There were no statistically significant differences or trends between treatment groups in the frequency of urolithiasis, as described in Section 1.5.5.9 above.

1.7.3.5.2 Urine Phosphorus

There were no statistically significant differences between treatment groups in median 24 hour urine phosphorus excretion at any visit or endpoint, although there was a trend of increase of about 1-2 mmol/d at month 12 for the LY333334 groups compared to the placebo group (p=0.056).

There were no statistically significant differences or trends between treatment groups in the frequency of abnormal 24 hour urine phosphorus excretion.

1.7.3.6 Effect of Serum 1,25-dihydroxyvitamin D on Urine Calcium

Because LY333334 is known to increase serum 1,25-dihydroxyvitamin D, and because increased 1,25-dihydroxyvitamin D is associated with hypercalciuria in some disease states, the relationship between 1,25-dihydroxyvitamin D and hypercalciuria was examined, using a logistic regression model. In this model, there was not a statistically significant relationship between the two variables. While the effect of LY333334 on 1,25-dihydroxyvitamin D may have influenced urinary calcium excretion, there was not a detectable relationship between 1,25-dihydroxyvitamin D and hypercalciuria in this study.

1.7.3.7 Effect of LY333334 on Serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D

Serum 25-hydroxyvitamin D was measured at baseline (visit 4), month 12 (visit 9), and the early discontinuation or study closeout visit. Serum 1,25-dihydroxyvitamin D was measured at baseline (visit 4), months 1, 3, 6, and 12 (visits 5, 6, 7, and 9), and the early discontinuation or study closeout visit.

In the 20 mcg group compared to the placebo group at 12 months, the median serum 25-hydroxyvitamin D was decreased from baseline by 14.0 nmol/L ($p<0.001$) and the median serum 1,25-dihydroxyvitamin D was increased from baseline by 21.6 pmol/L ($p<0.001$). In the 40 mcg group compared to the placebo group at 12 months, the median serum 25-hydroxyvitamin D was decreased from baseline by 13.5 nmol/L ($p<0.001$) and the median serum 1,25-dihydroxyvitamin D was increased

from baseline by 21.6 pmol/L ($p<0.001$). These findings may in part reflect renal conversion of 25-hydroxyvitamin D to 1, 25-dihydroxyvitamin D.

There were no statistically significant differences or trends between treatment groups in the frequency of abnormal 25-hydroxyvitamin D. For 1,25-dihydroxyvitamin D ,the numbers of patients with elevations above the upper limit of normal were: 34 (19.8%) in the placebo group, 93 (54.1%) in the 20 mcg group, and 91 (52.9%) in the 40 mcg group D concentrations in each treatment group, compared with placebo ($p<0.001$).

1.7.4 Endocrine and Metabolic Function

Serum nonfasting glucose, total cholesterol, and uric acid were measured at baseline (visit 4), months 1, 6, and 12 (visits 5, 7, and 9), and the early discontinuation or study closeout visit. In addition, serum fasting glucose and triglycerides were measured in a subset of about 170 patients per treatment group at baseline (visit 4), months 1, 3, 6, and 12, and the early discontinuation or study closeout visit.

There were no statistically significant differences or trends between treatment groups in median serum nonfasting glucose, fasting glucose, or total cholesterol, or in the frequency of abnormal nonfasting glucose, fasting glucose, or total cholesterol.

There were statistically significant increases in serum uric acid in the LY333334 groups compared to the placebo group. In the 20 mcg group the median increase at months 1,6, and 12 ranged from 36.3-54.0 mcmol/L ($p<0.01$). At endpoint, when most of the patients had been withdrawn from study drug for a median of 6 weeks, serum uric acid in the 20 mcg group had begun to return to baseline, although the median was still increased by 13.3 mcmol/L. In the 40 mcg group the median increase at months 1,6, and 12 ranged from 55.0-69.5 mcmol/L ($p<0.01$). At endpoint, when most of the patients had been withdrawn from study drug for a median of 6 weeks, serum uric acid in the 40 mcg group had begun to return to baseline, although the median was still increased by 23.8 mcmol/L.

The numbers of patients with serum uric acid levels above the upper limit of normal were: 4 (0.7%) in the placebo group, 15 (2.8%) in the 20 mcg group, and 27 (5.0%) in the 40 mcg group ($p<0.001$). For 20 mcg compared to placebo, $p=0.011$.

There were no statistically significant differences or trends between treatment groups in the frequency of gout, arthralgia, or urolithiasis, as discussed above in Sections 1.5.5.5 and 1.5.5.9.

There were no statistically significant differences or trends between treatment groups in median serum triglycerides during active treatment with study drug (months 1-12). At endpoint, when most patients had been withdrawn from study drug for a median of 6 weeks, the median triglycerides were increased in the LY333334 groups compared to the placebo group. The increase was 0.11 mmol/L in the 20 mcg group (p=0.077) and 0.17 mmol/L in the 40 mcg group (p=0.028).

There were no statistically significant differences or trends between treatment groups in the frequency of abnormal serum triglycerides.

1.7.5 Liver and Kidney Function

1.7.5.1 Liver Function

Serum total alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, and gamma glutamyl transferase were measured at baseline (visit 4), months 1, 6, and 12 (visits 5, 7, and 9), and the early discontinuation or study closeout visit.

There were statistically significant increases in serum total alkaline phosphatase in the LY333334 groups compared to the placebo group. The median increases were: at month 1, 3 U/L in the 20 mcg group and 10 U/L in the 40 mcg group; at month 6, 8 U/L in the 20 mcg group and 20 U/L in the 40 mcg group; and at month 12, 10 U/L in the 20 mcg group and 21U/L in the 40 mcg group ($p<0.001$ for all comparisons to the placebo group). By endpoint, when most of the patients had been withdrawn from study drug for a median of 6 weeks, the serum alkaline phosphatase had begun to fall, although there was still an increase of 2 U/L in the 20 mcg group and 7 U/L in the 40 mcg group, compared to the placebo group.

There was a statistically significant increase in the LY33334 groups in the frequency of elevations of serum total alkaline phosphatase above the upper limit of normal: 5 (0.9%) in the placebo group, 8 (1.5%) in the 20 mcg group, and 46 (8.5%) patients in the 40 mcg group ($p<0.001$). For 20 mcg compared to placebo, p=0.399. These findings were attributed to the known effects of LY333334 on bone.

There were no statistically significant differences or trends between the 20 mcg group and the placebo group in median serum alanine aminotransferase. In the 40 mcg group compared to the placebo group, the median serum alanine aminotransferase was decreased at months 1, 6, and 12 by 1 U/L (p=0.094, 0.030, and 0.001, respectively); this was not considered to be clinically significant. There were no statistically significant differences or trends between treatment groups in median serum gamma glutamyl transferase or aspartate aminotransferase.

The median total bilirubin was increased at month 1 by 0.55 mcmol/L in the 20 mcg group (p=0.05) and 1.0 mcmol/L in the 40 mcg group (p=0.004), compared to the placebo group. There were no other statistically significant differences or trends between treatment groups in median total bilirubin.

There were no statistically significant differences or trends between treatment groups in the frequency of abnormal alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, or total bilirubin.

1.7.5.2 Kidney Function

Serum creatinine, urea nitrogen, bicarbonate, chloride, potassium, magnesium, and sodium were measured at baseline (visit 4), months 1, 6, and 12 (visits 5, 7, and 9), and the early discontinuation or study closeout visit. Creatinine clearance was measured at each visit where serum creatinine was measured within 24 hours before or after the 24-hour urine creatinine.

There were no statistically significant differences or trends between treatment groups in median serum creatinine or measured creatinine clearance, or in the frequency of abnormal serum creatinine or abnormal measured creatinine clearance.

There were no statistically significant differences or trends in median serum urea nitrogen in the 20 mcg group compared to the placebo group. In the 40 mcg group compared to the placebo group, the median serum urea nitrogen was increased at months 6 and 12 by 0.20 mmol/L ($p \leq 0.001$ and p=0.003, respectively). At endpoint, when most of the patients had been withdrawn from study drug for a median of 6 weeks, there no longer were statistically significant differences between groups (p=0.484). The changes in serum urea nitrogen in the 40 mcg group were considered as probably not clinically significant.

There were no statistically significant differences or trends between treatment groups in the frequency of abnormal serum urea nitrogen.

There were statistically significant differences or trends between treatment groups in serum potassium, bicarbonate, and sodium. In the 20 mcg group compared to the placebo group: the median serum potassium was decreased at months 6 and 12 by <0.10 mmol/L (p=0.001 and 0.014, respectively); the median serum bicarbonate was increased at month 1 by 0.30 mmol/L (p=0.085) and at month 12 by 0.20 mmol/L (p=0.075); and the median serum sodium was increased at month 1 by <0.01 mmol/L (p=0.080). In the 40 mcg group compared to the placebo group: the median serum potassium was decreased at months 6 and 12 by <0.10 mmol/L (p<0.001and p=0.002, respectively); the median serum bicarbonate was increased at months 1, 6, and 12 by 0.30 mmol/L (p=0.072, p=0.017, and p=0.014, respectively); and the median serum sodium was increased at months 1, 6, and 12 by <0.01 mmol/L (p=0.075, p=0.033, and p=0.100, respectively). There were no statistically significant differences or trends between treatment groups in median serum chloride.

There were no statistically significant differences or trends between treatment groups in the frequency of abnormal serum potassium, bicarbonate, sodium, or chloride, compared to placebo.

There were statistically significant decreases in serum magnesium in the LY333334 groups compared to the placebo group. In the 20 mcg group compared to the placebo group, the median serum magnesium was decreased by 0.06-0.07 mmol/L at months 1, 6, and 12 (p<0.001). At endpoint, when most of the patients had been withdrawn from study drug for a median of 6 weeks, the difference was <0.01 mmol/L, although still statistically significant (p=0.009). In the 40 mcg group compared to the placebo group, the median serum magnesium was decreased by 0.07-0.10 mmol/L at months 1, 6, and 12 (p<0.001). At endpoint, when most of the patients had been withdrawn from study drug for a median of 6 weeks, the decrease was <0.01 mmol/L, although still statistically significant (p<0.001).

The numbers of patients with serum magnesium levels below the lower limit of normal were: 2 (0.4%) in the placebo group, 4 (0.7%) in the 20 mcg group, and 11 (2.0%) patients in the 40 mcg group (p=0.020). For 20 mcg compared to placebo, p=0.409.

1.7.6 Urinalysis

Urinalysis was performed at baseline (visit 4), months 1, 6, and 12 (visits 5, 7, and 9), and the early discontinuation or study closeout visit. The urinalysis included color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, and microscopic examination of sediment. The urinalyses were performed on random spot urine samples and not under conditions designed to test maximum concentrating or acidifying ability. The results for specific gravity and pH should be interpreted with. the use of reference ranges that are appropriate for random specimens.

In the 20 mcg group compared to the placebo group, there were no statistically significant differences or trends in median urine specific gravity. In the 40 mcg group, the median urine specific gravity at baseline and month 6 was <0.01 specific gravity units different from the median in the placebo group, although the differences were statistically significant (p=0.031 and p=0.032 respectively); there were no other statistically significant differences or trends in urine specific gravity.

There were no statistically significant differences or trends between treatment groups in the frequency of abnormal urine specific gravity.

In the 20 mcg group compared to the placebo group, the mean urine pH was increased by 0.25 units at baseline (p<0.001) and 0.37-0.56 units at months 1, 6, and 12 (p<0.001). There were no statistically significant differences or trends between the 2 groups at endpoint, or in the frequency of abnormal urine pH. In the 40 mcg group, the mean urine pH was 0.27 units higher than the mean in the placebo group at baseline (P<0.01) and was 0.62-0.66 units higher than the mean in the placebo group at months 1 and 6 (p<0.01). There were no statistically significant difference or trends between the 2 groups at 12 months or endpoint. There were no statistically significant differences or trends between treatment groups in the frequency of abnormal urine pH.

The other urinalysis variables (color, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrites, microscopic examination of sediment) showed no statistically significant differences or trends between treatment groups in the frequency of abnormal laboratory values except that fewer patients in the 40 mcg group compared to the placebo group had at least one abnormal white blood cell finding (p=0.018).

1.7..7 Hematology

Hematology was evaluated at baseline (visit 4), months 1, 6, and 12 (visits 5, 7, and 9), and the early discontinuation or study closeout visit. The hematology evaluation included: hemoglobin; hematocrit; erythrocyte count; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; counts of leukocytes, segmented neutrophils, juvenile neutrophils (bands), lymphocytes, monocytes, eosinophils, basophils, and platelets; and cell morphology.

There were statistically significant decreases or trends in hemoglobin, hematocrit, and erythrocyte counts in the LY333334 groups compared to the placebo group. In the 20 mcg group compared to the placebo group: the median hemoglobin was decreased at endpoint by 0.062 mmol/L-Fe ($p=0.089$); the median hematocrit was decreased at months 6 and 12 and endpoint by <0.01 ($p<0.01$); and the median erythrocyte count was decreased at month 6 and endpoint by <0.01 TI/L ($p<0.05$). In the 40 mcg group compared to the placebo group; the median hemoglobin was decreased at months 6 and 12 and endpoint by 0.062-0.124 mmol/L-Fe ($p<0.05$); the median hematocrit was decreased at months 6 and 12 and endpoint by <0.01 ($p<0.01$); and the median erythrocyte count was decreased at months 1, 6 and 12 and endpoint by <0.1 TI/L ($p=0.055$ for month 1 and $p<0.01$ for the other times).

There were no statistically significant differences or trends between treatment groups in mean cell volume, mean cell hemoglobin, or mean cell hemoglobin concentration. There were no statistically significant differences or trends between treatment groups in the frequency of abnormal values for any erythrocyte variable.
There were statistically significant increases or trends in leukocyte counts in the LY333334 groups compared to the placebo group.

In the 20 mcg group compared to the placebo group: the median leukocyte count was increased at months 1, 6, and 12 by 0.45-0.60 GI/L ($p<0.001$); the median segmented neutrophil count was increased at months 1, 6, and 12 by 0.44-0.53 GI/L ($p<0.001$); there was no statistically significant differences or trends in the band counts; there were no statistically significant differences or trends in the lymphocyte counts during months 1-12; the median monocyte count was increased at month 1, 6, and 12 by in 0.01- 0.03 GI/L ($p<0.05$); the median eosinophil count was decreased at month 1 by <0.01 GI/L ($p=0.086$); and the median basophil count was increased at month 12 by <0.01 GI/L ($p=0.056$). At endpoint, when most of the patients had been withdrawn from study drug for a median of 6 weeks, there were no longer statistically significant

differences or trends between the 20 mcg group and the placebo group in the leukocyte, segmented neutrophil, monocyte, eosinophil, or basophil counts.

In the 40 mcg group compared to the placebo group: the median leukocyte count was increased at months 1, 6, and 12 by 0.55-0.82 GI/L ($p<0.001$); the median segmented neutrophil count was increased at months 1, 6, and 12 by 0.60-0.69 GI/L ($p<0.001$); there was no statistically significant differences or trends in the band counts; there were no statistically significant differences or trends in the lymphocyte counts; the monocyte count was increased at endpoint by 0.13 GI /L ($p=0.004$); the median monocyte count was increased at months 1,6, and 12 by 0.03-0.06 GI/L ($p<0.001$); the median eosinophil count was increased at month 12 by 0.01 GI/L ($p=0.035$); and the median basophil count was increased at months 1, 6, and 12 by <0.01 GI/L ($p<0.05$). At endpoint, when most of the patients had been withdrawn from study drug for a median of 6 weeks, there were still statistically significant increases in the 40 mcg group in the leukocyte, monocyte, eosinophil, and basophil counts. Also, the median lymphocyte count was increased by 0.13 GI/L ($p=0.004$). There was no longer a statistically significant difference in segmented neutrophil counts.

LY333334 treatment was associated with a decrease in the frequency of low leukocyte counts. The numbers of patients with leukocyte counts below the lower limit of normal were: 60 (11.2%) in the placebo group, 37 (6.9%) in the 20 mcg group, and 39 (7.2%) in the 40 mcg group ($p=0.020$). For 20 mcg compared to placebo, $p=0.016$.

There were statistically significant increases in platelet counts in the LY333334 groups compared to the placebo group. In the 20 mcg group compared to the placebo group, the median platelet count was increased at month 1 by 7.50 GI/L ($p=0.009$). In the 40 mcg group compared to the placebo group, the median platelet count was increased at months 1, 6, and 12 by 7.00-10.00 GI/L ($p<0.05$).

There were no statistically significant differences or trends between treatment groups in the frequency of abnormal platelet counts.

1.7.8 Miscellaneous Serum Chemistry

Serum creatine phosphokinase, total protein, and albumin were measured at baseline (visit 4), months 1, 6, and 12 (visits 5, 7, and 9), and the early discontinuation or study closeout visit. Serum endogenous

parathyroid hormone, or PTH (1-84), was measured at baseline (visit 4) and month 12 (Visit 9) in a subset of about 170 patients per treatment group.

In the 20 mcg group compared to the placebo group, there were no statistically significant differences or trends in median serum creatine phosphokinase. In the 40 mcg group compared to the placebo group, the median creatine phosphokinase was decreased at months 1, 6, and 12 by 4.5-7.5 U/L ($p<0.05$). There were no statistically significant differences or trends at endpoint between the 40 mcg group and the placebo group.

There were no statistically significant differences or trends between treatment groups in the frequency of abnormal creatine phosphokinase.

There were no statistically significant differences or trends between treatment groups in median serum albumin or total protein, except that at month 12 serum albumin in the 20 mcg group compared to the placebo group was decreased by 1 g/L ($p=0.097$).

There were no statistically significant differences or trends between treatment groups in the frequency of abnormal serum albumin or total protein.

In the measurements of PTH (1-84), most of the samples were below the level of quantitation [redacted] in the placebo, 20 mcg, and 40 mcg groups, respectively). The blood samples were collected 2.3 hours after dosing with study drug, on average (range = 10 minutes to 5 hours). It is likely that PTH (1-84) was suppressed during this postdose interval for patients in the LY333334 groups, which would explain why a higher percentage of samples were below the limit of quantitation in the LY333334 groups compared to the placebo group. Nonetheless, the percentage of nonquantifiable samples was very high in all treatment groups. This was attributed to a more stringent limit of quantitation for the assay performed in the pharmacokinetic laboratory [redacted], compared with the limit in a typical clinical laboratory [redacted].

1.7.9 Antibodies to LY333334

An indirect test for antibodies to LY333334 was performed at baseline (visit 4), months 3 and 12 (visits 6 and 9), and the early discontinuation or study closeout visit. Two tests were performed, an initial binding assay and a confirmatory inhibition assay.

In the binding assay, radio-labeled PTH (1-34)-^{125}I was incubated at 4° C overnight with the serum specimen. The antibody-bound PTH (1-34)-^{125}I was separated from the free PTH(1-34)-^{125}I . The pellet remaining in the assay tube was counted in a gamma counter, with the response being proportional to the amount of protein-bound PTH(1-34)-^{125}I present in the specimen. A standard curve (run in every assay) constructed with a chicken-anti-N-terminal-PTH antibody was used to quantitate responses. Results were reported in Binding Units (BU); a 1:2000 dilution of the chicken-anti-N-terminal-PTH antiserum was assigned a value of 320 BU.

Inhibition testing was performed in all patients for whom binding increased at least 2-fold from baseline. In the inhibition assay, binding was tested with and without addition of an excess (100 ng) of unlabeled LY333334. Results were expressed as the percent of bound PTH (1-34)-^{125}I displaced by the unlabeled ligand.

A positive test for anti-LY333334 antibodies was defined as at least a 2-fold increase in binding plus at least 40% inhibition. A total of 62 patients had at least 1 positive antibody test during the study.

Table 11 on page 101 shows the numbers of patients with positive antibody tests by treatment group and study visit.

In the placebo group, 1 patient had a positive antibody test at the study closeout visit, with 103 BU and 66% inhibition.

In the 20 mcg group, a total of 15 (2.8%) patients had at least 1 positive antibody during the study; for comparison to the placebo group, $p<0.001$. One patient had a positive test at month 3 (80 BU and 90% inhibition), 10 had positive tests at month 12 (means: 432 BU and 70% inhibition), and 13 had positive tests at the study closeout visit (means: 1365 BU and 79% inhibition).

In the 40 mcg group, a total of 44 (8.0%) patients had at least 1 positive antibody test during the study; for comparison to the placebo group, $p<0.001$. One patient had a positive test at month 3 (2590 BU and 94% inhibition), 26 had a positive tests at month 12 (means: 1234 BU and 74% inhibition), and 41 had positive tests at the study closeout visit (means: 1165 BU and 74% inhibition).

Table 11 Positive Antibody Results by Treatment Group and Study Visit

Patients with ≥2x Increase in Binding and ≥40% Inhibition at:	Placebo N=544 n (%)	PTH20 N=541 n (%)	PTH40 N=552 n (%)	Total N=1637 n (%)
Month 3 (Visit 6)	0 (0)	1 (0.2)	1 (0.2)	2 (0.1)
Month 12 (Visit 9)	0 (0)	10 (1.8)	26 (4.7)	36 (2.2)
Study Closeout Visit (17 to 24 months)	1 (0.2)	13 (2.4)	41 (7.4)	55 (3.4)

Abbreviations: PTH20 = LY333334 20 µg/day; PTH40 = LY333334 40 µg/day; N = number of patients randomly assigned to each treatment group; n = maximum number of patients in each treatment group with ≥2x increase in binding and ≥40% inhibition by visit.

Preliminary data from follow-up testing about 6 months after study closeout indicates that the binding activity decreased and the inhibitory activity remain about the same. In both LY333334 groups, the mean and maximum BU in the patients tested 6 months after study closeout were lower than the mean and maximum BU at study closeout. The mean and maximum percent inhibition were similar at study closeout and 6 months later. No patients have resumed treatment, so no data are available on the antibody response to rechallenge.

No differences were found between the patients with and without positive antibody tests in serum calcium, BMD, or adverse events.

Hypocalcemia should be a sensitive indicator for impairment of PTH (1-84) activity by antibodies, and loss of BMD response should be an indicator for clinically significant neutralization of LY333334 by antibodies. Serum calcium and BMD response were similar in patients with or without positive antibody tests, which suggests that the serum binding activity did not have detectable adverse effects.

1.7.10 Last Visit on Study Drug

The laboratory test before the last dose of study drug was identified as the last visit on study drug (LVOSD), and the last laboratory test after the last dose of study drug was also identified. These tests were analyzed for effects of LY333334 and effects of withdrawal. No adverse laboratory effects were found that were not apparent in the by-visit analyses. The magnitude of effects in the LVOSD analyses were similar to those in the month 12 analyses, and the magnitude of effects in the withdrawal visit were similar to the study endpoint effects. Most effects of LY333334 on laboratory safety variables were found to be reversible within a short interval after treatment was discontinued.

1.7.11 Subgroup Analyses by Injection Site

Patients in this study were allowed to try injecting study drug in both sites (abdomen and thigh) during the first month of treatment. They were then asked to choose 1 site and use it for the rest of the study. Therefore, serum calcium, urine calcium, and serum uric acid were analyzed separately for the patients who injected in the thigh and those who injected in the abdomen. The effects of LY333334 on these laboratory tests in the two injection groups were similar to the effects overall.

1.7.12 Summary of Clinical Laboratory Evaluation

In the 20 mcg group:

The median 4-6 hour postdose serum calcium was increased throughout the study by 0.08-0.12 mmol/L, compared to the placebo group ($p<0.01$). There were 60 (11.1%) patients with at least 1 episode of hypercalcemia, compared to 8 (1.5%) in the placebo group ($p<0.001$); nearly all of these episodes were in the 4-6 hours after dosing. The majority of the 60.patients with hypercalcemia episodes were identified within 150 days after randomization. There were 16 (3.0%) patients with 2 or more consecutive episodes of hypercalcemia, compared to 1 (0.2%) in the placebo group ($p<0.001$). The hypercalcemia was associated with: adjustment of calcium supplements in 39 (7.2%) patients compared to 3 (0.6%) in the placebo group ($p<0.001$), adjustment of study drug in 15 (2.8%) patients compared to 3 (0.6%) in the placebo group ($p=0.004$), and study discontinuation for 1 (0.2%) patient compared to 1 (0.2) in the placebo group.

There were no statistically significant increases or trends in 24-hour postdose serum calcium compared to baseline, although at 6 months the median was increased by 0.05 mmol/L compared to the placebo group. ($p<0.001$)

The median serum 25-hydroxyvitamin D at 12 months was decreased from baseline by 14.0 nmol/L ($p<0.001$) and the median serum 1,25-dihydroxyvitamin D was increased at 12 months was increased from baseline by 21.6 pmol/L ($p<0.001$),compared to the placebo group.

The median 24 hour urine calcium excretion was increased at month 1 by 0.50 mmol ($p=0.005$), at month 6 by 0.76 mmol ($p<0.001$), and at month 12 by 0.30 mmol ($p=0.030$), compared to the placebo group; it was decreased by 0.20 mmol at endpoint ($p=0.124$), when most of the patients had been off study drug for a median of 6 weeks. There were no statistically significant differences or trends in the frequency of 24 hour

hypercalciuria or urolithiasis, compared to the placebo group. The 24 hour hypercalciuria episodes that occurred were associated with: adjustment of calcium supplements in 44 (8.1%) patients compared to 27 (5.0%) in the placebo group (p=0.035), adjustment of study drug in 16 (3.0%) patients compared to 7 (1.3%) in the placebo group (p=0.056), and study discontinuation in 1 (0.2%) patient compared to 3 (0.6%) in the placebo group.

The median serum phosphorus was decreased at month 6 by 0.04 mmol/L, compared to the placebo group (p=0.036). There were no other statistically significant differences or trends in median serum phosphorus, There were no statistically significant differences or trends in the frequency of abnormal serum phosphorus, compared to the placebo group.

There were no statistically significant differences in median 24 hour urine phosphorus excretion, compared to the placebo group, although there was a trend toward an increase at month 12 of 1.00 mmol/d (p=0.037). There were no statistically significant differences or trends in the frequency of abnormal 24 hour urine phosphorus excretion, compared to the placebo group.

There were no statistically significant differences or trends in median nonfasting glucose, fasting glucose, or total cholesterol, or in the frequency of abnormal nonfasting glucose, fasting glucose, or total cholesterol, compared to the placebo group.

The median serum uric acid was increased at months 1, 6, and 12 by 36.3-54.0 mcmol/L compared to the placebo group (p<0.01). At endpoint, when most of the patients had been off study drug for a median of 6 weeks, it was still increased by 13.3 mcmol/L. There were 15 (2.8%) patients with elevations of serum uric acid above the upper limit of normal compared to 4 (0.7%) in the placebo group (p=0.011). There were no statistically significant differences or trends in the frequency of gout, arthralgia, or urolithiasis, compared to the placebo group.

There were no statistically significant differences or trends in median triglycerides during treatment (months 1-12), although at endpoint there was an upward trend of 0.11 mmol/L (p=0.077), compared to the placebo group. There were no statistically significant differences or trends in the frequency of abnormal triglycerides, compared to the placebo group.

The median serum total alkaline phosphatase was increased at months 1, 6, and 12 by 3-10 U/L, compared to the placebo group (p<0.001); at endpoint, it was still increased by 2 U/L. There were 8 (1.5%) patients with

serum total alkaline phosphatase above the upper limit of normal compared to 5 (0.9%) in the placebo group (p=0.399). These findings were attributed to the known effects of LY333334 on bone.
There were no statistically significant differences or trends in median serum alanine aminotransferase, gamma glutamyl transferase, or aspartate aminotransferase, compared to the placebo group.

The median total bilirubin was increased at month 1 by 0.55 mcmol/L (p=0.05), compared to the placebo group; there were no other statistically significant differences or trends in median total bilirubin.

There were no statistically significant differences or trends in the frequency of abnormal alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, or total bilirubin, compared to the placebo group.

There were no statistically significant differences or trends in median serum creatinine or measured creatinine clearance, or in the frequency of abnormal serum creatinine or abnormal measured creatinine clearance compared to the placebo group.

There were no statistically significant differences or trends in median serum urea nitrogen or in the frequency of abnormal serum urea nitrogen, compared to the placebo group.

The median serum potassium was decreased at months 6 and 12 by <0.10 mmol/L (p=0.001 and 0.014, respectively), the median serum bicarbonate was increased at month 1 by 0.30 mmol/L (p=0.085) and month 12 by 0.20 mmol/L (p=0.075), the median serum sodium was increased at month 1 by <0.01 mmol/L (p=0.080), and there were no statistically significant changes in the median serum chloride, compared to the placebo group. There were no statistically significant differences or trends in the frequency of abnormal serum potassium, bicarbonate, sodium, or chloride, compared to the placebo group.

The median serum magnesium was decreased by 0.06-0.07 mmol/L at month 1, 6, and 12, compared to the placebo group (p<0.001). At endpoint, when most of the patients had been off study drug for a median of 6 weeks, the decrease was < 0.01 mmol/L, although still statistically significant (p=0.009). There were 4 (0.7%) patients with serum magnesium measurements below the lower limit of normal, compared to 2 (0.4%) in the placebo group (p=0.409)

There were no statistically significant differences or trends in median urine specific gravity or in the frequency of abnormal urine specific gravity, compared to the placebo group.

The mean urine pH was increased by 0.25 units baseline ($p<0.001$) and 0.37-0.56 units at months 1, 6, and 12 ($p<0.001$), compared to the placebo group. There was not a statistically significant difference or trend at endpoint. There were no statistically significant differences or trends in the frequency of abnormal urine pH, compared to the placebo group.

The other urinalysis variables (color, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrites, microscopic examination) showed no statistically significant differences or trends in the frequency of abnormal laboratory values, compared to the placebo group.

The median hemoglobin was decreased at endpoint by 0.062 mmol/L-Fe ($p=0.089$), the median hematocrit was decreased at months 6 and 12 and endpoint by <0.01 ($p<0.01$), and the median erythrocyte count was decreased at month 6 and endpoint by <0.01 TI/L ($p<0.05$), compared to the placebo group. There were no statistically significant differences or trends in mean cell volume, mean cell hemoglobin, or mean cell hemoglobin concentration, compared to the placebo group. There were no statistically significant differences or trends in the frequency of abnormal values for any of the erythrocyte variables, compared to the placebo group.

The median leukocyte count was increased at months 1, 6, and 12 by 0.45-0.60 GI/L ($p<0.001$), the median segmented neutrophil count was increased at months 1, 6, and 12 by 0.44-0.53 GI/L ($p<0.001$), there were no statistically significant differences or trends in the band counts, there were no statistically significant differences or trends in lymphocyte counts, the median monocyte count was increased at month 1, 6, and 12 by 0.01- 0.03 GI/L ($p<0.05$), the median eosinophil count was decreased at month 1 by <0.01 GI/L ($p=0.086$), and the median basophil count was increased at month 12 by <0.01 GI/L ($p=0.056$), compared to the placebo group.
At endpoint, when most of the patients had been off study drug for a median of 6 weeks, there were no longer statistically significant differences or trends in the leukocyte, segmented neutrophil, monocyte, eosinophil, or basophil counts, compared to the placebo group.

There were 37 (6.9%) patients with leukocyte counts below the lower limit of normal, compared to 60 (11.2%) in the placebo group ($p=0.016$).

The median platelet count was increased at month 1 by 7.50 GI/L (p=0.009), compared to the placebo group. There were no statistically significant differences or trends in the frequency of abnormal platelet counts, compared to the placebo group.

There were no statistically significant differences or trends in median serum creatine phosphokinase compared to the placebo group. There were no statistically significant differences or trends in the frequency of abnormal creatine phosphokinase, compared to the placebo group.

There were no statistically significant differences or trends in median serum albumin or total protein, except that at month 12 the median serum albumin was decreased by 1 g/L, compared to the placebo group (p=0.097). There were no statistically significant differences or trends in the frequency of abnormal serum albumin or total protein, compared to the placebo group.

Of the blood samples obtained for measuring PTH (1-84), 89.1% were below the level of quantitation, compared to 71.7% in the placebo group. The blood samples were collected 2.3 hours after dosing with study drug, on average, and it is likely that PTH (1-84) was suppressed during this postdose interval in the patients receiving LY333334.

A positive test for anti-LY333334 antibodies was defined as at least a 2-fold increase in binding plus at least 40% inhibition. Fifteen (2.8%) patients had at least 1 positive antibody test compared to 1 (0.2%) in the placebo group (p<0.001). Preliminary data from follow-up testing about 6 months after study closeout indicated that the binding activity decreased and the inhibitory activity remain about the same.

No differences were found between the patients with and without positive antibody tests in serum calcium, BMD, or adverse events. Hypocalcemia should be a sensitive indicator for impairment of PTH (1-84) activity by antibodies, and loss of BMD response should be an indicator for clinically significant neutralization of LY333334 by antibodies. Serum calcium and BMD response were similar in patients with or without positive antibody tests, which suggests that the serum binding activity did not have detectable adverse effects.

In the 40 mcg group:

The median 4-6 hour postdose serum calcium was increased throughout the study by 0.12-0.17 mmol/L, compared to the placebo group ($p<0.01$). There were 153 (27.7%) patients with episodes of hypercalcemia, compared to 8 (1.5%) in the placebo group ($p<0.001$); nearly all of these episodes were in the 4-6 hours after dosing. The majority of the 60.patients with hypercalcemia nearly all of these episodes . The majority of the 153 patients with hypercalcemia were identified within 300 days after randomization. There were 53 (9.6%) patients with 2 or more consecutive episodes of hypercalcemia, compared to 1 (0.2%) in the placebo group ($p<0.001$). The hypercalcemia was associated with: adjustment of calcium supplements in 102 (18.5%) patients compared to 3 (0.6%) in the placebo group ($p<0.001$), adjustment of study drug in 62 (11.2%) patients compared to 3 (0.6%) in the placebo group ($p<0.001$), and study discontinuation for 9 (1.6%) patients compared to 1 (0.2%) in the placebo group ($p=0.012$).

There were no statistically significant increases or trends in 24-hour postdose serum calcium except at 6 months, when the median was increased by 0.03 mmol/L compared to baseline and 0.07 mmol/L compared to the placebo group ($p<0.001$ for both comparisons).

The median serum 25-hydroxyvitamin D at 12 months was decreased from baseline by 13.5 nmol/L ($p<0.001$) and the median serum 1,25-dihydroxyvitamin D was increased at 12 months was increased from baseline by 21.6 pmol/L ($p<0.001$), compared to the placebo group.

The median 24 hour urine calcium excretion was increased at month 6 by 0.40 mmol ($p=0.003$), compared to the placebo group; it was decreased by 0.50 mmol at endpoint ($p<0.001$), when most of the patients had been off study drug for a median of 6 weeks. There were no other statistically significant differences or trends in the median 24 hour urine calcium excretion, compared to the placebo group. There were no statistically significant differences or trends in the frequency of 24 hour hypercalciuria or urolithiasis, compared to the placebo group. The 24 hour hypercalciuria episodes were associated with: adjustment of calcium supplements in 48 (8.7%) patients compared to 27 (5.0%) in the placebo group ($p=0.014$), adjustment of study drug in 20 (3.6%) patients compared to 7 (1.3%) in the placebo group ($p=0.013$), and study discontinuation for 2 (0.4%) patients compared to 3 (0.6%) in the placebo group.

The median serum phosphorus was decreased at month 6 by 0.04 mmol/L, (p=0.049) and increased at endpoint by 0.04 mmol/L (p=0.001), compared to the placebo group. There were no other statistically significant differences or trends in median serum phosphorus, There were no statistically significant differences or trends in the frequency of abnormal serum phosphorus, compared to the placebo group.

There were no statistically significant differences in the median 24 hour urine phosphorus excretion, compared to the placebo group, although there was a trend toward and increase at month 12 of 1.73 mmol/d (p=0.039). There were no statistically significant differences or trends in the frequency of abnormal 24 hour urine phosphorus excretion, compared to the placebo group.

There were no statistically significant differences or trends in median nonfasting glucose, fasting glucose, or total cholesterol, or in the frequency of abnormal nonfasting glucose, fasting glucose, or total cholesterol, compared to the placebo group.

The median serum uric acid was increased at months 1, 6, and 12 by 55.0-69.5 mcmol/L compared to the placebo group (p<0.01). At endpoint, when most of the patients had been off study drug for a median of 6 weeks, it was still increased by 23.8 mcmol/L. There were 27 (5.0%) patients with elevations of serum uric acid above the upper limit of normal compared to 4 (0.7%) in the placebo group (p<0.001). There were no statistically significant differences or trends in gout, arthralgia, or urolithiasis AEs, compared to the placebo group.

There were no statistically significant differences or trends in median triglycerides during active treatment (months 1-12), although at endpoint triglycerides were increased by 0.17 mmol/L (p=0.028), compared to the placebo group. There were no statistically significant differences or trends in the frequency of abnormal triglycerides, compared to the placebo group.

The median serum total alkaline phosphatase was increased at months 1, 6, and 12 by 10-21 U/L, compared to the placebo group (p<0.001); at endpoint, it was still increased by 7 U/L. There were 46 (8.5%) patients with serum total alkaline phosphatase above the upper limit of normal compared to 5 (0.9%) in the placebo group (p<0.001). These findings were attributed to the known effects of LY333334 on bone.

The median serum alanine aminotransferase was decreased at months 1, 6, and 12 by 1.0 U/L, compared to the placebo group (p=0.094, 0.030,

and 0.001, respectively); this was not considered to be clinically significant. There were no statistically significant differences or trends in median serum gamma glutamyl transferase or aspartate aminotransferase, compared to the placebo group.

The median total bilirubin was increased at month 1 by 1.0 mcmol/L (p=0.004), compared to the placebo group; there were no other statistically significant differences or trends in median total bilirubin.

There were no statistically significant differences or trends in the frequency of abnormal alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, or total bilirubin, compared to the placebo group.

There were no statistically significant differences or trends in median serum creatinine or measured creatinine clearance, or in the frequency of abnormal serum creatinine or abnormal measured creatinine clearance, compared to the placebo group.

The median serum urea nitrogen was increased at months 6 and 12 by 0.20 mmol/L, compared to the placebo group ($p<0.001$ and $p= 0.003$, respectively); at endpoint, when most of the patients had been off study drug for a median of 6 weeks, there was not a statistically significant difference. There were no statistically significant differences or trends in the frequency of abnormal serum urea nitrogen, compared to the placebo group.

The median serum potassium was decreased at months 6 and 12 by <0.10 mmol/L ($p=<0.001$ and $p=0.002$, respectively), the median serum bicarbonate was increased at months 1, 6, and 12 by 0.3 mmol/L ($p=0.072$, $p=0.017$, and $p=0.014$, respectively), the median serum sodium was increased at months 1, 6, and 12 by <0.01 mmol/L ($p=0.075$, $p=0.033$, and $p=0.010$, respectively), and there were no statistically significant changes in the median serum chloride, compared to the placebo group. There were no statistically significant differences or trends in the frequency of abnormal serum potassium, bicarbonate, sodium, or chloride, compared to the placebo group.

The median serum magnesium was decreased by 0.07-0.10 mmol/L at month 1, 6, and 12, compared to the placebo group ($p<0.001$). At endpoint, when most of the patients had been off study drug for a median of 6 weeks, the difference was < 0.01 mmol/L, although still

statistically significant (p<0.001). Eleven (2.0%) patients had serum magnesium measurements below the lower limit of normal, compared to 2 (0.4%) in the placebo group (p=0.013)

The median urine specific gravity at baseline and month 6 was <0.01 specific gravity units different from the median in the placebo group, although the differences were statistically significant (p=0.031 and p=0.032, respectively); there were no other statistically significant differences or trends in median urine specific gravity. There no statistically significant differences or trends in the frequency of abnormal urine specific gravity, compared to the placebo group.

The mean urine pH was increased by 0.27 units at baseline (p<0.01) and 0.62-0.66 units at months 1 and 6 (p<0.001), compared to the placebo group; there was not a statistically significant difference or trend at month 12 or endpoint. There were no statistically significant differences or trends in the frequency of abnormal urine pH, compared to the placebo group.

The other urinalysis variables (color, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrites, microscopic examination) showed no statistically significant differences or trends in the frequency of abnormal laboratory values, compared to the placebo group.

The median hemoglobin was decreased at months 6 and 12 and endpoint by 0.062-0.124 mmol/L-Fe (p<0.01), the median hematocrit was decreased at months 6 and 12 and endpoint by <0.01 (p=<0.01), and the median erythrocyte count was decreased at months 1, 6, and 12 and endpoint by <0.01 TI/L (p=0.055 for month 1 and p<0.01 for the other times), compared to the placebo group. There were no statistically significant differences or trends in mean cell volume, mean cell hemoglobin, or mean cell hemoglobin concentration, compared to the placebo group. There were no statistically significant differences or trends in the frequency of abnormal values for any of the erythrocyte variables, compared to the placebo group.

The median leukocyte count was increased at months 1, 6, and 12 by 0.55-0.82 GI/L (p<0.001), the median segmented neutrophil count was increased at months 1, 6, and 12 by 0.60-0.69 GI/L (p<0.001), there were no statistically significant differences or trends in band counts, there were no statistically significant differences or trends in lymphocyte counts during months 1-12; the median monocyte count was increased at months 1, 6, and 12 by 0.03-0.06 GI/L (p<0.001), the median eosinophil

count was decreased at month 12 by 0.01 GI/L (p=0.035), and the median basophil count was increased at months 1,6, and 12 by <0.01 GI/L (p<0.05), compared to the placebo group.

At endpoint, when most of the patients had been off study drug for a median of 6 weeks, there were still statistically significant differences or trends in the leukocyte, monocyte, eosinophil, and basophil counts, compared to the placebo group. Also, the median lymphocyte count was increased at endpoint by 0.13 GI/L (p=0.004). There was no longer a statistically significant difference in the segmented neutrophil count. There was not a statistically significant increase or trend in the frequency of leukocyte counts above the upper limit of normal. There were 39 (7.2%) patients with leukocyte counts below the lower limit of normal, compared to 60 (11.2%) in the placebo group (p=0.020).

The median platelet count was increased at months 1, 6, and 12 by 7.00-10.00 GI/L (p<0.05), compared to the placebo group. There were no statistically significant differences or trends in the frequency of abnormal platelet counts, compared to the placebo group.

The median creatine phosphokinase was decreased at months 1, 6, and 12 by 4.5-7.5 U/L (p<0.05), compared the placebo group. There were no statistically significant differences or trends in the frequency of abnormal creatine phosphokinase, compared to the placebo group.

There were no statistically significant differences or trends in median serum albumin or total protein, or in the frequency of abnormal serum albumin or total protein, compared to the placebo group.

Of the blood samples obtained for measuring PTH (1-84), 83.7% were below the level of quantitation, compared to 71.7% in the placebo group. The blood samples were collected 2.3 hours after dosing with study drug, on average, and it is likely that PTH (1-84) was suppressed during this postdose interval in the patients receiving LY333334.

A positive test for anti-LY333334 antibodies was defined as at least a 2-fold increase in binding plus at least 40% inhibition. Forty-four (8.0%) patients had at least 1 positive antibody test compared to 1 (0.2%) in the placebo group (p<0.001). Preliminary data from follow-up testing about 6 months after study closeout indicates that the binding activity decreased and the inhibitory activity remain about the same.

No differences were found between the patients with and without positive antibody tests in serum calcium, BMD, or adverse events. Hypocalcemia

should be a sensitive indicator for impairment of PTH (1-84) activity by antibodies, and loss of BMD response should be an indicator for clinically significant neutralization of LY333334 by antibodies. Serum calcium and BMD response were similar in patients with or without positive antibody tests, which suggests that the serum binding activity did not have detectable adverse effects.

1.8 Conclusions

In the 20 mcg and 40 mcg groups compared to the placebo group, there were statistically significant decreases in the reporting of back pain. This may represent a clinical benefit, although AE reports of back pain were an efficacy outcome.

In the 20 mcg and 40 mcg groups compared to the placebo group, the was a trend toward an increase in the reporting of mild to moderate leg cramps, which is supported by data from other clinical trials.

In the 40 mcg group compared to the placebo group, there were statistically significant increases in nausea and headache in the 40 mcg group compared to the placebo group. The nausea led to a statistically significant increase in study discontinuation in the 40 mcg group.

There were numerous other statistically significant increases or decreases, or trends, in the reporting of AEs. These findings should be evaluated further in data from other clinical trials.

Subgroup analyses did not show any statistically significant differences or trends in the risk of treatment-related AEs for any subgroups of patients compared to the risk in the overall study population.

There were no consistent statistically significant differences or trend between treatment groups in routine measurements of blood pressure and pulse.

Laboratory testing did not identify serious safety problems. There were statistically significant increases in the 4-6 hour postdose serum calcium and in 24 hour urine calcium excretion in the LY333334 groups compared to the placebo group. There were no statistically significant increases or trends in kidney disorders or other clinical AEs that might be associated with increased serum or urine calcium.

The results of tests of carbohydrate and lipid metabolism were similar in the 3 treatment groups. There were statistically significant increases in uric

acid in the LY333334 groups compared to the placebo group, but there were no increases in gout, arthralgia, or urolithiasis.

There were statistically significant increases in serum total alkaline phosphatase in the LY333334 groups compared to the placebo group, which were attributed to the known effects of LY333334 on bone. The results of other liver function tests were similar in the 3 treatment groups. The results of tests of kidney function were similar in the 3 treatment groups, except that serum magnesium was decreased in the LY333334 groups compared to the placebo group. No clinical AEs related to low serum magnesium were reported.

There were small changes in hematology in the LY333334 groups compared to the placebo group, which were not considered to be clinically significant.

Sixty-two patients developed antibodies to LY333334. The antibody formation did not appear to be associated with any clinical AEs.

The differences between treatment groups in laboratory tests appeared to be reversible upon stopping treatment, and most of the changes were no longer detectable by the study closeout visit.

2. Study GHAJ: Effects of LY333334 in the Treatment of Men with Osteoporosis

The safety findings in study GHAJ were generally similar to those in study GHAC. The report will therefore be brief.

2.1 Study Design

Study GHAJ was a randomized, double-blind, placebo-controlled, parallel-group clinical trial of LY333334 conducted at 37 centers in 11 countries between July 1997 and December 1998. The patients were 437 men 30-85 years of age with intact L2-L4 vertebrae and lumbar spine BMD at least 2.0 standard deviations below that of healthy young men.

The patients were randomized to placebo (n=147), 20 mcg (n=151), or 40 mcg (n=139). All patients received 1000 mg of calcium and 400-1200 IU of vitamin D per day. The planned duration of the treatment was 2 years. The actual duration ranged from 3-458 days; most patients were treated for 6-14 months.

The primary efficacy endpoint was vertebral BMD. Other efficacy endpoints included: hip, wrist, and total body BMD; height; serum markers of bone formation (bone-specific alkaline phosphatase and procollagen I carboxy-terminal propeptide); urine markers of bone resorption (N-telopeptide and free deoxypyridinoline); 1,25-dihydroxyvitamin D; and LY333334 pharmacokinetics and pharmacodynamics.

The main safety variables were reported adverse events, physical examinations, and laboratory tests of: hematology; clinical chemistry, including serum calcium and albumin; urinalysis; serum calcium and albumin 4-6 hours after dosing with study drug; urinalysis; 24 hour urine calcium, phosphorus, and creatinine excretion; creatinine clearance; testosterone; 25 hydroxyvitamin D; PTH (1-84); and LY333334 antibodies. An electrocardiogram was obtained during the screening/run-in phase.

The study was planned to have 2 phases: a calcium and vitamin D run-in phase of 1-2 months (visits 0-2) and a treatment phase of 24 months (visits 2-8). However, the study was stopped in December 1998 due to the finding of osteosarcoma in a rat carcinogenicity study. The clinical investigators were advised to have all patients complete and early discontinuation visit, which served as the study close-out visit. Lilly offered the patients the option of enrolling in an observational post-treatment follow-up study, and 81.2% the eligible patients enrolled.

The schedule of study visits and other events is presented in Table 1 on this page and page 116.

Table 1 Schedule of Study Events

Month Visit	-2 to 0 1	0 2	1 3	3 4	6 5	12 6	18 7	24 8	E D
Activity									
Informed consent document signed	X								
Patient number assigned	X								
Review of inclusion/exclusion criteria	X	X							
Medical history	X								
Physical examination	X					X		X	X
Sitting blood pressure, pulse	X	X	X	X	X	X	X	X	X
Concomitant medication reporting	X	X	X	X	X	X	X	X	X
Patient education regarding injections	X	X							
Record of adverse event reporting	X	X	X	X	X	X	X	X	X
Height[a]	X					X		X	X
Weight	X		X	X	X	X	X	X	X
Assessments of smoking, alcohol, caffeine	X					X		X	X
Assessment of dietary calcium	X							X	X
Patient assigned to treatment group		X							
Study material dispensed		X		X	X	X	X		
Laboratory Assessments									
TSH	X								
Estradiol, FSH, LH	X								
Morning total and free testosterone	X	X	X						
LY333334 antibodies	X					X		X	X
Hematology, clinical chemistry, urinalysis	X				X	X	X	X	X
Serum calcium, albumin (4-6 hours postdose)			X	X	X	X	X	X	X
25-hydroxyvitamin D	X					X		X	X
PTH(1-84)	X					X		X	X
24-hour urine calcium, creatinine, phosphorous	X		X		X	X		X	X
Biochemical markers of bone formation and resorption[b]		X	X	X	X	X	X	X	X
1,25-dihydroxyvitamin D		X	X	X	X	X	X	X	X
LY333334 serum concentrations			X	X	X	X	X	X	X
Technical Assessments									
Lateral thoracic and lumbar spinal x-ray films[c]	X								
Electrocardiogram	X								
PA lumbar spine BMD	X[d,e]			X	X	X	X	X	X
Hip BMD	X[d,e]					X		X	X
Total body and radial (forearm) BMD[f]	X[e]					X		X	X
Miscellaneous									
Medical resource utilization		X			X	X	X	X	X
Health-related quality of life		X			X	X	X	X	X

X = Performed during this time interval.

Table 1-continued.

Abbreviations: ED = Early Discontinuation; TSH = thyroid-stimulating hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; PTH = parathyroid hormone; PA = posterior-anterior; BMD = bone mineral density.

[a] Height measurements were made via [redacted] stadiometer or other suitable stadiometer at approximately the same time of day throughout the study. Three separate measurements were made and recorded on the clinical report form.

[b] Were obtained in the morning.

[c] Spinal x-ray films obtained in the 3 calendar months prior to randomization were used in place of this procedure.

[d] The results of only one PA lumbar spine OR one hip BMD need assessment prior to proceeding with further screening procedures.

[e] Two BMDs at each specified body site were required before randomization occurred. If both assessments of any given body site were obtained on the same day, the patient was completely removed from the DEXA scanner and repositioned between the first and second scans.

[f] At study sites where available.

2.2 Baseline Characteristics of the Patients

The patients were men 30-85 years of age with intact L2-L4 vertebrae and with a lumbar spine or hip BMD at least 2 standard deviations below the average for healthy young men. The patients were ambulatory and free of severe or chronically disabling conditions. Laboratory values for serum calcium, PTH (1-84), and urine calcium were within the normal range and the value for 25-hydroxyvitamin D was between the lower limit and 3 times the upper limit of normal.

The exclusion criteria were certain disorders or diseases depending on recency and severity, the use of certain drugs depending on recency, dose, route of administration, and duration of use, and other criteria.

The excluded disorders and diseases were: metabolic bone disorders other than osteoporosis; any disease which affects bone metabolism; carcinoma (except excised superficial lesions); urolithiasis or nephrolithiasis, sprue, inflammatory bowel disease, malabsorption syndrome or any indication of poor intestinal absorption of calcium; significantly impaired hepatic or renal function; allergy to LY333334, LY333334 diluents or excipients, PTH or a PTH analog.

The excluded drugs were: bisphosphonates; fluorides (except fluoridated water and topical dental fluoride);calcitriol, calcitriol analogs or agonists; calcitonins; antacids containing calcium or aluminum; vitamin D; estrogens, estrogen analogs, agonists or antagonists); androgens or other anabolic steroids; corticosteroids (with exceptions for some topical formulations); heparins, coumarins, or indandione derivatives; anticonvulsants (except benzodiazepines); or any other drug known to

affect bone metabolism (except oral calcium and vitamin D supplements, and diuretics which were stable in dose); previous LY333334, PTH, or PTH analog; or any investigational drug.

The other exclusion criteria were: a total nondietary calcium intake of >1200 mg per day, including supplements and antacids; consumption of more than 4 per day of 30 mL distilled spirits, 340 mL beer, or 120 mL wine; drug abuse; and poor medical or psychiatric risk.

Table 2 on this page summarizes demographic and other characteristics of the patients at baseline.

The majority of patients were Caucasian (99.1%), nonsmokers (70.3%), and used caffeine (87.9%); 70.0% used alcoholic beverages. There were no statistically significant differences or trends between treatment groups in baseline characteristics.

Table 2 Baseline Characteristics of Patients

Characteristic	Placebo (N=147)	PTH20 (N=151)	PTH40 (N=139)	Total (N=437)	p-value
Age (Years) (Mean ± SD)	58.65±12.87	59.29±13.40	58.06±12.68	58.68±12.98	0.724
Origin n (%)					0.725
Caucasian	147 (100)	149 (98.7)	137 (98.6)	433 (99.1)	
Asian	0	1 (0.7)	1 (0.7)	2 (0.5)	
Other	0	1 (0.7)	1 (0.7)	2 (0.5)	
Body-mass index (kg/m^2) (Mean ± SD)*	25.21±3.61	25.37±3.72	24.86±3.60	25.15±3.64	0.483
Height cm (Mean ± SD)**	173.63±7.40	173.72±7.34	172.99±7.45	173.46±7.39	0.665
Weight kg (Mean ± SD)	75.98±11.54	76.59±12.25	74.47±12.16	75.71±11.99	0.305
Current smoker n (% Yes)	47 (32.0)	45 (29.8)	38 (27.3)	130 (29.7)	0.693
Alcohol n (% yes)	102 (69.4)	114 (75.5)	90 (64.7)	306 (70.0)	0.134
Previous osteoporosis drug user n (% yes)	17 (11.6)	22 (14.6)	25 (18.0)	64 (14.6)	0.308
Osteoporosis type n (%)					0.974
Idiopathic	74 (50.3)	78 (51.7)	71 (51.1)	223 (51.0)	
Hypogonadal	73 (49.7)	73 (48.3)	68 (48.9)	214 (49.0)	
Previous non-vertebral fracture n (% yes)	79 (53.7)	100 (66.2)	79 (56.8)	258 (59.0)	0.139
Baseline vertebral BMD (Mean ± SD)	0.85±0.14	0.89±0.15	0.87±0.14	0.87±0.14	0.053
Dietary Calcium (Mean ± SD)	0.86±0.57	0.84±0.54	0.80±0.50	0.84±0.54	0.667
Caffeine n (% yes)	130 (88.4)	128 (84.8)	126 (90.6)	384 (87.9)	0.425

Abbreviations: n = number of patients in a category; N = number of patients randomly assigned to each treatment group; PTH20 = LY333334 20 µg/day; PTH40 = LY333334 40 µg/day; SD = standard deviation; BMD = bone mineral density.

*One patient was excluded from the body-mass index analysis because of a missing value

**One patient was excluded from the height analysis because of a missing value

2.3 Compliance and Duration of Treatment

Compliance with treatment was evaluated by recording the number of used, partly used, and unused injection cartridges returned at each visit. On average, patients in each treatment group took at least 79% of the study drug . The percentages of patients who took at least 50% of the study drug were 87.8% in the placebo group, 82.1% in the 20 mcg group, and 77.0% in the 40 mcg group.

Table 3 on this page shows the numbers of patients by treatment group and duration of treatment. Most patients were treated for 6-14 months, including 93.9% in the placebo group, 87.4% in the 20 mcg group, and 79.9% in the 40 mcg group. The patient-years of treatment were 126.0 for placebo, 121.6 for 20 mcg, and 106.9 for 40 mcg.

Table 3 Number of Patients by Treatment Group and Duration of Exposure

THERAPY(Treatment Name) EXP_MTH

Frequency	0-2	3-5	6-8	9-11	12-14	15-17	Missing	Total
Placebo	8	1	24	62	52	0	0	147
PTH20	13	5	27	54	51	0	1	151
PTH40	16	10	22	48	41	1	1	139
Total	37	16	73	164	144	1	2	437

PTH 20 = LY333334 20 MCG
PTH 40 = LY333334 40 MCG
EXP MTH = EXPOSURE IN MONTHS

2.4 Patient Disposition

A total of 959 patients were screened for the study, of whom 437 (45.6%) enrolled and randomized to placebo (n=147), 20 mcg (n=151), or 40 mcg (n=139); all patients received 1000 mg/day of calcium and 400-1200 IU/day of vitamin D.

Of the 437 patients randomized, 356 (81.5%) discontinued the study due to sponsor's decision: 130 (88.4%) in the placebo group, 123 (81.5%) in the 20 mcg group, and 103 (74.1%) in the 40 mcg group. A total of 39 (8.9%) patients discontinued due to adverse events: 7 (4.8%) in the placebo group, 14 (9.3%) in the 20 mcg group, and 18 (12.9%) in the 40 mcg group (p=0.052). A total of 25 (5.7%) patients discontinued due to patient decision: 4 (2.7%) in the placebo group, 8 (5.3%) in the 20 mcg group, and

13 (9.4%) in the 40 mcg group (p=0.052). There were no statistically significant differences or trends between treatment groups for other reasons for discontinuation (protocol violation, death, significant laboratory findings, lost to follow-up, moved, physician decision, lack of efficacy, noncompliance, or other).

2.5 Adverse Events

An adverse event (AEs) was defined as any undesirable experience or unexpected benefit that occurred after informed consent was obtained. At each study visit, patients were questioned about the occurrence of AEs, and the reported events were classified as mild, moderate, or severe. The discussion below pertains to treatment-emergent AEs, defined as AEs that first occurred or worsened after study drug was started.

In the AE analyses, overall differences between treatment groups were tested for statistical significance with Pearson' s chi-square test, Fisher's exact test, and the Cochran-Mantel-Haenszel test, stratifying by country. Dose–response was analyzed with a Mantel-Haenszel test. The primary analyses were based on Pearson's chi-square test, with the other tests serving as confirmatory. Pairwise comparisons between groups were done if needed to further evaluate a significant overall difference.

Note: A biologically plausible interpretation is not apparent for some of the statistically significant findings or trends described below. These may have been due to chance, since many comparisons were made, without adjustment of the statistics for multiple comparisons. Findings of this kind are generally qualified with a statement that "interpretation is not clear."

2.5.1 Serious Adverse Events

Serious adverse events (SAEs) are defined as adverse events that are fatal or life-threatening, result in hospitalization, prolongation of hospitalization, severe or permanent disability, cancer, congenital abnormality, or drug overdose, or are significant for any other reason.

A total of 45 (10.3%) patients reported at least 1 SAE: 16 (10.9%) in the placebo group, 15 (9.9%) in the 20 mcg group, and 14 (10.1%) in the 40 mcg group (p=0.959).

2.5.1.1 Deaths

Two (0.5%) patients died during the study, both in the 20 mcg group. One was due to pneumonia in an 84 year old man with carcinoma of the lung, and the other was due to pulmonary edema in a 78 year old man who had undergone surgery for metastatic carcinoma of the neck. Neither death appeared to be related to study drug. For further information see Table 2 and Figure 1 on pages 30-33.

2.5.1.2 Any Serious Adverse Event

There were 63 different SAEs (i.e. SAE terms), with no statistically significant differences or trends between treatment groups in the frequency of any specific SAE.

2.5.2 Discontinuations due to Adverse Events

A total of 39 (8.9%) patients discontinued the study due to AEs: 7 (4.8%) in the placebo group, 14 (9.3%) in the 20 mcg group, and 18 (12.9%) in the 40 mcg group (p=0.052). Nausea was the only specific AE that showed a statistically significant difference or trend between treatment groups as a reason for discontinuation: none in the placebo group or 20 mcg group, and 5 (3.6%) in the 40 mcg group (p=0.004). The reasons for the larger numbers of other AE discontinuations in the 20 mcg and 40 mcg groups compared to the placebo group were diverse.

Two patients discontinued the study due to laboratory abnormalities: 1 in the placebo group due to worsening of preexisting normocytic anemia, and 1 in the 40 mcg group due to hypercalcemia (2.69 mmol/L).

2.5.3 Adverse Events of Any Severity

A total of 345 (78.9%) patients reported at least 1 AE: 112 (76.2%) in the placebo group, 121 (80.1%) in the 20 mcg group, and 112 (80.6%) in the 40 mcg group (p=0.600). AEs were classified as mild, moderate, or severe on the basis of patient reporting. This is discussed for selected AEs

The 10 most common AEs and the percentages of patients reporting them were: pain (15.6%), surgical procedure (11.0%), rhinitis (10.3%), back pain (10.1%), nausea (8.9%), asthenia (8.2%), arthralgia (7.3%), flu syndrome (7.3%), infection (7.3%) and headache (6.6%). Of these, there was a statistically significant difference or trend between treatment groups only for nausea (see below).

Table 4 on page 122 shows the numbers of patients in the 3 treatment groups reporting AEs that occurred in at least 1% of patients in any group and showed statistical differences between groups at the alpha=0.10 level.

Nausea and headache occurred at similar frequency in the placebo and 20 mcg groups but were increased in the 40 mcg group. For nausea, the numbers of patients were: 5 (3.4%) in the placebo group, 8 (5.3%) in the 20 mcg group, and 26 (18.7%) in the 40 mcg group ($p<0.001$). An analysis of time-to-onset showed that the excess episodes of nausea in the 40 mcg group were in the first 50 days of treatment. For headache, the numbers of patients were: 6 (4.1%) in the placebo group, 8 (5.3%) in the 20 mcg group, and 15 (10.8%) in the 40 mcg group ($p=0.053$).

For sinusitis and depression, there was inconsistency in dose-response, and for the other AEs the numbers of patients were small. Interpretation of the findings for these AEs is not clear.

Table 4 Adverse Events in at Least 1% of Patients in Any Treatment Group With Statistical Differences Between Groups at alpha = 0.10

EVENTS	PLACEBO (N=147) n (%)	PTH20 (N=151) n (%)	PTH40 (N=139) n (%)	TOTAL (N=437) n (%)	P-VALUES# P_PCHI	P_CMHGA	_EXACT_
OVERALL INCIDENCE	112(76.2)	121(80.1)	112(80.6)	345(78.9)	0.600	0.543	0.608
NAUSEA	5(3.4)	8(5.3)	26(18.7)	39(8.9)	<0.001	<0.001	<0.001
HEADACHE	6(4.1)	8(5.3)	15(10.8)	29(6.6)	0.053	0.052	0.066
SINUSITIS	3(2.0)	1(0.7)	7(5.0)	11(2.5)	0.054	0.052	0.056
DEPRESSION	1(0.7)	7(4.6)	1(0.7)	9(2.1)	0.022	0.020	0.034
URINARY FREQUENCY	1(0.7)	1(0.7)	5(3.6)	7(1.6)	0.076	0.111	0.134
HERNIA	1(0.7)	0(0.0)	5(3.6)	6(1.4)	0.021	0.024	0.010
WEIGHT LOSS	1(0.7)	0(0.0)	4(2.9)	5(1.1)	0.057	0.053	0.029
NERVOUSNESS	0(0.0)	0(0.0)	4(2.9)	4(0.9)	0.013	0.020	0.010

P-VALUES ARE FROM THE FOLLOWING TESTS:
P_PCHI: PEARSON'S CHI SQUARE TEST
P_CMHGA: COCHRAN-MANTEL-HAENSZEL TEST FOR GENERAL ASSOCIATION CONTROLLING FOR INVESTIGATOR
EXACT: FISHER'S EXACT TEST
Program Stored as RMP.B3DSGHAJ.SASPGM(ABS041CT) BY PTH-CTG 06JUL00
Data is from RMP.SAS.B3DM.MCGHAJSW.SUBMISS

Abbreviations: PTH20 = LY333334 20 µg/day; PTH40 = LY333334 40 µg/day; N = number of randomly assigned patients in treatment group(s); n = number of patients in treatment group(s) reporting the treatment-emergent adverse event; vs = versus; Pbo = placebo.
= Combined incidence rate less than 5 and Pearson's chi-square p-value not calculated.

2.5.4 Further Analysis of Selected Adverse Events

Back pain, accidental injury, nausea, headache, gout and arthralgia, dizziness and vertigo, leg cramps, syncope, urolithiasis, and cancer were selected for further discussion based on their occurrence in this study or study GHAC, related laboratory findings, or other clinical or non-clinical experience.

2.5.4.1 Back pain

The numbers of patients reporting back pain were: 19 (12.9%) in the placebo group, 14 (9.3%) in the 20 mcg group, and 11(7.9%) in the 40 mcg group (p=0.342). For severe back pain, the numbers were 4 (2.7%) in the placebo group, none in the 20 mcg group, and 2 (1.4%) in the 40 mcg group (p=0.130). A lower frequency of vertebral fractures in this study compared to study GHAC may account for the difference in findings regarding back pain.

2.5.4.2 Accidental Injury

The numbers of patients reporting accidental injury were: 9 (6.1%) in the 20 mcg group, 9 (6.0%) in the 20 mcg group, and 8 (5.8%) in the 40 mcg group (p=0.991). For severe accidental injury, the numbers of patients were: 4 (2.7%) in the placebo group, 1 (0.7%) in the 20 mcg group, and none in the 40 mcg group (p=0.076). The finding for severe accidental injury is consistent with the corresponding finding in study GHAC.

2.5.4.3 Nausea

The numbers of patients reporting nausea were: 5 (3.4%) in the placebo group, 8 (5.3%) in the 20 mcg group, and 26 (18.7%) in the 40 mcg group (p<0.001). In the lowest tertile of age, the frequency of nausea was similar between treatment groups, whereas in the middle and highest tertiles the frequency of nausea was increased in the 40 mcg group (p=0.020). None of the patients reported severe nausea.

2.5.4.4 Headache

The numbers of patients reporting headache were: 6 (4.1%) in the placebo group, 8 (5.3%) in the 20 mcg group, and 15 (10.8%) in the 40 mcg group (p=0.053). For severe headache, the numbers were: none in the placebo group or 20 mcg group, and 2 (1.4%) in the 40 mcg group.

2.5.4.5 Gout and Arthralgia

Two patients reported gout: 1 (0.7%) in the placebo group and 1 (0.7%) in the 40 mcg group. Neither patient reported severe gout.

The numbers of patients reporting arthralgia were: 9 (6.1%) in the placebo group, 14 (9.3%) in the 20 mcg group, and 9 (6.5%) in the 40 mcg group (p=0.521). For severe arthralgia, the numbers were: none in the placebo group, 2 (1.3%) in the 20 mcg group, and 2 (1.4%) in the 40 mcg group.

2.5.4.6 Dizziness and Vertigo

The numbers of patients reporting dizziness were: 4 (2.7%) in the placebo group, 5 (3.3%) in the 20 mcg group, and 9 (6.5%) in the 40 mcg group (p=0.231). For vertigo, the numbers of patients were: 1 (0.7%) in the placebo group, 2 (1.3%) in the 20 mcg group, and 4(3.9%) in the 40 mcg group (p=0.316). None of the patients reported severe dizziness or vertigo.

2.5.4.7 Leg Cramps

The numbers of patients reporting leg cramps were: 3 (2.0%) in the placebo group, 1 (0.7%) in the 20 mcg group and 1 (0.7%) in the 40 mcg group (p=0.455). For severe leg cramps, the numbers were: 2 (1.4%) in the placebo group and none in the 20 mcg group or 40 mcg group. LY333334 does not appear to increase the frequency of leg cramps in men.

2.5.4.8 Syncope

The numbers of patients reporting syncope were: 1 (0.7%) in the placebo group, 1 (0.7%) in the 20 mcg group, and 1 (0.7%) in the 40 mcg group. The patients in the placebo and 20 mcg groups reported severe syncope.

2.5.4.9 Urolithiasis

Urolithiasis and other urinary tract AEs were reviewed because LY333334 increases urine calcium excretion and serum uric acid. The numbers of patients reporting urinary tract AEs were: 1 in the placebo group (kidney calculus), 2 in the 20 mcg group (both kidney calculus), and 2 in the 40 mcg group (1 kidney calculus, 1 kidney pain) (p=0.807).

2.5.4.10 Cancer

The numbers of patients reporting cancer were: 3 (2.0%) in the placebo group, 3(2.0%) in the 20 mcg group, and none in the 40 mcg group. The 3 cancers in the placebo group were thyroid, lung, and basal cell, and the 3 cancers in the 20 mcg group were bladder, epidermoid, and lung.

2.5.5 Summary of Adverse Events

There were 2 deaths, neither of which appears to have been related to treatment. A total of 45 (10.3%) patients reported at least 1 SAE. There were no statistically significant differences or trends between treatment groups in the frequency of at least 1 SAE or any specific SAE.

A total of 39 patients discontinued the study due to AEs: 7 (4.8%) in the placebo group, 14 (9.3%) in the 20 mcg group, and 18 (12.9%) in the 40 mcg group (p=0.052). There was a statistically significant difference between treatment groups in discontinuations for nausea: none in the placebo group or 20 mcg group, and 5 (3.6%) in the 40 mcg group (p=0.004). There were no statistically significant differences or trends between treatment groups in discontinuations for other AEs.

LY333334 at the 40 mcg dose appears to have increased the occurrence of nausea and headache. For nausea, the numbers of patients were: 5 (3.4%) in the placebo group, 8 (5.3%) in the 20 mcg group, and 26 (18.7%) in the 40 mcg group (p<0.001). No patients reported severe nausea. For headache, the numbers of patients were: (4.1%) in the placebo group, 8 (5.3%) in the 20 mcg group, and 15 (10.8%) in the 40 mcg group (p=0.053). Severe headache was reported by no patients in the placebo group or the 20 mcg group, and 2 (1.4%) patients in the 40 mcg group.

2.6 Vital Signs, Physical Examinations, and Electrocardiograms

Blood pressure and pulse were taken in the sitting position at each study visit. There were no consistent statistically significant differences or trends between treatment groups. Measurements of blood pressure or pulse at specified intervals after dosing with study drug were not obtained.

A physical examination was done and weight and height were measured at baseline, intervals during the study, and the early discontinuation or study closeout visit. There were no consistent statistically significant differences or trends between treatment groups.

Electrocardiograms were obtained during the screening/run-in phase but not subsequently.

.7 Clinical Laboratory Evaluation

2.7.1 Laboratory Safety Variables

The following laboratory safety variables were measured for all patients: hematology; clinical chemistry, including serum calcium and albumin; serum calcium and albumin 4-6 hours after dosing with study drug; urinalysis; 24 hour urine calcium, phosphorus, and creatinine excretion; creatinine clearance; testosterone; 25-hydoroxyvitamin D; PTH (1-84); and LY333334 antibodies.

2.7.2 Evaluation of Laboratory Safety Variables

Laboratory safety variables were evaluated at each visit where measured, from baseline to endpoint, with the last observation carried forward.

For continuous laboratory safety variables, actual measurements and changes from baseline were evaluated for each visit where data were collected. Because the laboratory values were generally not normally distributed, results were summarized using medians and analyses were based on ranked data, except where otherwise noted. For the continuous variables, baseline differences between treatment groups were generally not statistically significant. Therefore, ANOVA rather than ANCOVA was used for analysis, with the model including effects of treatment and country. For binary variables (normal vs. abnormal), treatment group differences were evaluated with Pearson's chi-square test.

The analyses of laboratory safety variables included data from all study visits, including those at which testing was not scheduled. The testing schedule is described at the start of each discussion of laboratory results. The visits not in the testing schedule were mainly early discontinuation or study closeout visits. The laboratory data from these visits may not provide meaningful comparisons between treatment groups, because of heterogeneity in the portions of the study population that were tested at these visits. Therefore, the results from visits in the testing schedule were used in the safety evaluation.

To interpret the results of the laboratory safety variable analyses, overall treatment group differences in actual measurements were examined first. Pairwise and change from baseline analyses were considered if there was

a statistically significant difference or trend in the overall analysis. Because these analyses had great statistical power for detecting small differences, and because no adjustments of the statistics were made for multiple comparisons, it was likely that some statistically significant findings would be artifacts or not clinically significant.

2.7.3 Calcium and Phosphorus

2.7.3.1 Serum Calcium

Table 5 on this page shows the numbers of patients with 4-6 hour postdose hypercalcemia at scheduled study visits according to month/study visit, calcium level, and treatment group.

Table 5 Number of Patients with 4-6 Hour Postdose Hypercalcemia by Study Month/Visit, Calcium Level, and Treatment Group

	Baseline (Visit 1)	Month 1 (Visit 3)	Month 3 (Visit 4)	Month 6 (Visit 5)	Month 12 (Visit 6)
Placebo (N)	145	144	139	139	134
Total	0	0	0	0	0
PTH20 (N)	151	146	140	135	127
2.64-2.70	0	1	0	0	1
2.70-2.76	0	1	0	2	1
2.76-2.81	0	0	1	1	0
2.81-2.85	0	0	1	0	0
2.95-3.0	0	0	0	1	0
3.0 and up	0	1	1	0	0
Total	0	3	3	4	2
PTH40 (N)	139	130	125	121	111
2.64-2.70	0	2	2	3	1
2.70-2.76	0	1	4	3	0
2.76-2.81	0	1	0	1	0
2.81-2.85	0	1	1	1	1
2.85-2.90	0	0	2	1	0
Total	0	5	9	9	2

Abbreviations: PTH20 = LY333334 20 µg/day; PTH40 = LY333334 40 µg/day ; N = number of patients with lab tests.

Table 6 on page 128 shows that a total of 31 patients had at least 1 episode of hypercalcemia (at a scheduled study visit or other time): none in the placebo group, 9 (6.0%) in the 20 mcg group, and 22 (15.8%) in the 40 mcg group ($p<0.001$). Ten patients had at least 2 consecutive episodes: none in the placebo group, 2 (1.3%) in the 20 mcg group, and 8 (5.8%) in the 40 mcg group($p=0.003$).

Table 6 also describes the management of the 31 patients with at least 1 episode of hypercalcemia. The calcium supplements were reduced for none in the placebo group, 4 (2.6%) in the 20 mcg group, and 12 (8.6%) in the 40 mcg group (p<0.001). Study drug was reduced for none in the placebo group or 20 mcg group, and 7 (5.0%) in the 40 mcg group (p<0.001). Study drug was discontinued for none in the placebo group, 3 (2.0%) patients in the 20 mcg group, and 6 (4.3%) in the 40 mcg group (p=0.037).

Table 6 Number of Patient with at Least 1 and at Least 2 Consecutive Episodes of Hypercalcemia by Treatment Group; Management of Hypercalcemia Patients

	PLACEBO (N=147) n (%)	PTH 20 (N=151) n (%)	PTH40 (N=139) n (%)	Total N=437 n (%)
Patients with ≥1 elevated postdose serum calcium	0	9 (5.96)	22 (15.8)	31 (7.1)
Patients with ≥2 consecutive postdose elevated serum calcium	0	2 (1.3)	8 (5.8)	10 (2.3)
Patients with calcium supplement adjustments related to elevated postdose serum calcium	0	4 (2.6)	12 (8.6)	16 (3.7)
Patients with study drug adjustments related to elevated postdose serum calcium	0	0 (0.0)	7 (5.0)	7 (1.6)
Patients who discontinued study drug due to elevated postdose serum calcium	0	3 (1.98)	6 (4.3)	9 (2.1)

Abbreviations: PTH 20=LY333334 20-µg/day; PTH40 = LY333334 40-µg/day; N = number of patients randomly assigned to treatment; n = number of patients.

2.7.3.2 Urine Calcium

Table 7 on page 129 shows the numbers of patients with 24 hour hypercalciuria at scheduled study visits according to study month/visit, calcium level, and treatment group.

Table 7 Number of Patients with 24 Hour Hypercalciuria by Study Month/Visit, Calcium Level, and Treatment Group

	Baseline (Visit 1)	Month 1 (Visit 3)	Month 3 (Visit 4)	Month 6 (Visit 5)	Month 12 (Visit 6)	Month 18 (Visit 7)
Placebo (N)	143	140	3	137	128	47
7.5-8.0	7	7	0	6	3	0
8.0-8.5	5	5	0	6	4	0
8.5-9.0	2	2	0	1	4	3
9.0-9.5	3	2	0	4	2	2
9.5-10.0	3	2	0	1	5	0
10.0-10.5	1	3	0	3	2	0
10.5-11.0	0	4	1	3	2	0
11.0 and up	4	4	0	6	8	1
Total	25	29	1	30	30	6
PTH20 (N)	146	143	2	133	120	43
7.5-8.0	7	7	0	4	3	1
8.0-8.5	5	5	0	6	3	0
8.5-9.0	4	6	0	3	2	1
9.0-9.5	2	7	0	4	1	1
9.5-10.0	2	1	0	4	1	0
10.0-10.5	1	6	0	1	2	0
10.5-11.0	1	0	1	1	1	0
11.0 and up	6	10	0	8	6	2
Total	28	42	1	31	19	5
PTH40 (N)	139	129	3	118	103	35
7.5-8.0	9	7	0	7	3	0
8.0-8.5	2	5	0	9	2	0
8.5-9.0	4	1	0	4	3	1
9.0-9.5	1	6	0	2	1	1
9.5-10.0	0	5	0	2	5	0
10.0-10.5	1	2	0	1	0	0
10.5-11.0	4	2	0	5	0	0
11.0 and up	2	6	0	4	3	0
Total	23	34	0	34	17	2

Abbreviation: N = number of patients with lab tests; PTH20 = LY333334 20 µg/day; PTH40 = LY333334 40 µg/day.

Table 8 on page 130 shows that a total of 10 patients had at least 1 episode of 24 hour hypercalciuria (at a scheduled study visit or other time): 2 (1.4%) in the placebo group, 3 (2.0%) in the 20 mcg group, and 5 (3.6%) in the 40 mcg group (p=0.429). Four patients had at least 2 consecutive episodes: none in the placebo group, 2 (1.3%), and 2 (1.4%) in the 40 mcg group (p=0.472).

Table 8 also describes the management of the 10 patients with at least 1 episode of 24 hour hypercalciuria. The calcium supplements were reduced for 1 (0.7%)in the placebo group, 2 (1.3%) in the 20 mcg group, and 1 (0.7%) in the 40 mcg group(p=1.0). Study drug was reduced for no patients in any group, and study drug was discontinued only for 1 patient, in the 20 mcg group.

Table 8 Number of Patients with at Least 1 and at Least 2 Consecutive Episodes of Hypercalciuria by Treatment group; Management of Hypercalciuria Patients

	PLACEBO (N=147) n (%)	PTH 20 (N=151) n (%)	PTH40 (N=139) n (%)	Total N=437 n (%)
Patients with ≥1 elevated urine calcium and urinary calcium to creatinine ratio	2 (1.4)	3 (2.0)	5 (3.6)	10 (2.3)
Patients with ≥2 consecutive elevated urine calcium and urinary calcium to creatinine ratio	0	2 (1.3)	2 (1.4)	4 (0.9)
Patients with calcium supplement adjustments related to elevated urine calcium and urinary calcium to creatinine ratio	1 (0.7)	2 (1.3)	1 (0.7)	4 (0.9)
Patients with study drug adjustments related to elevated urine calcium and urinary calcium to creatinine ratio	0	0	0	0
Patients who discontinued study drug due to elevated urine calcium and urinary calcium to creatinine ratio	0	1 (0.7)	0	1 (0.2)

Abbreviations: PTH20=LY333334 20-µg/day; PTH40 = LY333334 40-µg/day; N = number of patients randomly assigned to treatment; n = number of patients.

2.7.3.3 Effect of Serum 1,25-dihydroxyvitamin D on Urine Calcium

Because LY333334 is known to increase serum 1,25-dihydroxyvitamin D, and because increased 1,25-dihydroxyvitamin D is associated with hypercalciuria in some disease states, the relationship between 1,25-dihydroxyvitamin D and hypercalciuria was examined, using a logisitic regression model. In this model, a 10 pmol/L increase in 1,25-dihydroxyvitamin D was associated with a 7.5% increase in the odds of hypercalciuria (p=0.017).

2.7.4 Other Laboratory Safety Variables

2.7.4.1 Overview

The results for laboratory safety variables other than serum or urine calcium showed numerous statistically significant differences or trends between treatment groups, at one time or another during the study. These differences were generally similar to those seen in study GHAC, were small, and were not associated with clinical AEs.

The variables other than serum and urine calcium with statistically significant increases or trends in 1 or both LY333334 groups at 1 or more times, compared to the placebo group, included: serum total cholesterol,

uric acid, total alkaline phosphatase, urea nitrogen, creatinine clearance, urine pH, leukocyte count, lymphocyte count, platelet count, serum total protein, and serum free testosterone.

The variables with statistically significant decreases or trends in 1 or both LY333334 groups at 1 or more times, compared to the placebo group, included: serum phosphorous, creatinine, sodium, potassium, chloride, magnesium, erythrocyte count, and 25-hyedroxyvitamin D.

The percentage of blood samples obtained for measuring PTH (1-84) that were below the level of quantitation ranged from 88.1-91.9% in the 3 treatment groups.

No patients developed antibodies to LY333334 (defined as binding greater than 40 BU with a 2-fold or greater increase from baseline, and inhibitory activity of at least 40 %).

2.7.4.2 Frequency of Abnormal Values

There were no statistically significant differences or trends between treatment groups in the frequency of abnormal laboratory values for: serum calcium (except 4-6 hours after study drug injection) or phosphorus; 24 hour urine calcium or phosphorus; serum nonfasting glucose, total cholesterol, or uric acid; serum total alkaline phosphatase, alanine transferase, aspartate transferase, gamma-glutamyl transferase, or total bilirubin; serum creatinine, urea nitrogen, bicarbonate, chloride, potassium, or magnesium; urine color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, nitrites, or microscopic findings (erythrocytes, leukocytes, casts, etc.); hemoglobin, hematocrit, erythrocyte count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration; counts of leukocytes, segmented neutrophils, basophils, eosinophils, lymphocytes, monocytes, or platelets; blood cell morphology; serum total protein, creatine phosphokinase, 25-hydroxyvitamin D, total testosterone, free testosterone, or intact PHT.

As shown in Table 9 on page 133, the frequency of abnormally increased creatinine clearance was 9.7% in the placebo group, 20.5% in the 20 mcg group, and 17.2% in the 40 mcg group (p=0.058). Serum sodium was abnormally increased in 2.1% of patients in the placebo group, such that the frequency of normal serum sodium was 97.9% in the placebo group and 100% in the 20 mcg and 40 mcg groups (p=0.060). Interpretation of these findings is not clear.

Table 9 Laboratory Safety Variables with Statistically Significant Differences or Trends Between Treatment Groups in the Frequency of Abnormal Values

Laboratory Test	Abnormal	Placebo (N=146) %	PTH20 (N=142) %	PTH40 (N=130) %	Overall p-value*	Placebo vs. PTH20	Placebo vs. PTH40	PTH20 vs. PTH40
SODIUM	Low	0	0	0	-	-	-	-
	High	2.1	0	0	-	-	-	-
	Normal	97.9	100	100	0.060	-	-	-

Laboratory Test	Abnormal	Placebo (N=124) %	PTH20 (N=122) %	PTH40 (N=116) %	Overall p-value*	Placebo vs. PTH20	Placebo vs. PTH40	PTH20 vs. PTH40
Estimated Creatinine Clearance	Low	35.5	36.1	37.9	0.920	0.924	0.694	0.766
	High	9.7	20.5	17.2	0.058	0.018	0.085	0.522
	Normal	54.8	43.4	44.8	0.149	0.074	0.121	0.830

2.7.5 Summary of Clinical Laboratory Evaluation

The effects of LY333334 on laboratory safety variables in this study of men with osteoporosis diagnosed by low BMD were similar to the effects in the study of women with vertebral fractures (study GHAC).

2.8 Conclusions

The safety results for treatment with LY333334 in this study of men with osteoporosis diagnosed by low BMD were similar to the safety results in study of women with vertebral fractures (study GHAC).

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/s/

Bruce Stadel
9/7/01 10:24:05 AM
MEDICAL OFFICER

Eric Colman
9/10/01 05:46:19 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

Date: 7 October 2002

From: Bruce V. Stadel, MD, MPH
Medical Officer, DMEDP

Subject: Safety Update #4, dated 16 September 2002;
Addendum dated 3 October 2002
NDA 21-318/Forteo (teriparatide), Eli Lilly & Company

To: The File

Previous Safety Updates:

Safety Update #1 (22 Mar 01), reviewed in original NDA review.
Safety Update #2 (13 Nov 01), reviewed in Memo To File (24 Apr 02).
Safety Update #3 (23 Apr 02), reviewed in Memo To File (24 Apr 02).

Contents of Safety Update #4:

(1) Overview of a special rat carcinogenicity study, designed to evaluate the effect of age at starting treatment and duration of treatment, with LY333334, on the incidence of osteosarcoma and other proliferative bone lesions. For further information about this study, see Pharmacology/Toxicology review.

(2) Review of the Lilly [redacted]

(3) Review of 6 ongoing clinical studies, including 5 studies in which patients are being treated with LY333334, and 1 follow-up study of patients previously treated with LY333334 in completed studies, and

(4) Review of 2 completed clinical pharmacology studies.

For the clinical studies in 3-4 above, the review focused on deaths, serious adverse events, discontinuations due to adverse events, and serum calcium results.
See Appendix for study titles.

Findings in Safety Update #4:

Osteosarcoma. No cases of osteosarcoma or other primary bone cancer in humans treated with LY333334 were identified in any patient treated with LY333334 in any previous or ongoing clinical study

Deaths and Adverse Events. The review of deaths, serious adverse events, and discontinuations due to adverse events, in the ongoing and completed clinical studies, did not identify any new safety issues.

Serum Calcium. Serum calcium data were presented for:
(1) Study GHBM, a randomized, double-blind, clinical trial comparing LY333334 20 mg/day to oral alendronate 10 mg/day.
(2) The first phase of Study GHBQ, in which patients are first treated with open-label LY333334 20 mg/day and later randomized to oral raloxifene 60 mg or placebo (GHBQ), and
(3) Study GHBU, which is an open-label study of LY333334 20 mg/day in patients previously treated with oral alendronate 10 mg/day or raloxifene 60 mg/day. The duration of prior treatment with alendronate ranged from 18-32 months, and the duration of prior treatment with raloxifene ranged from 29 to 39 months. Baseline values were within normal limits for serum parathyroid hormone, 25-hydroxyvitamin D, creatine, and other laboratory safety variables.

Studies GHBM and BHBQ will be considered together because the results were similar. In studies GHBM and GHBQ, mean serum calcium prior to dosing with LY333334 20 mcg/day increased by about 0.02 mmol/L, after 1 month of treatment compared to baseline. In the larger of the 2 studies (GHBQ), the result was statistically significant. However, in combined data from the 2 studies, a clinically important increase in serum calcium, defined as reaching a level of >2.76 mmol/L, was observed in 4/417 (1.0%) patients at baseline -- and only 2/380 (0.5%) patients after 1 month of treatment. Longer-term data from these studies are just becoming available. The results thus far do not suggest an important increase in serum calcium, prior to dosing, in patients treated with LY333334 20 mcg/day. This conclusion is also supported by the original NDA data.

However, in Study GHBU, mean serum calcium prior to dosing with LY333334 20 mcg/day increased, at 1 month compared to baseline, by about 0.09 mmol/L in patients previously treated with raloxifene and 0.10 mmol/L in patients previously treated with alendronate; at 6 months compared to baseline, the increase was about 0.11 mmol/L in patients previously treated with raloxifene and 0.14 mmol/L in patients previously treated with alendronate. The results were statistically significant for both treatement groups at both time points. A clinically important increase in serum calcium, defined as reaching a level of >2.76 mmol/L was, observed in 3/26 (11.5%) of the patients treated with raloxifene and 3 (9.0%) of the patients treated with alendronate (Table 1). None of these patients had symptoms of hypercalcemia and none were discontinued from the study due to elevated calcium measurements.

The results from Study GHBU suggest that LY333334 may increase serum calcium more in women previously treated with alendronate or raloxifene than in other women. Further information is needed from a randomized, double-blind, placebo-controlled clinical trial in which women previously treated with raloxifene, and alendronate, are randomized to LY333334 20 mg/day or placebo, with measurement of serum calcium prior to dosing with study drug, and at baseline, 1 month and at least 1 later time.

Table 1 Patients with Serum Calcium >2.76 mmol/L
Study GHBU: 6-Month Interim Analysis

Patient Number	Prior Therapy	Visit Number	Collection Date	Teriparatide Duration of Therapy (days)	Calcium* (mmol/L)
7	RALOXIFENE	1	20-Aug-01	-22	
		3	8-Oct-01	29	
		5	13-Mar-02	185	
18	ALENDRONATE	1	5-Sep-01	-29	
		2	3-Oct-01	-1	
		3	31-Oct-01	29	
		5	27-Mar-02	176	
31	RALOXIFENE	1	24-Sep-01	-29	
		3	19-Nov-01	29	
		5	10-Apr-02	171	
34	ALENDRONATE	1	26-Sep-01	-31	
		3	28-Nov-01	34	
		4	21-Jan-02	88	
		5	17-Apr-02	174	
50	RALOXIFENE	1	31-Oct-01	-17	
		3	19-Dec-01	34	
		4	6-Feb-02	83	
		5	15-May-02	181	
54	ALENDRONATE	1	31-Oct-01	-17	
		3	17-Dec-01	32	
		4	13-Feb-02	90	
		5	22-May-02	188	

* Serum calcium measured by central laboratory. Confirmatory measurements for patients 7, 18, 34, and 50 that were obtained at the investigator's local laboratory after Visit 5 are described in the text, but are not included in this table.

Source: RMP.B3DSGHBM.SASPGM.(CALCLIST)

--APPENDIX--

Table of Contents (continued)

cc:

HFD 510: Colman/Schneider

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/s/

Bruce Stadel
10/7/02 12:47:04 PM
MEDICAL OFFICER

Eric Colman
10/7/02 01:13:47 PM
MEDICAL OFFICER

MEMORANDUM

Date: 24 April 2002

From: Bruce V. Stadel, MD, MPH
Medical Officer, DMEDP

Subject: Review of Safety Updates
NDA 21-318/Forteo (teriparatide), Eli Lilly & Company

To: The File

Safety Update #1 dated 22 March 2001:

This Safety Update was reviewed in detail as part of the NDA review.

Safety Update # 2 dated 13 November 2001:

This Safety Update included data from the ongoing Phase 3 clinical studies B3D-MC-GHBJ, B3D-MC-GHBM, B3D-MC-GHBQ, and B3D-MC-GHBU, and from the completed Phase 1 clinical studies B3D-FW-GHBO and B3D-LC-GHBR. There were no new findings or significant changes in the safety profile of LY333334 No cases of osteosarcoma or other primary bone tumors were identified. The analyses of mortality, serious adverse events, and discontinuations due to adverse events did not suggest any new safety concerns. The analyses of adverse events of any severity in Study GHBJ were consistent with those described in the NDA review and/or Safety Update #1. The small differences between treatment groups in mortality rates and in the frequency of elevated serum creatine levels, that were noted Safety Update #1, did not persist in the data reported here.,

Safety Update #3 dated 23 April 2002:

This Safety Update included data from the ongoing Phase 3 clinical studies B3D-MC-GHBJ, B3D-MC-GHBM, B3D-MC-GHBQ, and B3D-MC-GHBU and from the completed Phase 1 clinical study, H7D-EW-GNAB. There were no new findings or significant changes in the safety profile of LY333334. No cases of osteosarcoma or other primary bone tumors were identified. The analyses of mortality, serious adverse events, and discontinuations due to adverse events did not suggest any new safety concerns. The analyses of adverse events of any severity in Study GHBJ were consistent with those described in the NDA review and/or Safety Updates #1 and #2.

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Bruce Stadel
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MEDICAL OFFICER

Eric Colman
4/29/02 08:36:38 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: 1 October 2001

FROM: Bruce V. Stadel, MD, MPH
Medical Officer/Epidemiology

TO: The File

SUBJECT: NDA 21-318/Forteo (teriparatide)/Eli Lilly & Co.
ECG Changes/Consultation with
Division of Cardio-renal Drug Products (DCRDP), HFD-110

A consultation was requested with the Division of Cardio-renal Drug Products (DCRDP) to evaluate ECG changes that were reported from the phase I clinical studies of teriparatide. During the several hours after drug administration, there were decreases in the RR and heart-rate-corrected QT intervals. Dose-related decreases in blood pressure and increases in heart rate were also reported. DCRDP reviewed the data and made seven recommendations. The response of DMEDP to these recommendations is discussed below.

The most important recommendation was to review the human exposure database for episodes of arrhythmia or events that may reflect arrhythmias, such as syncope, hypotension, palpitations, or dizziness. Review of the phase 3 clinical trials showed no biologically plausible, statistically significant differences ($p<0.05$) or trends ($p<0.10$) between the placebo, teriparatide 20 mcg, and teriparatide 40 mcg group for reported arrhythmias or potentially related events. There were some non-significant increases in the reporting of tachycardia at 40 mcg but not at 20 mcg, which is the dose proposed for marketing.

The second most important recommendation was to obtain post-dose ECGs, blood pressures, and heart rates after multiple doses of teriparatide in studies of sufficient duration to ensure that steady state is reached for ECG changes. This was recommended because most of the data available for review by DCRDP were from single-dose studies. A phase 4 commitment has been made to obtain multiple-dose data, and an acceptable study plan has been submitted. This would provide for additional labeling regarding ECG changes as the drug market evolves. Requiring these further data in phase 3 would be difficult to justify in the absence of evidence from the phase 3 clinical trials of treatment-related differences in the reporting of arrhythmias or potentially related events.

Two recommendations referred to possible studies of other drugs in the same class: (1) evaluate effects on ECGs, blood pressure, and heart rate, and (2) in particular, determine if shortening of the heart-rate-corrected QT interval is a class effect. Action on these recommendations would be appropriate if/when other drugs in the same class reach the stage of clinical evaluation.

Two recommendations were general in nature: (1) screen for adrenergic, cholinergic, and dopaminergic activities, to determine the reason for the ECG, blood pressure, and heart rate effects of the drug, and (2) perform animal studies to determine if the drug or a contaminant binds to or otherwise interacts with channels that are involved in cardiac repolarization. Action on these recommendations would not provide information directly relevant to the regulatory issues that DMEDP must address.

Finally, one recommendation was that, if additional consultation with DCRDP is requested, this should include Dr. Koerner or Dr. Proakis, who are experts in electrophysiology.

cc: NDA 21-318
HFD 510 Stadel/Schneider/Colman/Orloff/Hedin

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/s/

Bruce Stadel
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MEDICAL OFFICER

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