3
Weight (kg)	Mean 65.8, median 65.0, range 28.15 – 138.0
Caffeine use	Yes 84.3%; no 15.7%
Alcohol use	Yes 37.3%; no 62.7%
Smoker	Yes 17.0%; no 83.0%
Number years smoked	Mean 10.92; range 0-64
Dietary calcium (gm/day)	Mean 0.76, median 0.70, range 0.01-3.42
Years postmenopausal	Mean 21.41, median 21.0, range 5.0-51.0
Hysterectomy	No 77.1%; yes 22.9%
Previous use of osteoporosis drug	No 85.5%; yes 14.5%
Baseline spine BMD (gm/cm²)	0.82; median 0.80; range 0.33-2.07
Baseline number of vertebral fractures:	
0	9.8%
1	30.2%
2	24.3%
3	14.2%
4	9.8%
5	5.1%
>5	6.6%

These baseline characteristics are fairly typical of patients in postmenopausal osteoporosis treatment trials. In nearly all of the previous trials, approximately 97% of the women have been Caucasian. Consequently, we have very limited osteoporosis trial experience with postmenopausal women of other races. The BMI and weight ranges are rather broad. In general, the trial population encompasses a broad range of baseline characteristics, enabling subset analyses that could lead to new hypotheses or rule out lack of efficacy in defined sub-groups of patients.

B.1.8.5 Efficacy outcomes

B.1.8.5.1 New vertebral fractures

Prevalent and incident fractures in the T-4 to L-4 vertebral bodies were to have been determined at baseline, Month 24, and the Early Discontinuation and study closeout visits. In addition, the results of examination of any additional unscheduled spinal x-ray films were included in the analysis.

A total of 1326 patients had evaluable baseline and endpoint spine radiographs. Of these, 105 patients experienced at least one new vertebral fracture. As shown in Table GHAC.11.7, each dose of LY333334 significantly reduced the proportion of patients with new vertebral fractures, compared to placebo.

Table GHAC.11.7. Summary of New Vertebral Fracture Results Overall and by Substudy All Randomly Assigned Patients B3D-MC-GHAC

	Placebo	PTH20	PTH40	Combined PTH	Total
Overall Analysis	n=448	n=444	n=434	n=878	n=1326
Number of patients with ≥1 new fracture (%)	64 (14.3%)	22 (5.0%)	19 (4.4%)	41 (4.7%)	105 (7.9%)
Relative risk reduction compared with placebo	—	65%	69%	67%	—
Relative risk (95% CI) compared with placebo	—	0.347 (0.218, 0.553)	0.306 (0.187, 0.503)	0.327 (0.225, 0.476)	—
Comparison with placebo	—	p<0.001	p<0.001	p<0.001	—
Overall Treatment Comparison	—	—	—	—	p<0.001
Substudy I	n=212	n=204	n=203	n=407	n=619
Number of patients with ≥1 new fracture (%)	32 (15.1%)	9 (4.4%)	13 (6.4%)	22 (5.4%)	54 (8.7%)
Relative risk reduction compared with placebo	—	71%	58%	64%	—
Relative risk (95% CI) compared with placebo	—	0.292 (0.143, 0.597)	0.424 (0.229, 0.785)	0.358 (0.214, 0.600)	—
Comparison with placebo	—	p<0.001	p=0.004	p<0.001	—
Overall Treatment Comparison	—	—	—	—	p<0.001
Substudy II	n=236	n=240	n=231	n=471	n=707
Number of patients with ≥1 new fracture (%)	32 (13.6%)	13 (5.4%)	6 (2.6%)	19 (4.0%)	51 (7.2%)
Relative risk reduction compared with placebo	—	60%	81%	71%	—
Relative risk (95% CI) compared with placebo	—	0.399 (0.215, 0.742)	0.192 (0.062, 0.449)	0.298 (0.172, 0.513)	—
Comparison with placebo	—	p=0.002	p<0.001	p<0.001	—
Overall Treatment Comparison	—	—	—	—	p<0.001

Abbreviations: PTH20 = LY333334 20 µg/day; PTH40 = LY333334 40 µg/day; Combined PTH = LY333334 20 µg and LY333334 40 µg combined; n = number of patients with evaluable baseline and endpoint x-ray films; CI = confidence interval.

Source: EFS0010W, EFS0120W, FR10109P, FR10109Q.

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Comments: These data demonstrate a significant reduction in the proportion of patients with at least one new vertebral fracture during the study period. The results of the combined analysis were very similar to those of each of the two originally planned sub-studies. There was no difference in efficacy between the 20 and 40 µg doses; indeed, the consistency with which fractures are reduced across all treatment “cells,” compared to placebo, is impressive.

Overall, there was a 65% reduction in proportion of patients with ≥ 1 new morphometric vertebral fracture. This corresponds to an absolute risk reduction of about 9.3-9.9%. The fracture rate in the placebo group is consistent with results of earlier studies that applied the same analytical

methodology to similar populations. For example, in the Vertebral Fracture Study arm of FIT, 15% of postmenopausal women with low femoral neck BMD and a prevalent vertebral fracture (the entry criteria for the Vertebral Fracture Study) suffered one or more morphometric vertebral fractures over 36 months in the placebo group, vs 7.9% in the alendronate group [relative risk 0.53, relative risk reduction 47%, 95% CI (0.41, 0.68), $p < 0.001$; absolute risk reduction 7.1%]. For risedronate, the relative risk reduction was 41%. The present study yielded somewhat better fracture efficacy data after about 22 months of treatment. Further comparisons of the efficacy of LY333334 vs anti-resorptive agents appear in the overall summaries.

B.1.8.5.2 Other fracture outcomes

Comments: This section of the submission includes further evaluations of morphometric vertebral fracture efficacy, followed by analyses of non-vertebral fracture outcomes. While the analyses of non-vertebral fractures were pre-specified secondary endpoints, this is not true of many of the parameters included in the additional evaluations of morphometric fractures. In addition, the sponsor made no statistical adjustments for multiplicity of outcomes. The use of p-values in these added analyses of morphometric vertebral fractures is, in my opinion, inappropriate. Accordingly, claims made on the basis of these additional analyses of morphometric vertebral fractures should not be used in labeling or in promotional material.

In these additional evaluations of morphometric fractures, the sponsor determined the number of patients with multiple new vertebral fractures, the proportion of women with new moderate and severe vertebral fractures, the proportion of women with new severe vertebral fractures, the rates of new vertebral fracture occurrence, the number needed to treat to prevent a vertebral fracture, and the fracture efficacy within sub-groups of patients. Many of these analyses can provide insight into the potential benefits of LY333334. However, to uphold strict scientific standards for the acceptance of evidence and maintain consistency in regulations, it is necessary that endpoints be clearly and consistently stated throughout protocols and applications. With rare exceptions, efficacy claims must be based only on achieving these pre-specified endpoints. Inconsistencies present in the application (e.g., compare inconsistencies in use of “rates” and “proportions” of new fractures on pages 92 and 148) have been subsequently clarified in correspondence with the sponsor. The original endpoints are correctly stated on page 148 as “rates of new vertebral fractures,” and “the proportion of patients with new nonvertebral fractures alone and the proportion of patients with new nonvertebral and vertebral fractures combined.”

At no point in the entire NDA submission is there a clearly stated hypothesis. Inclusion of a hypothesis (in addition to the description of primary or secondary endpoints) allows for a rigorous interpretation of outcomes and statistical analyses.

The proposed labeling makes claims for proportions (not rates) of patients with one or more new vertebral fractures, multiple new vertebral fractures, new moderate or severe vertebral fractures, and new severe vertebral fractures. The last three outcomes are not listed as pre-specified secondary endpoints. Rather, they are best considered as method- or protocol-derived data outcomes. As discussed further below, these endpoints should not form the basis of labeling claims. In addition, the attachment of p-values to any of these is inappropriate.

The following is a review of these secondary efficacy claims.

Multiple new vertebral fractures

As shown in the sponsor's table below, there was a statistically significant and substantial reduction in the proportion of patients with multiple new vertebral fractures.

	Placebo n=448	PTH20 n=444	PTH40 n=434	Combined PTH n=878	Total n=1326
Overall Analysis					
Number of patients with multiple new vertebral fractures (%)	22 (4.9%)	5 (1.1%)	3 (0.7%)	8 (0.9%)	30 (2.3%)
Relative risk reduction compared with placebo	—	77%	86%	82%	—
Relative risk (95% CI) compared with placebo	—	0.229 (0.088, 0.600)	0.141 (0.042, 0.467)	0.186 (0.083, 0.413)	—
Comparison with placebo	—	p<0.001	p<0.001	p<0.001	—
Overall Treatment Comparison	—	—	—	—	p<0.001

Abbreviations: PTH20 = LY333334 20 µg/day; PTH40 = LY333334 40 µg/day; Combined PTH = LY333334 20 µg and LY333334 40 µg combined; n = number of patients with evaluable baseline and endpoint x-ray films; CI = confidence interval.

The data indicate an absolute risk reduction of 3.8% for the 20 µg group. There was no significant difference between the 20 and 40 µg groups.

New moderate and severe vertebral fractures

As shown in the next table, there was a statistically significant reduction in the proportion of patients with new moderate or severe vertebral fractures. Again, there was no significant difference between the two LY333334 dose groups; if anything, the 20 µg dose was slightly more effective.

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	Placebo n=448	PTH20 n=444	PTH40 n=434	Combined PTH n=878	Total n=1326
Overall Analysis					
Number of patients with new moderate or severe vertebral fractures (%)	42 (9.4%)	4 (0.9%)	9 (2.1%)	13 (1.5%)	55 (4.1%)
Relative risk reduction compared with placebo	—	90%	78%	84%	—
Relative risk (95% CI) compared with placebo	—	0.096 (0.035, 0.266)	0.221 (0.109, 0.449)	0.158 (0.086, 0.291)	—
Comparison with placebo	—	p<0.001	p<0.001	p<0.001	—
Overall Treatment Comparison	—	—	—	—	p<0.001

Abbreviations: PTH20 = LY333334 20 µg/day; PTH40 = LY333334 40 µg/day; Combined PTH = LY333334 20 µg and LY333334 40 µg combined; n = number of patients with evaluable baseline and endpoint x-ray films; CI = confidence interval.

New severe vertebral fractures

Fourteen (3.1%) patients in the placebo group experienced a new severe vertebral fracture, compared to none in the 20 µg (p<0.001 vs placebo) and 3 (0.7%) in the 40 µg (p<0.009 vs placebo) groups (Table GHAC.11.10 of the NDA).

Comments: It is well established that the majority of morphometric vertebral fractures are clinically silent. It is, therefore, not possible to judge the overall clinical impact of these data without subsequent analysis of clinical and non-vertebral fractures. Clinical fractures were not analyzed separately in this trial. However, it is worth noting that, of the 64 placebo patients with ≥ 1 new vertebral fracture, 42 had at least one new moderate or severe fracture. Of these 42, 14 had severe fractures. From the summary data, one cannot determine the severity grades of the 22 placebo patients with multiple fractures. In contrast, only 4 patients in the LY333334 20 µg group had moderate or severe fractures. This means that 18 of the 22 patients who experienced vertebral fractures while taking 20 µg LY333334 had Grade 1 fractures. No patients in this treatment group had Grade 3 fractures. The results for the 40 µg group were numerically slightly less impressive, although there were no statistically significant differences between the two active LY333334 treatment groups. These data are of great interest and may provide insight into the action and potential clinical benefits of LY333334. They strongly suggest that the efficacy of LY333334 extends beyond the number of morphometric fractures prevented. However, as stated above, they cannot form the basis for labeling or promotional claims.

Number needed to treat

The sponsor calculated the number of patients needed to treat to prevent a patient from having one or more new vertebral fractures by taking the inverse of the difference in % of patients with fractures in the treated and placebo groups. For the 20 µg dose, this worked out to $1/(14.3\% - 5.0\%) = 11$ patients. For the 40 µg group, this is $1/(14.3\% - 4.4\%) = 10$ patients.

Comments: These results could be stated more accurately as the number of patients needed to be treated for 19 months to prevent one

morphometric vertebral fracture of any severity. Using the same approach, one could also calculate the number of patients needed to be treated with 20 µg LY333334 to prevent one moderate or severe new vertebral fracture as $1/(9.4\% - 0.9\%) = 12$. For severe fractures, this would work out to $1/(3.1\% - 0\%) = 32$ patients. The same calculation for the 40 µg group would yield 14 patients for moderate plus severe fractures and 42 patients needed to treat to prevent one severe fracture.

These calculations are informative if the intended target population is the same as the trial population. If the drug is used on women with less severe disease, the numbers needed to treat may be far greater. In this regard, it is interesting to consider the sub-groups that derived the greatest benefit from the drug (in the section on sub-group analysis, below).

New vertebral fracture rates

This was a pre-specified secondary endpoint. Adjusting for the various exposure times (from randomization to endpoint x-ray) for each patient, the sponsor calculated the incidence of new vertebral fractures/1000 patient-years of exposure for each of the 3 treatment groups. The median exposure time was approximately 19 months.

The fracture rate for the placebo group was 136 fractures/1000 patient-years, which is consistent with results of other osteoporosis studies. The outcome of this analysis was very similar to the results of the analyses of proportions of patients with fractures. There were 156 vertebral fractures in all: 101 in the placebo group, 33 in the 20 µg group, and 22 in the 40 µg group. The fracture rates/1000 patient-years were: placebo, 135.56; 20 µg, 49.24; and 40 µg, 30.30. The overall treatment effect was statistically significant ($p < 0.001$).

Comments: I do not believe that this is the proper way to do this analysis. Apparently, the sponsor reported the mean fracture rate per treatment group as the number of fractures/1000 person-years. A more meaningful way is simply to count the total number of fractures and divide that number by the total exposure (standardized to 1000 person-years). This works out to roughly similar results. This issue is discussed in greater detail in the Statistics Review.

In addition, it should be noted that the time of morphometric fracture is not known, further limiting the usefulness of these calculations. Again, a thorough analysis of this issue is provided in the Statistics Review.

Subgroup analyses for new vertebral fractures

The sponsor performed this analysis to confirm that the reduction in proportion of patients with new vertebral fractures is present within each of the population sub-groups. The analysis was not done to search for differential treatment effects.

Sub-groups examined were: age, body weight tertiles, BMI tertiles, baseline number of vertebral fractures, baseline spine BMD (cutoff at T-score of -2.5 , and tertiles), biochemical markers at baseline, endogenous PTH at baseline, occurrence of study drug dose reduction (Y/N), and whether the patient ever had a 4-6 hr post-dose serum calcium > upper limit of normal (Y/N).

There were only 105 patients with new vertebral fractures. Consequently, the number of patients in each sub-group was too small to yield sufficient statistical power to show significant treatment-related differences. In addition, bone turnover markers were measured in only one third of the patients, and fewer than 30 patients with new vertebral fractures also had bone turnover marker assessments.

The sponsor found no statistically significant treatment-by-subgroup interactions with the exception of age tertiles. Patients in the lowest and middle tertiles (cut-off ages 66.6 and 73.0 years) demonstrated statistically significant treatment differences favoring the LY333334 groups ($p < 0.001$). In the upper age tertile there was a numerical reduction in the proportion of patients with new vertebral fractures in the LY333334 groups ($p = 0.231$). When the sponsor used age cut-off points of 65 and 75 years, there was no significant therapy-by-subgroup interaction. In this analysis, LY333334-treated patients in the lower tertiles had a significant reduction in vertebral fractures ($p < 0.002$). There was a numerical decrease in fractures in the LY333334-treated patients in the group > 75 years ($p = 0.054$).

BMI tertiles had no differential effect on fracture reduction efficacy of LY333334.

Patients with 2 or more vertebral fractures at baseline were more likely to have additional new vertebral fractures than individuals with fewer than 2 baseline fractures. When patients were divided according to baseline fracture status, the group with ≥ 2 baseline fractures demonstrated statistically significant drug efficacy, compared with placebo. In the group with 0 or 1 baseline fracture, there was numerical fracture reduction associated with LY333334, but this did not reach statistical significance, probably due to insufficient power (in this category, there were only 9 placebo patients who experienced a new fracture, Table GHAC 11.13 of the NDA).

In general, patients with higher baseline spinal BMD scores were less likely to fracture during the study. There was a consistent trend towards fracture reduction with LY333334 treatment in all BMD tertiles, compared with placebo. The treatment group differences were statistically significant for the lower 2 BMD

tertiles and for the group with T-score < -2.5. There were only 12 new vertebral fractures in the placebo patients in the highest BMD tertile.

Baseline biochemical markers of bone formation and resorption were measured in about 1/3 of all patients, further diminishing the power of the subgroup analysis. Vertebral fracture incidence was greatest in the highest tertiles for all 4 markers. There was a numerical reduction in incidence of new vertebral fractures in all levels of these subgroups. There were no significant treatment-by-subgroup interactions for any of the four biochemical markers.

There was no effect of baseline endogenous PTH level on LY333334 efficacy and no significant treatment-by-subgroup interaction.

Only 6 of the 105 patients with new vertebral fractures had study drug dose reduction, making it impossible to interpret the results of this sub-group analysis. Similarly, only 8 of the 105 patients with new vertebral fractures had at least one elevated 4-6 hr. serum calcium level, again making it impossible to gain information from this analysis (about 13% of all patients, most of them in the LY333334 groups, had at least one elevation of serum calcium post-dose).

Height

Treatment-related change in height in the overall population was a pre-specified secondary endpoint. Analysis of height change was conducted using LOCF and included all randomized individuals. Patients in all three treatment arms lost height during the trial. There were no differences in height loss according to treatment group, irrespective of whether the analysis was conducted by visit or only at endpoint. The height loss at endpoint was: placebo, 3.61 mm; LY333334 20 µg, 2.81 mm; LY333334, 40 µg, 3.16 mm. All mean within-group reductions from baseline were statistically significant ($p < 0.001$ compared to baseline). The mean rate of height loss during the first 12 months of the study was also similar across the 3 groups: 0.20 mm/month, 0.17 mm/month, and 0.21 mm/month in placebo, 20 µg, and 40 µg LY333334 groups, respectively. However, the mean rate of loss for the final 8 months of the study was 40% lower in the LY333334 treatment groups than in the placebo patients.

The sponsor also analyzed height loss in the 105 patients who experienced a new vertebral fracture. Here, the treatment groups differed significantly. The losses were 11.09 mm in placebo and 2.05 and 3.11 mm in the 20 µg and 40 µg groups, respectively. The treatment difference was statistically significant ($p = 0.002$).

Comments: As discussed below, this subgroup analysis lacks scientific validity. Overall, the drug was ineffective in retarding height loss. It is possible that LY333334-related effects might have become evident with

further treatment; however, there is no evidence for this on the basis of data from the first 19 months of treatment.

Loss of height is an important clinical consequence of spinal osteoporosis. The rate and magnitude of height loss reported in this study are consistent with results from earlier osteoporosis trials. Most of these trials have reported height loss in postmenopausal osteoporotic and osteopenic women, regardless of treatment group assignment. Most (but not all) trials have also reported some slowing of height loss in postmenopausal osteoporotic women treated with anti-resorptive agents for periods of 3-4 years, although the placebo-subtracted differences have been small. For example, in the clinical fracture arm of FIT, the investigators reported a placebo-subtracted difference in stature loss of 1.3 mm as a result of 48 months of alendronate treatment. In the review of FIT, I calculated the treatment-related effect as about 17% of the total height loss over the treatment period.

Thus it appears that osteoporotic or osteopenic postmenopausal populations tend to lose height steadily, even if treated with either anti-resorptive agents or an anabolic drug. As noted in earlier reviews of the alendronate studies, the inexorable loss of height in treatment groups that are steadily gaining spinal BMD is somewhat counter-intuitive. In the case of LY333334, the increases in spinal BMD are significantly greater than observed with alendronate or any other anti-resorptive agent. One is left with the tentative conclusion that other mechanisms (including intervertebral disk disease) contribute substantially to this "background" loss of height in the postmenopausal population.

In GHAC, the 105 patients with incident vertebral fractures (those that occurred during the study) sustained greater height loss than those without such fractures. Within this sub-group of patients, there was a pronounced and statistically significant reduction in height loss associated with LY333334 treatment, relative to placebo. It is tempting to relate the result of this subgroup analysis to the observation that vertebral fractures sustained by patients treated with LY333334 are milder than those experienced by patients treated with calcium and vitamin D alone. Indeed, as noted above, 42 of the 64 (65%) placebo patients with fractures had moderate or severe scores, vs 4/22 in the 20 µg group (18%) and 9/19 (47%) in the 40 µg group, or 13/41 (32%) in the combined PTH treatment group. In addition, 4.9% of placebo patients had multiple vertebral fractures, vs 0.9% of the overall PTH group.

Despite the appeal and biological plausibility of this subgroup analysis, it is not scientifically valid, because the two subgroups (fracture vs no fracture) were defined by an outcome that occurred during the trial, following patient randomization. Such definitions yield what have been

termed “improper subgroups” by Yusuf et al [*JAMA* 226 (1) 93-98, 1991] in a paper on the analysis of treatment effects in subgroups of patients in randomized trials. Other flaws in this section of the present submission include the *post hoc* nature of the overall analysis and missing statistical adjustment for multiplicity of endpoints.

Thus, claims relating to preservation of height should not be made on the basis of this analysis. Of interest, in an earlier trial of alendronate, an even more substantial and highly statistically significant treatment effect was seen in an identically-defined subset of patients (i.e., the subset of patients who experienced vertebral fractures during the trial). In a subsequent trial of the same drug the treatment effect was not replicated. Although there was a similar enhancement of stature loss in patients who suffered a vertebral fracture during the second trial, there was no reduction in height loss associated with alendronate treatment within this subgroup.

Non-vertebral fractures

Another secondary endpoint was the proportion of patients with new non-vertebral fractures alone, and with new vertebral and non-vertebral fractures combined. Non-vertebral fractures were assessed only when clinically indicated. Fractures were confirmed either by a radiologist's written report or by review of the x-ray film. Investigators judged whether fractures were traumatic, as defined per protocol. This study lacked sufficient power to detect treatment-related differences in fracture occurrence at specific anatomical sites (e.g., hip or wrist).

Results: Non-vertebral fractures occurred in 119 patients during the trial. Both LY333334 treatment groups showed a statistically significantly lower proportion of patients with fractures (6.3% for the 20 µg and 5.8% for the 40 µg group, compared with 9.7% in the placebo group; relative risk reduction for the 20 µg and 40 µg LY333334 treatment groups, compared to placebo, was 35% and 40%, respectively ($p < 0.05$). The two active LY333334 treatment groups did not differ significantly in fracture risk reduction.

The analysis of non-traumatic non-vertebral fractures yielded essentially the same results. Fractures in this category occurred in 58 patients: 5.5% of placebo, 2.6% of the 20 µg group, and 2.5% of the 40 µg group.

For vertebral and non-vertebral fractures combined, the three treatment groups showed statistically significant differences in the proportions of patients with at least one fracture, compared to placebo (the 20 µg and 40 µg groups had fracture reduction rates of 51% ($p < 0.001$) and 54% ($p < 0.001$), respectively).

The sponsor presents a tabulation of number of patients reporting at least one new non-vertebral fracture, by anatomic location of the fracture. In this table, the numbers of fractures for each of the anatomical sites do not necessarily add up

to the total numbers of patients because some patients had more than one fracture.

	Placebo	PTH20	PTH40	Combined PTH	Total
N	544	541	552	1093	1637
Body site (n)					
Hip	4	2	3	5	9
Radius	13	7	10	17	30
Ankle	4	2	2	4	8
Humerus	5	4	3	7	12
Ribs	10	5	5	10	20
Foot	4	1	4	5	9
Pelvis	3	1	0	1	4
Other	16	14	9	23	39
Total #					
n (%)	53 (9.7%)	34 (6.3%)	32 (5.8%)	66 (6.0%)	119 (7.3%)
Relative risk reduction compared with placebo	—	35%	40%	38%	—
Relative risk (95% CI) compared with placebo	—	0.645 (0.426, 0.976)	0.595 (0.390, 0.908)	0.620 (0.438, 0.877)	—
Pairwise comparison with placebo	—	p=0.036	p=0.015	P=0.007	—
Overall Treatment Comparison	—	—	—	—	p=0.024
Total without "Other"					
n (%)	41 (7.5%)	21 (3.9%)	24 (4.3%)	45 (4.1%)	86 (5.3%)
Relative risk reduction compared with placebo	—	48%	42%	45%	—
Relative risk (95% CI) compared with placebo	—	0.515 (0.309, 0.860)	0.577 (0.354, 0.941)	0.546 (0.362, 0.824)	—
Pairwise comparison with placebo	—	p=0.010	p=0.025	P=0.003	—
Overall Treatment Comparison	—	—	—	—	p=0.013

The statistical significance is maintained after the category "other" has been removed. There were numerically fewer patients with fractures at each anatomical site except the foot. For the 20 µg group (the proposed indicated dose), the numbers of fractures were smaller than in the placebo group at every site.

For the 58 patients with non-traumatic non-vertebral fractures, the results of the analysis were similar. The data are provided in the following table:

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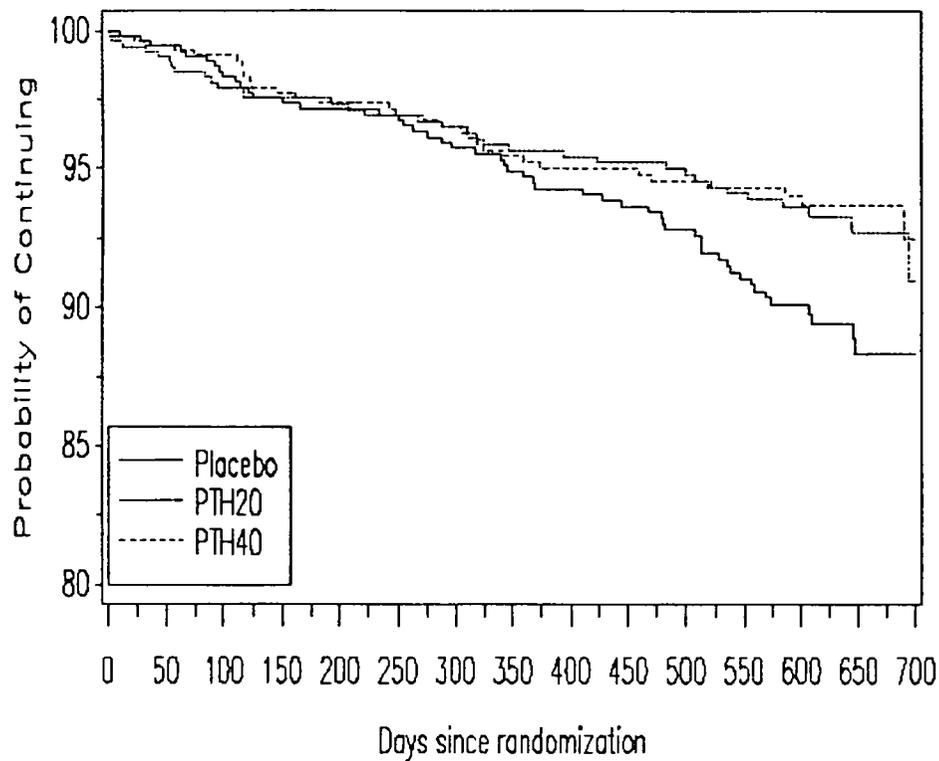
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	Placebo	PTH20	PTH40	Combined PTH	Total
N	544	541	552	1093	1637
Body site (n)					
Hip	4	1	3	4	8
Radius	7	2	3	5	12
Ankle	3	1	1	2	5
Humerus	2	2	2	4	6
Ribs	5	3	2	5	10
Foot	1	0	3	3	4
Pelvis	3	0	0	0	3
Other	8	6	3	9	17
Total*					
n (%)	30 (5.5%)	14 (2.6%)	14 (2.5%)	28 (2.6%)	58 (3.5%)
Relative risk reduction compared with placebo	—	53%	54%	54%	—
Relative risk (95% CI) compared with placebo	—	0.469 (0.252, 0.875)	0.460 (0.247, 0.858)	0.465 (0.280, 0.769)	—
Pairwise comparison with placebo	—	p=0.015	p=0.012	p=0.002	—
Overall Treatment Comparison	—	—	—	—	p=0.010
Total without "Other"					
n (%)	25 (4.6%)	9 (1.7%)	12 (2.2%)	21 (1.9%)	46 (2.8%)
Relative risk reduction compared with placebo	—	64%	53%	58%	—
Relative risk (95% CI) compared with placebo	—	0.362 (0.171, 0.768)	0.473 (0.240, 0.932)	0.418 (0.236, 0.740)	—
Pairwise comparison with placebo	—	p=0.006	p=0.026	p=0.002	—
Overall Treatment Comparison	—	—	—	—	p=0.008

The sponsor also presents Kaplan-Meier curves for time to first non-vertebral fracture. This analysis (note that this analysis was not pre-specified) indicated that the three treatment groups did not diverge until after the first year of treatment. However, after the first year, there was clear divergence, with more patients with non-vertebral fractures in the placebo group than in either of the two LY333334 groups. These differences were shown to be significant using the log-rank test ($p=0.042$), but not significant ($p=0.071$) using the Wilcoxon test.

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P-VALUE OF LOG-RANK 0.042 P-VALUE OF WILCOXON 0.071

Comments: While the clinical consequences of most morphometric vertebral fractures are not readily apparent in individual patients, the pain and disability resulting from fractures of the hip, wrist, and other non-vertebral sites are obvious in nearly all cases. Thus, an ideal osteoporosis treatment modality should dramatically reduce the incidence of these non-vertebral fractures. For this reason, this subset of fracture results of GHAC may appear to be somewhat disappointing at first appraisal, given the impressive results for vertebral fractures and the overall pharmacodynamic potency of LY333334. The reasons for this can be attributed to the relatively low background rates of clinically important peripheral fractures (including hip fractures) in the trial population, the relatively small sample size, and the early termination of the trial. In addition, it is also probable that LY333334 is not as effective at skeletal sites that are rich in cortical bone, compared to efficacy at the lumbar spine.

In GHAC, there were only 9 hip fractures in the entire trial population (0.5% of all randomized patients and 0.7% of the placebo patient group) during approximately 19 months of treatment. In the Vertebral Fracture Cohort of FIT, by comparison, 1.6% of the trial population experienced a hip fracture

[2.2 % of placebo and 1.1% of alendronate-treated patients, relative risk 0.49 (0.23, 0.99), p=0.047] after 36 months of treatment. The only other cohort of FIT that demonstrated statistically significant reductions in hip fractures was the Combined Osteoporotic Cohort of 5093 patients treated for 3-4 years. In this group, the numbers of patients with hip fractures were 1.7% in placebo and 1.1% in the alendronate group, relative risk 0.60 (0.37, 0.96), p=0.034. Although there were numerical trends towards reduction in relative risk of hip fracture in alendronate treatment groups within the other cohorts of FIT (including the Osteoporotic Clinical Cohort of the 4-year study), none were statistically significant. I believe that the Vertebral Fracture Cohort of FIT most closely resembles the postmenopausal patients in GHAC, with the additional risk of a required low femoral neck BMD for entry into FIT. This last entry criterion (and significant risk factor), plus the longer duration of the trial, were probably of substantial importance in increasing the background hip fracture rate in FIT over that which was seen in the present study. Similar increases in background fracture rates at other peripheral sites, relative to GHAC, were found in the Vertebral Fracture arm of FIT, with statistical significance (in favor of alendronate over placebo) achieved at the wrist, as well as for clinical fractures of the spine (this last category was not specifically measured in GHAC).

Thus there was a substantial treatment-associated relative risk reduction for non-vertebral fractures taken as a whole, with numerical reductions at several individual sites. LY333334, 20 µg/day, prevented about 19 non-vertebral fractures (combined), 2 hip fractures, and 6 fractures of the radius in 541 patients treated for about 19 months.

Although the sponsor expresses data in terms of relative risk reduction (with percentages ranging from 35-65%, depending on the comparison), the absolute risk reduction should be indicated as well, in order to place the efficacy of the drug in perspective. Indeed, over the past two years, the policy of our Division has been to require presentations of absolute risk reductions in labeling of osteoporosis drugs. For the 20 µg treatment group, the overall absolute risk reduction for all non-vertebral fractures equals about 3.4%. To prevent one of these fractures would require treatment of about 29 (similar) patients with LY333334 for 19 months.

New vertebral and non-vertebral fractures combined

The analysis of new vertebral and non-vertebral fractures combined was a secondary endpoint of GHAC. As shown in the table below, there was a significant reduction in incidence of these fractures combined.

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	Placebo n=448	PTH20 n=444	PTH40 n=434	Combined PTH n=878	Total n=1326
Overall Analysis					
Number of patients with combined vertebral and nonvertebral fractures (%)	99 (22.1%)	48 (10.8%)	44 (10.1%)	92 (10.5%)	191 (14.4%)
Relative risk reduction compared with placebo	—	51%	54%	52%	—
Relative risk (95% CI) compared with placebo	—	0.489 (0.356, 0.673)	0.459 (0.330, 0.638)	0.474 (0.366, 0.615)	—
Comparison with placebo	—	p<0.001	p<0.001	p<0.001	—
Overall Treatment Comparison	—	—	—	—	p<0.001

Comments: The absolute risk reduction is 11.3% in the LY333334 20 µg group, with very similar results in the 40 µg group. Again, there is no significant or meaningful effect difference between the 20 µg and 40 µg groups. The overall treatment effect is substantial, in terms of numbers of fractures prevented. However, the magnitude and the robustness of the effect are driven by the efficacy of the drug at the lumbar spine. Despite the fact that this was a pre-specified analysis, it is my opinion that the mixing of these two outcomes (morphometric vertebral deformities and clinical non-vertebral fractures) yields a potentially misleading impression regarding the overall efficacy of the drug.

B.1.8.5.3 Changes in bone mineral density

In all patients lumbar spine BMD was to have been measured at baseline; at Months 12, 18, and 24; and at Early Discontinuation or study closeout visit. All patients were to have received hip BMD measurements at baseline, at Months 12 and 24, and at Early Discontinuation or study closeout visit. Approximately 33% of patients had additional lumbar spine BMD measurements at Months 3 and 6. At specified study sites patients (N = 425) were to have received DXA scans of the radius at baseline, Month 24, and Early Discontinuation or study closeout visit. At most of these sites, patients were to have received total body DEXA scans at baseline, Months 12 and 24, and Early Discontinuation or study closeout visit. A demographic analysis of this subset of patients is provided in the NDA.

Data were analyzed as the mean % change in BMD from baseline to endpoint at each skeletal site, using ITT. The sponsor used data from all randomly assigned patients who had a baseline and one post-randomization BMD value. The last post-randomization value was considered to be the endpoint (LOCF).

Results:

Treatment with LY333334 produced statistically significant and very substantial increases in BMD at many, but not all, skeletal sites by study endpoint. Anatomical locations in which there was considerable increase, relative to placebo, included the lumbar spine, the total hip, the femoral neck, the intertrochanteric region, and Ward's Triangle. There was a small increase in total body BMD, relative to placebo. However, there were reductions in BMD at the distal and ultradistal radius in all three treatment groups. In no case did the radius BMD reductions in LY333334 treatment groups exceed those of the

placebo, except for LY333334, 40 µg, at the distal radius. Because these results have important clinical implications, I have reproduced the sponsor's Table GHAC.11.18 below:

Variable	Placebo (N=544)	PTH20 (N=541)	PTH40 (N=552)
Lumbar Spine (L-1 through L-4) (g/cm²)			
n	504	498	497
Mean baseline	0.82 ± 0.17	0.82 ± 0.17	0.82 ± 0.17
Mean change from baseline	0.01 ± 0.04	0.07 ± 0.05	0.11 ± 0.07
Mean percent change from baseline	1.13% ± 5.47%	9.70% ± 7.41% ^a	13.73% ± 9.69% ^a
Total Hip (g/cm²)			
n	230	222	232
Mean baseline	0.71 ± 0.12	0.70 ± 0.12	0.70 ± 0.11
Mean change from baseline	-0.01 ± 0.03	0.02 ± 0.03	0.02 ± 0.04
Mean percent change from baseline	-1.01% ± 4.25%	2.58% ± 4.88% ^a	3.60% ± 5.42% ^a
Femoral Neck (g/cm²)			
n	479	479	482
Mean baseline	0.64 ± 0.11	0.64 ± 0.11	0.64 ± 0.11
Mean change from baseline	-0.00 ± 0.03	0.02 ± 0.04	0.03 ± 0.04
Mean percent change from baseline	-0.69% ± 5.39%	2.79% ± 5.72% ^a	5.06% ± 6.73% ^a
Trochanter (g/cm²)			
n	479	479	482
Mean baseline	0.57 ± 0.12	0.57 ± 0.12	0.57 ± 0.12
Mean change from baseline	-0.00 ± 0.04	0.02 ± 0.04	0.02 ± 0.04
Mean percent change from baseline	-0.21% ± 6.30%	3.50% ± 6.81% ^a	4.40% ± 7.45% ^a
Intertrochanter (g/cm²)			
n	257	250	254
Mean baseline	0.86 ± 0.16	0.85 ± 0.16	0.85 ± 0.14
Mean change from baseline	-0.01 ± 0.04	0.02 ± 0.04	0.03 ± 0.05
Mean percent change from baseline	-1.29% ± 4.53%	2.62% ± 5.52% ^a	3.98% ± 5.96% ^a
Ward's Triangle (g/cm²)			
n	479	479	482
Mean baseline	0.47 ± 0.13	0.47 ± 0.14	0.47 ± 0.13
Mean change from baseline	-0.00 ± 0.06	0.02 ± 0.05	0.03 ± 0.06
Mean percent change from baseline	-0.80% ± 11.73%	4.19% ± 11.93% ^a	7.85% ± 13.24% ^a
Total Body^c (g/cm²)			
n	140	134	131
Mean baseline	0.94 ± 0.10	0.93 ± 0.09	0.95 ± 0.10
Mean change from baseline	-0.00 ± 0.03	0.00 ± 0.02	0.01 ± 0.03
Mean percent change from baseline	-0.46% ± 3.08%	0.56% ± 2.55% ^a	1.51% ± 3.34% ^a
Ultradistal Radius (Forearm)^c (g/cm²)			
n	154	152	145
Mean baseline	0.32 ± 0.08	0.31 ± 0.07	0.32 ± 0.07
Mean change from baseline	-0.01 ± 0.02	-0.00 ± 0.02	-0.01 ± 0.03
Mean percent change from baseline	-1.64% ± 8.27%	-0.11% ± 7.16%	-1.49% ± 8.44%

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Distal Radius (Forearm) ^c (g/cm ²)	154	152	145
n			
Mean baseline (SD)	0.58 ± 0.11	0.58 ± 0.10	0.59 ± 0.11
Mean change from baseline	-0.01 ± 0.02	-0.01 ± 0.02	-0.02 ± 0.03
Mean percent change from baseline	-1.28% ± 3.34%	-2.07% ± 4.15%	-3.21% ± 4.52% ^a

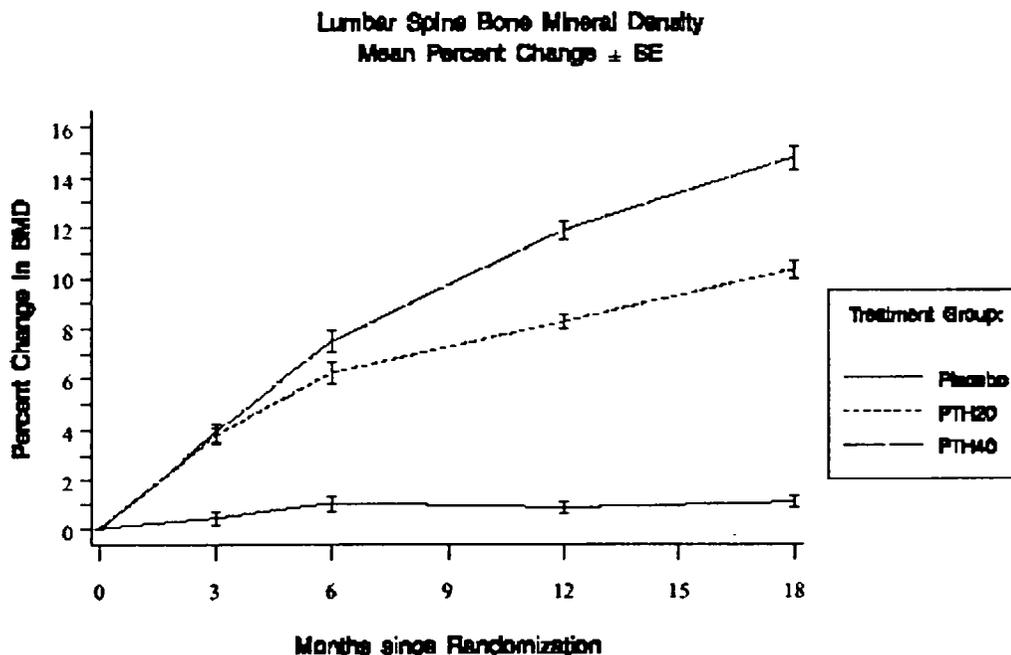
Abbreviations. N = number of patients randomly assigned to each treatment group; PTH20 = LY333334 20 µg/day; PTH40 = LY333334 40 µg/day; n = maximum number of patients with a baseline and at least one postbaseline measurement.

^a p < 0.001 compared with placebo.

^b p < 0.01 compared with placebo.

^c Total body and radius bone mineral density were measured in a subset of patients.

The time course of changes in lumbar spine BMD for the three treatment groups is shown in the next figure.



As indicated above, data for months 3 and 6 were derived from a pre-defined subset of patients (about 33% of the total). During the 18 months, there was a dramatic increase in BMD at the lumbar spine in both LY333334 treatment groups. Consistent with the earlier clinical pharmacology studies and the known anabolic action of the drug, the increases were noted as early as 3 months. There were small increases in lumbar spine BMD in the placebo group, about 1% over baseline by Month 12, possibly due to the effects of treatment with calcium

and vitamin D. Differences between either LY333333 dose group and placebo were statistically significant ($p < 0.001$) at every time point after baseline. For the 20 μg group, the placebo-subtracted differences from baseline were 7.42% at 12 months and 9.25% at 18 months. For the 40 μg group, the corresponding placebo-subtracted BMD increases were 11.03% and 13.07%. The responses of the two dose treatment groups were similar until between 3 and 6 months. By 6 months, the spinal BMD was consistently greater in the 40 μg treatment group than in the group receiving 20 μg ($p < 0.001$). Further analyses of by-visit BMD changes are included in the NDA.

Comments: These increases in lumbar spine BMD exceed those that have been reported for bisphosphonates or any known anti-resorptive agent. With alendronate, BMD increases of about 5% are usually reported after treatment for 12 months, and about 6-7% after 18 months. In the longest study of the effects of alendronate, increases up to 9.4% were noted after 60 months of treatment with alendronate 10 mg/day. In that study, mean spinal BMD had increased to about 7.5% by 24 months. The present data do not permit extrapolation past 18-21 months of treatment with LY333334, although there is no evidence that a plateau has been reached by this time point. Due to early termination of GHAC, we do not know how far the BMD increases would have progressed. Direct comparisons of LY333334 and alendronate are provided in study GHAH, which is included in this submission.

Responder analysis: In the following figure, the sponsor presents, for each treatment group, the distribution of patients according to their mean % increment in baseline-to-endpoint lumbar spine BMD. Approximately 42% of the placebo group lost BMD, compared with 4% of the patients in the LY333334 treatment groups. Nearly all patients in the LY333334 treatment groups gained spinal BMD, with most of the patients increasing BMD by $> 5\%$. About 2%, 18%, and 38% of patients in placebo, 20 μg , and 40 μg groups, respectively, increased spinal BMD by $> 15\%$ over baseline.

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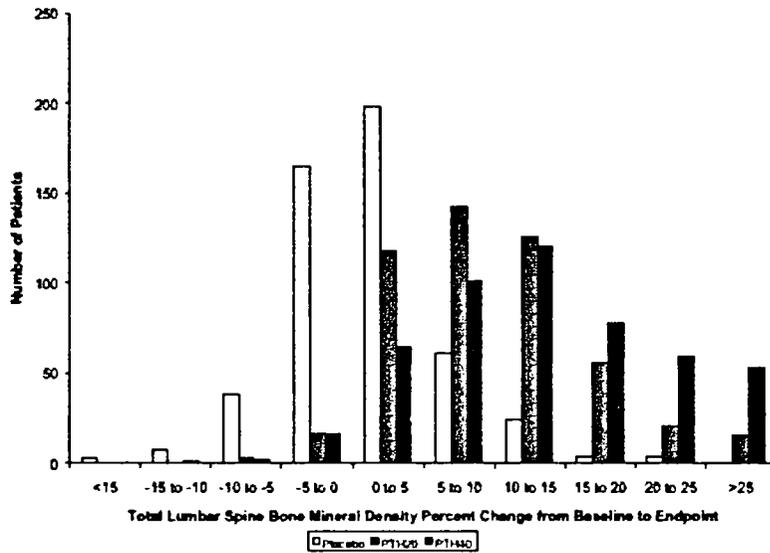


Figure GHAC.11.21. Categories of Total Lumbar Spine Bone Mineral Density Percent Change from Baseline to Endpoint All Randomly Assigned Patients B3D-MC-GHAC

The sponsor presents by-visit analyses of BMD data at all skeletal sites, according to treatment group. Numbers of patients analyzed at each visit are also presented. These data will not be reproduced here. Instead, I have summarized BMD responses at all non-vertebral skeletal sites at the final planned month for that particular measurement and at study endpoint. Relevant statistical comparisons are also provided in the (reviewer's) table below:

SKELETAL SITE	% BMD CHANGE FROM BASELINE		
	PLACEBO	LY333334 20 µg	LY333334 40 µg
Total hip ^a	-.53 at month 12; -1.01 at end	+1.70 month 12; + 2.58 at end	+2.55 month 12; + 3.60 at end
Femoral neck ^b	0 at month 12 (ns); -0.69% at end	+ 1.54 month 12 +2.79 at end	+3.06 month 12; +5.04 at end
Trochanter ^c	-0.06 at month 12; -0.21 at end (ns)	+2.68 month 12; +3.71 at end	+3.67 month 12; +4.40 at end
Intertrochanter ^d	-0.94 at month 12; -1.29 at end	+1.82 month 12; +2.62 at end	+2.61 month 12; +3.98 at end
Ward's triangle ^e	+0.29 month 12 (ns); -0.80 at end (ns)	+2.65 month 12; +4.19 at end	+5.43 month 12; +7.85 at end
Ultradistal radius ^f	-1.19 month 12; -1.64 at end	-0.59 month 12 (ns); -0.11 at end (ns)	+0.22 month 12 (ns); -1.49 at end
Distal 1/3 radius ^g	-1.1 month 12; -1.28 at end	-1.80 month 12; -2.07 at end	-3.24 month 12; -3.21 at end
Total body BMC ^h	-0.40 month 12; -0.74 at end	-0.02 month 12 (ns); +1.30 at end	+0.54 month 12 (ns); +2.28 at end