

**NDA 21-318: LY333334 (Teriparatide) for Osteoporosis
Medical Safety Review**

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LY333334 is parathyroid hormone (1-34), also known as teriparatide. It was administered by daily subcutaneous injection in the studies discussed here. The dose proposed for marketing is 20 mcg/day.

The criterion for statistical significance was a 2-sided alpha = 0.05, and the criterion for a statistical trend was a 2-sided alpha = 0.10.

1. Summary and Recommendations

1.1 Summary

Preclinical and phase 1 clinical studies of LY333334 raised 3 potential safety issues for review in clinical trial data: hypotension and tachycardia within 6 hours after subcutaneous injection (rats, dogs, and man), renal histopathology and malfunction (monkeys), and osteosarcoma (rats).

In the phase 1 clinical studies, there were also some decreases in RR and heart-rate-corrected QT intervals on electrocardiograms. A phase 4 study commitment has been made to further evaluate these findings in osteoporosis patients.

The phase 2/3 clinical trials of LY333334 appear to have been carefully done, and to provide the basis for thorough evaluation of safety. The main trials began in 1996-97 and ended in December 1998. Since then, most of the patients have been in a post-treatment follow-up study.

In the phase 2/3 clinical trials, the longest treatment with LY333334 was 2 years. The total number of patients treated for ≥ 3 months was 1453 (82% women, 18% men). This provides 95% confidence for observing an event that occurs once in 484 or fewer treated patients. If an event occurs less frequently, it will not be reliably detected. The annual incidence of osteosarcoma in women and men 50 years of age or older is about 4 cases per million.

During the phase 2/3 clinical trials, the rates of mortality and morbidity were similar between the LY333334 groups and the placebo or active control groups, and the 20 mcg dose was associated with few adverse symptoms or changes in laboratory safety variables. Information about the potential for adverse interactions between LY333334 and digitalis glycosides or other drugs that may be used by patients in the osteoporosis age-range was limited. The potential for interaction with digitalis glycosides is being investigated further in a clinical pharmacology study. Regarding the issues raised in preclinical and early clinical studies: The rates of syncope or other cardiovascular adverse events, and urinary tract adverse events, were similar between the LY333334 groups and the placebo or active control groups. In the 40 mcg group compared to the placebo group, there were statistically significant differences or trends of increase in pulse rates within 6 hours after dosing with study drug. The largest mean increase in standing pulse rate, at 1 hour after dosing, was 5 beats per minute, in the 40 mcg group compared to the placebo group. One hour after injection, the range of standing pulse rates in the

placebo group was 47-100 beats per minute and the range in the LY333334 group was 68-104 beats per minute. Post-dose pulse rates were not measured for the 20 mcg dose, and post-dose electrocardiograms were not done for either dose. In both LY333334 groups compared to the placebo group, there were statistically significant increases in 4-6 hour post-dose serum calcium, and in the frequency of hypercalcemia. In the 20 mcg group compared to the placebo group, the median increase in 4-6 hour post-dose serum calcium was 0.08-0.12 mmol/L during the study, and the frequency of patients with ≥ 1 episode of hypercalcemia increased from 1.5% in the placebo group to 11.1% in the 20 mcg group. The median increase in 24 hour urine calcium excretion was 0.30-0.76 mmol, over the course of the study, and there was no clear increase in the frequency of hypercalciuria. There was no evidence of renal malfunction in the LY333334 groups compared to the placebo group. No osteosarcomas were reported.

During the post-treatment follow-up study, the rates of mortality, morbidity, syncope, other cardiovascular adverse events, and urinary tract adverse events were similar between the patients from the LY333334 groups and the patients from the placebo or active control groups. In the patients from the largest clinical trial, there were statistical trends of increase in the frequency of patients with abnormally high serum creatinine, from 1.7% in the placebo group to 3.9% in the LY333334 groups. These patients are being evaluated further. There were no statistically significant differences or trends between the LY333334 groups and the placebo group for measured creatinine clearance.

No osteosarcomas or other malignant or benign bone tumors have been reported for any patient treated with LY333334.

One 64 year old man who was treated with the 40 mcg dose for about 13 months developed Paget's disease of the pelvis. This was diagnosed with scintigraphy and x-rays about 2 months after the drug was stopped, and classified as a serious adverse event. Scintigraphy had been done in the month before LY333334 treatment began, and no Paget's disease was found. The investigator assessed the event as possibly related to LY333334 treatment. Lilly assessed the event as probably coincidental. Paget's disease is associated with an increased risk of osteosarcoma.

1.2 Recommendations

If LY333334 is approved:

Heart rates and electrocardiograms within 6 hours after initial and subsequent subcutaneous injections of the 20 mcg dose should be evaluated in osteoporosis patients. A phase 4 study commitment has been made for this.

The product label should communicate effectively that: (1) LY333334 has been found to cause osteosarcoma in rats, and that the relevance of this finding to the use of LY333334 in the treatment of human osteoporosis has not been determined; (2) no information is available about the safety of treatment with LY333334 for longer than 2 years. The currently proposed label describes the osteosarcoma finding in bold letters under Warnings, and states in regular letters under Adverse Reactions that the maximum exposure to LY333334 in clinical studies was 2 years. These 2 issues should be discussed together. A black box would be the most effective way to ensure communication.

Also, the currently proposed label states under Warnings that "Patients with metabolic bone disease other than primary osteoporosis (including hyperparathyroidism and Paget's disease of the bone) and those with otherwise unexplained elevations of alkaline phosphatase generally should be excluded from treatment..." Consideration should be given to placing Paget's disease and otherwise unexplained elevations of alkaline phosphatase under Contraindications. These conditions should not be grouped together with metabolic bone disease in general, or with hyperparathyroidism.

A phase 4 study should be developed for active monitoring of new cases of osteosarcoma or other primary bone cancer in women and men, for histories of exposure to LY333334. This study should be conducted in 1 or more geographic areas where LY333334 is marketed, and where there is population-based cancer registration. If exposed cases are identified, a case-control study should be initiated, to compare the prevalence of LY333334 exposure in the osteosarcoma cases to the prevalence in controls without osteosarcoma, from the same geographic areas.

2. Issues from Preclinical and Phase 1 Clinical Studies

The main safety issues identified in the preclinical studies for review in the clinical trial data were: hypotension and tachycardia within 6 hours after subcutaneous injection (rats, dogs); renal histopathology (monkeys); and osteosarcoma (rats).

The main safety issues identified in the Phase I clinical studies for review in the clinical trial data were: orthostatic or other hypotension and tachycardia within 6 hours after subcutaneous injection, and increases in serum calcium or urine calcium. Other issues included headache, dizziness, nausea, and vomiting.

In the phase 1 clinical studies, there were also some decreases in RR and heart-rate-corrected QT intervals on electrocardiograms. A phase 4 study commitment has been made to further evaluate these findings in osteoporosis patients.

The doses and durations of LY333334 treatment which produced these disorders are discussed in the Appendix.

3. Findings in Phase 2/3 Studies

LY333334 20 mcg and 40 mcg were the main doses studied. The dose proposed for marketing is 20 mcg.

3.1 Description of Studies

The clinical studies of LY333334 have 9-digit, 3-part names such as "B3D-MC-GHAC." Only the last 4 digits will be used here, since these are unique to each study.

There have been 11 phase 2/3 studies: 3 phase 2 and 6 phase 3 randomized clinical trials, a study of patients withdrawn from the main phase 3 trial due to rapid bone loss, and a post-treatment follow-up study of patients who were in the phase 3 trials. The phase 2 trials were studies GHAA, GHAM, and GHAO. The main phase 3 trial was study GHAC, and the other phase 3 trials were studies GHAF, GHAF, GHAF, GHAF, and GHAF. The study of patients withdrawn from study GHAC was study GHAL. The post-treatment follow-up study of patients who were in the phase 3 trials is study GHBJ. All of the studies except GHBJ began in 1996-1997 and were stopped in December 1998, due to the osteosarcoma finding in rats. Study GHBJ began after the 7 phase 3 trials ended and is still in progress.

The 9 phase 2/3 clinical trials were all randomized and parallel-group in design. Six were double-blind (GHAA, GHAC, GHAF, GHAF, GHAF, and GHAM) and 3 were open-label (GHAO, GHAF, and GHAF). Patients in all of the trials were randomized equally to the treatments studied.

The 9 phase 2/3 clinical trials enrolled a total of 2627 patients, including 2190 postmenopausal women and 437 men. Of the 2190 women, 1637 (74.7%) were in study GHAC, 393 (17.9%) were in studies GHAF and GHAF, and 160 (7.3%) were in studies GHAA, GHAO, GHAM, GHAF, and GHAF. The 437 men were in study GHAF. The main osteoporosis criterion for the enrollment of women in study GHAC was the presence on x-rays of ≥ 1 vertebral fractures. In the other studies of women and the study of men, the main osteoporosis criterion was low bone mineral density (BMD). The 6 patients in study GHAL had previously been in study GHAC. Study GHBJ enrolled 1930 (77.6%) of the 2486 patients who had been in studies GHAC, GHAF, GHAF, GHAF, GHAF, GHAF, and GHAF. The numbers of patients by study are shown in Table 1.

For LY333334 treatment of women, study GHAC compared 20 mcg and 40 mcg to placebo, study GHAF compared 40 mcg to placebo in women taking HRT, study GHAH compared 40 mcg to oral alendronate, study GHAM compared 40 mcg to placebo in women taking raloxifene or HRT, and the other trials compared various doses to placebo. In study GHAL, all women were treated with 40 mcg. For LY333334 treatment of men, study GHAJ compared 20 mcg and 40 mcg to placebo.

The planned durations of treatment were: ≥ 2 years in studies GHAC, GHAH, GHAU, GHAV, and GHAJ; 1-1.5 years in studies GHAF and GHAL; and < 1 year in studies GHAA, GHAM, and GHAO. The actual durations were shorter because of the studies being stopped in December 1998.

The main efficacy endpoints were vertebral fractures, BMD, or serum/urine biochemical markers of bone formation and resorption, except in study GHAM, where the main efficacy endpoint was renal concentrating ability.

The main safety variables were physical examinations, vital signs, AEs, and laboratory tests of: hematology; clinical chemistry, including serum calcium and albumin; urinalysis; 24 hour urine calcium, phosphorus, and creatinine excretion; creatinine clearance; and LY333334 antibodies. Mammograms and pap smears were done in the studies involving HRT. Other variables were measured in some studies. The safety variables were measured at baseline, endpoint, and 3-monthly or longer intervals during the studies, depending of the variable. Bone biopsies were done and are discussed in the review of efficacy. Electrocardiograms were not done.

Note: The rest of section 3 will focus primarily on the four main randomized clinical trials, which were studies GHAC, GHAF, and GHAH, and GHAJ.

The terms "20 mcg" and "40 mcg" will be used to mean "LY333334 20 mcg" and "LY333334 40 mcg," respectively.

3.2 Demographics and Disposition of Patients

The patients in studies GHAC, GHAF, and GHAH (women) and study GHAJ (men) were 28-86 years of age at enrollment. In study GHAC, the women were 98.7% Caucasian, the mean age was 69.5 years, and the mean body mass index (BMI) was 26.6. In study GHAF, the women were 66.8% Caucasian and 31.6% Hispanic, the mean age was 61.5 years, and the mean BMI was 25.9. In study GHAH, the women were 82.2% Caucasian and 16.4% Hispanic, the mean age was 65.4 years, and the mean BMI was 24.2. In study GHAJ, the men were 99.1% Caucasian, the mean age was 58.7 years, and the mean BMI was 25.2.

In study GHAC, 9347 women were screened, of whom 1637 (17.5%) were enrolled and randomized to placebo (n=544), 20 mcg (n=541), or 40 mcg (n=552). Of the 7710 excluded patients, 68.8% did not meet x-ray criteria at the initial reading, 18.3% did not meet protocol entry criteria, 5.8% withdrew due to patient's decision, 5.1% were excluded for unknown reasons, and the other 2.0% were excluded for 10 different reasons. Of the 1411 women who did not meet protocol entry criteria, 1145 (80.8%) did not meet x-ray criteria at a confirmatory reading. Among the other exclusions, 6 women had abnormally high alkaline phosphatase levels and 2 had metabolic bone disease. The study population appears to have been generally representative of women with osteoporosis defined by ≥ 1 vertebral fractures on x-ray.

In study GHAF, 518 patients were screened, of whom 247 (47.7%) were enrolled and randomized to placebo injection and HRT (n=122) or 40 mcg and HRT (n=125). In study GHAH, 265 patients were screened, of whom 146 (55.1%) were enrolled and randomized to placebo injection and alendronate (n=73) or 40 mcg and oral placebo (n=73). In study GHAJ, 959 patients were screened, of whom 437 (45.6%) were enrolled and randomized to placebo (147), 20 mcg (151), or 40 mcg (n=139). The higher enrollment rates in these studies compared to study GHAC appear to be due to the differences in the criteria used to define osteoporosis (vertebral fractures versus low BMD).

Most of the patients in these studies were discontinued due to sponsor's decision when Lilly stopped the studies in December 1998: 79.1% in study GHAC, 79.4% in study GHAF, 74.0% in study GHAH, and 81.6% in study GHAJ. The 2 most common other reasons for discontinuation were AEs and patient decision. AEs were a more common reason in the 40 mcg group than in the 20 mcg group or the placebo or active control groups. Discontinuations due to AEs are discussed further in section 3.4.2 below.

3.3 Duration of Treatment

The actual duration of treatment with study drug was 12-23 months for 1398 (85.4%) of the women in study GHAC, 12-17 months for 307 (78.1%) of the women in studies GHAF and GHAH, and 6-14 months for 381 (87.2%) of the men in study GHAJ. The duration of treatment in the other studies was from 6 weeks to 4 months. The total number of women and men treated with LY333334 for ≥ 3 months was 1453 (82.2% women, 17.8% men). This number provides 95% confidence for observing an event which occurs once in 484 or fewer treated patients.

3.4 Adverse Events

The adverse events (AEs) discussed here were clinical events reported after treatment in the phase 2/3 studies had begun.

3.4.1 Serious Adverse Events

Serious adverse events (SAEs) are defined as AEs which 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. There were 406 patients with SAEs in the Phase 2/3 studies: 315 (77.6%) in study GHAC, 24 (5.9%) in study GHAF, 18 (4.4%) in study GHAH, 45 (11.1%) in study GHAJ, and 4 (1.0%) in the other studies.

In study GHAC, the numbers of patients with ≥ 1 SAE were: 113 (20.8%) in the placebo group, 93 (17.2%) in the 20 mcg group, and 109 (19.7%) in the 40 mcg group ($p=0.305$). In study GHAF, there were 11 (8.8%) in the HRT group and 13 (10.7%) in the 40 mcg+HRT group ($p=0.622$). In study GHAH, there were 9 (12.3%) in the alendronate group and 9 (12.3%) in the 40 mcg group ($p=1.00$). In study GHAJ, there were 16 (10.9%) in the placebo group, 15 (9.9%) in the 20 mcg group, and 14 (10.1%) in the 40 mcg group ($p=0.959$).

3.4.1.1 Deaths

There were 20 deaths in the phase 2/3 studies, including 16 in study GHAC, 2 in study GHAJ, 1 in study GHAH, and 1 in study GHAL. The death rates by treatment group are the number of deaths/number of patients in a group. Combining data from studies GHAC and GHAJ accounts for 18 (90.0%) of the deaths and provides a valid comparison between placebo and the 2 LY333334 groups. The death rates in these studies were: 4/691 (0.6%) in the placebo group, 8/692 (1.2%) in the 20 mcg group, and 6/691 (0.9%) in the 40 mcg group ($p=0.512$).

In study GHAH, the death rates were 0/73 for alendronate and 1/73 for 40 mcg. In study GHAL, all patients were treated with 40 mcg and the death rate was 1/6. There were no deaths in the other studies.

In studies GHAC and GHAJ, the mean ages and (age ranges) in years of the patients who died were: 74.9 (66.9-78.0) in the placebo group, 75.4 (65.8-85.4) in the 20 mcg group, and 75.3 (66.3-84.4) in the 40 mcg group. The mean durations of treatment and (duration ranges) in days were: 320 (89-452) in the placebo group, 327 (32-538), in the 20 mcg group, and

327 (60-459) in the 40 mcg group. The reported causes of death were: in the placebo group, myocardial infarction, cardiovascular disorder, respiratory disorder, and shock; in the 20 mcg group, myocardial infarction, heart arrest (n=2), pneumonia, pancreatitis, death not otherwise specified (nos), carcinoma of larynx, and carcinoma of lung; and in the 40 mcg group, iron deficiency anemia, cerebrovascular accident, pneumonia (n=2), bladder neoplasm, and lung cancer.

The death in study GHAH was a 74.8 year old woman with hypertension and thyroiditis who was treated with 40 mcg for 313 days and died of cardiac arrest. The death in study GHAL was a 74.6 year old woman with angina pectoris, hypertension, heart failure, and ventricular arrhythmia who entered study GHAL from the placebo group of study GHAC, was treated with 40 mcg for 79 days and died in her sleep.

3.4.1.2 Cancer

A total of 57 SAEs in 55 patients were reported with cancer as the “reason serious” in studies GHAC, GHAF, GHAH, and GHAJ.

Combining data from studies GHAC and GHAJ accounts for 48 (84.2%) of the cancer SAEs and provides a valid comparison between placebo and the 2 LY333334 groups. (There were 42 cancer SAEs in 40 patients in study GHAC and 6 cancer SAEs in 6 patients in study GHAJ). In studies GHAC and GHAJ, the numbers of patients with cancer SAEs were: 24 (3.5%) in the placebo group, 11 (1.6%) in the 20 mcg group, and 11 (1.6%) in the 40 mcg group ($p=0.023$). The decrease in the LY333334 groups is largely due to a decrease in breast cancer in study GHAC: 7 (1.3%) in the placebo group, 1 (0.2%) in the 20 mcg group, and 1 (0.2%) in the 40 mcg group ($p=0.017$). This finding should be interpreted cautiously due to the small numbers of patients and the numerous comparisons.

In study GHAF, the numbers of patients with cancer SAEs were: 2 (1.6%) in the HRT group and 2 (1.6%) in the 40 mcg+HRT group. In study GHAH, there were: 2 (2.8%) in the alendronate group and 3 (4.2%) in the 40 mcg group.

The types of cancer were: 13 skin, 12 breast, 8 lung, 5 gastrointestinal, 3 bladder, 3 larynx, 1 cervix, 1 endometrium, 1 uterine, and 1 carcinoma or neoplasm not otherwise specified. There were no statistically significant differences or trends between treatment groups for the cancers at sites other than the breast.

Further analyses of cancer are presented in section 4.2.2.

3.4.1.3 Any Serious Adverse Event

In study GHAC, there were 197 different SAEs (i.e., AE terms). The only specific SAE with a statistically significant difference or trend between treatment groups was breast cancer (see section 3.4.1.2). In study GHAF, there were 27 different SAEs, in study GHAH there were 28, and in study GHAJ there were 63. There were no statistically significant differences or trends between treatment groups for any SAE in these studies.

3.4.2 Discontinuations due to Adverse Events

In study GHAC, the numbers of patients who discontinued due to AEs were: 32 (5.9%) in the placebo group, 35 (6.5%) in the 20 mcg group, and 59 (10.7%) in the 40 mcg group ($p=0.005$). This finding is due to the increased rate of discontinuation because of AEs in the 40 mcg group. Nausea was the only specific AE with a statistically significant difference or trend between treatment groups as a reason for discontinuation: 1 (0.2%) in the placebo group, 2 (0.4%) in the 20 mcg group, and 9 (1.6%) in the 40 mcg group ($p=0.009$). There was not a statistically significant difference or trend between the placebo group and the 20 mcg group in the frequency of nausea (see section 3.4.4).

In study GHAF, the numbers of discontinuations due to AEs were: 11 (8.8%) in the HRT group and 18 (14.8%) in the 40mcg+HRT group ($p=0.146$). In study GHAH, there were: 7 (9.6%) in the alendronate group and 14 (19.2%) in the 40 mcg group ($p=0.099$). In each of these studies, there were none due to nausea in the control (HRT or alendronate) group, compared to 3 in the 40 mcg group. In study GHAJ, the numbers of discontinuations due to AEs were: 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 with a statistically significant difference or trend between treatment groups: none in the placebo group or the 20 mcg group, and 5 (3.6%) in the 40 mcg group ($p=0.004$).

3.4.3 Adverse Events of Any Severity

In study GHAC, the numbers of patients with ≥ 1 AE of any severity were: 473 (86.9%) in the placebo group, 447 (82.6%) in the 20 mcg group, and 476 (86.2%) in the 40 mcg group ($p=0.098$). In study GHAF, there were 107 (85.6%) in the HRT group and 107 (87.7%) in the 40 mcg+HRT group ($p=0.627$). In study GHAH, there were 61 (83.6%) in the alendronate group and 66 (90.4%) in the 40 mcg group ($p=0.219$). In study GHAJ, there were 112 (76.2%) in the placebo group, 121 (80.1%) in the 20 mcg group, and

112 (80.6%) in the 40 mcg group ($p=0.600$). The statistical trend at the 20 mcg dose in study GHAC is not replicated in study GHAJ, and may be due to chance.

In studies GHAC, GHAF, GHAH, and GHAJ, there were no statistically significant differences or trends between treatment groups for any specific cardiovascular or urogenital AE. In study GHAJ, the frequency of patients with ≥ 1 cardiovascular AE was higher in the 40 mcg group (17.3%) than in the 20 mcg group (12.6%) or the placebo group (8.8%) ($p=0.103$), but this finding was not present in study GHAC, where the frequency of patients with ≥ 1 cardiovascular AE was 149 (27.4%) in the placebo group, 144 (26.6%) in the 20 mcg group, and 147 (26.6%) in the 40 mcg group ($p=0.947$).

In studies GHAC and GHAJ, screening evaluations were done which identified AEs with statistical differences between the placebo, 20 mcg, and 40 mcg groups at a 2-sided alpha =0.10. In study GHAC, the screening was applied to AEs with an incidence of $\geq 1\%$ in any treatment group, and in study GHAJ it was applied to AEs occurring in ≥ 4 patients. The remaining discussion of patients with any AE will focus on the findings for 20 mcg, since this is the dose proposed for marketing.

In study GHAC, the screening process identified 16 AEs, of which 7 were statistically different between 20 mcg and placebo. Of these, back pain, diabetes mellitus, and breast cancer were less common in the 20 mcg group, and leg cramps, nail disorder, hypokalemia, and tooth caries were more common. The findings for back pain and leg cramps were based on 214 and 23 patients, respectively, and were supported by data from other trials. These AEs are discussed further in section 3.4.4. The findings for the other disorders were each based on 10 or fewer patients and were not supported by data from other studies, indicating that they may have been due to chance.

In study GHAJ, the screening process identified 8 AEs, of which only depression was statistically different between 20 mcg and placebo. There were 1 (0.7%) in the placebo group, 7 (4.6%) in the 20 mcg group, and 1 (0.7%) in the 40 mcg group ($p=0.022$). This finding is based on only 9 patients, does not show a dose-response, and is not supported by data from other studies, indicating that it may be due to chance.

3.4.4 Further Analysis of Selected Adverse Events

Further analyses of selected AEs were done in studies GHAC and GHAJ. The results presented here include data on both 20 mcg and 40 mcg for evaluation of dose-response. Back pain, accidental injury, nausea, headache, and leg cramps were selected for further analysis because of the initial AE findings. Gout, arthralgia, and urolithiasis were selected because LY333334 increases serum uric acid levels and urine calcium excretion (see section 3.7). Dizziness, vertigo, and syncope, were selected because of the hypotensive effects of LY333334 in the phase I clinical pharmacology studies. In study GHAC, AEs were also analyzed for patients taking digitalis glycosides and patients with congestive heart failure.

Back Pain: In study GHAC, the numbers of patients with back pain were: 123 (22.6%) in the placebo group, 91 (16.8%) in the 20 mcg group, and 87 (15.8%) in the 40 mcg group ($p=0.007$). For severe back pain, there were: 29 (5.3%) in the placebo group, 13 (2.4%) in the 20 mcg group, and 21 (3.8%) in the 40 mcg group ($p=0.043$). These findings are similar for the 20 mcg and 40 mcg groups, and are consistent with the decreased incidence and severity of vertebral fractures in the LY333334 groups compared with the placebo group. In study GHAJ, the numbers of patients with 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 ($p=0.130$). The difference in findings between studies GHAC and GHAJ may be related to the severity of osteoporosis and frequency of fractures, since 1 or more prevalent fractures was the main entry criterion for study GHAC, whereas low BMD was the main criterion for study GHAJ.

Accidental Injury: In study GHAC, the numbers of patients with accidental injury were: 82 (15.1%) in the placebo group, 58 (10.7%) in the 20 mcg group, and 71 (12.9%) in the 40 mcg group ($p=0.101$). For severe accidental injury, there were: 13 (2.4%) in the placebo group, 4 (0.7%) in the 20 mcg group, and 6 (1.1%) in the 40 mcg group ($p=0.051$). These findings are similar for the 20 mcg and 40 mcg groups, and may be related to the findings for back pain. In study GHAJ, the numbers of patients with accidental injury were: 9 (6.1%) in the placebo group, 9 (6.0%) in the 20 mcg group, and 8 (5.8%) in the 40 mcg group ($p>0.990$). For severe accidental injury, there were: 4 (2.7%) in the placebo group, 1 (0.7%) in the 20 mcg group, and none in the 40 mcg group ($p=0.076$).

Nausea: In study GHAC, the numbers of patients with nausea were: 41 (7.5%) in the placebo group, 51 (9.4%) in the 20 mcg group, and 98 (17.8%) in the 40 mcg group ($p < 0.001$). For severe nausea, there were: none in the placebo group, 4 (0.7%) in the 20 mcg group, and 6 (1.1%) in the 40 mcg group ($p = 0.062$). In study GHAJ, the numbers of patients with 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 ($p < 0.001$). There was no severe nausea. There were not a statistically significant difference or trend between the placebo group and the 20 mcg group in the frequency of nausea, in either study.

Headache: In study GHAC, the numbers of patients with headache were: 45 (8.3%) in the placebo group, 44 (8.1%) in the 20 mcg group, and 72 (13.0%) in the 40 mcg group ($p = 0.008$). For severe headache, there were: 4 (0.7%) in the placebo group, 3 (0.6%) in the 20 mcg group, and 7 (1.3%) in the 40 mcg group ($p = 0.411$). In study GHAJ, the numbers of patients with 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, there were none in the placebo group or the 20 mcg group, and 2 (1.4%) in the 40 mcg group. There was not a statistically significant difference or trend between the placebo group and the 20 mcg group in the frequency of headache, in either study.

Leg Cramps: In study GHAC, the numbers of patients with leg cramps were: 6 (1.1%) in the placebo group, 17 (3.1%) in the 20 mcg group, and 13 (2.4%) in the 40 mcg group ($p = 0.069$). For severe leg cramps, there were: 2 (0.4%) in the placebo group, 2 (0.4%) in the 20 mcg group, and none in the 40 mcg group. The overall frequency of leg cramps was similar for the 20 mcg and 40 mcg groups, and an increase in the frequency of leg cramps in women treated with 40 mcg was also found in studies GHAF and GHAH. In study GHAJ, the numbers of patients with 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 ($p = 0.455$). Two patients in the placebo group and none in the 20 mcg or 40 mcg groups had severe leg cramps.

Gout and Arthralgia: In studies GHAC and GHAJ, there were no statistically significant differences or trends between treatment groups in the frequency of gout, arthralgia, or severe arthralgia.

Urolithiasis: In study GHAC, the numbers of patients with urolithiasis or other urinary tract AEs were: 2 (0.4%) in the placebo group (both kidney calculus), 6 (1.1%) in the 20 mcg group (1 kidney and ureter calcification, 2 kidney calculus, 3 kidney pain), and 2 (0.4%) in the 40 mcg group (1 kidney calcification, 1 kidney pain) ($p = 0.192$). In study GHAJ, there

were: 1 (0.7%) in the placebo group (kidney calculus), 2 (1.3%) in the 20 mcg group (both kidney calculus), and 2 (1.4%) in the 40 mcg group (1 kidney calculus, 1 kidney pain ($p=0.807$)).

Dizziness and Vertigo: In study GHAC, the numbers of patients with dizziness were: 33 (6.1%) in the placebo group, 50 (9.2%) in the 20 mcg group, and 44 (8.0%) in the 40 mcg group ($p=0.144$). For severe dizziness, there were: none in the placebo group, 6 (1.1%) in the 20 mcg group, and 2 (0.4%) in the 40 mcg group ($p=0.028$). These findings suggest an increase in the frequency of severe dizziness in the 20 mcg and 40 mcg groups, but the numbers of patients are small. For vertigo, there were: 18 (3.3%) in the placebo group, 24 (4.4%) in the 20 mcg group, and 27 (4.9%) in the 40 mcg group ($p=0.407$). There were 3 patients with severe vertigo, 1 in each treatment group. In patients receiving treatment with nitrates, the numbers of patients with dizziness or vertigo were: 8/52 (15.4%) in the placebo group, 20/70 (28.6%) in the 20 mcg group, and 7/54 (13.0%) in the 40 mcg group ($p=0.063$). In patients not receiving nitrates, there was no statistically significant difference or trend between treatment groups in the frequency of dizziness or vertigo. In study GHAJ, the numbers of patients with 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 ($p=0.231$). There was no severe dizziness. For vertigo, there 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 ($p=0.316$). There was no severe vertigo.

Syncope: In study GHAC, the numbers of patients with syncope were: 9 (1.7%) in the placebo group, 17 (3.1%) in the 20 mcg group, and 4 (0.7%) in the 40 mcg group ($p=0.011$). The statistical significance here is mainly due to the difference between the 20 mcg and 40 mcg groups; for the 20 mcg group compared to the placebo group, $p=0.109$. For severe syncope, there were: 2 (0.4%) in the placebo group, 3 (0.6%) in the 20 mcg group, and 1 (0.2%) in the 40 mcg group ($p=0.594$). None of the syncope events were considered by the investigators to be related to study drug. Examination of case reports for the patients with syncope revealed potential causes unrelated to the study for 3/9 in the placebo group, 8/17 in the 20 mcg group, and 1/4 in the 40 mcg group. In study GHAJ, the numbers of patients with 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 had severe syncope. None of the patients appeared to sustain an injury as the result of these syncope events.

Patients Taking Digitalis Glycosides: In study GHAC, 55 patients took digitalis glycosides: 20 in the placebo group, 20 in the 20 mcg group, and 15 in the 40 mcg group. In these patients, there were no statistically significant differences or trends between treatment groups for patients with ≥ 1 AE or any specific AE, except for decreases in the 20 mcg group in the frequency of pain and depression. These findings were not seen in the 40 mcg group and may have been due to chance. The potential for interactions between LY333334 and digitalis glycosides is being evaluated further in a clinical pharmacology study.

Patients with Congestive Heart Failure: In study GHAC, 48 patient had congestive heart failure: 13 in the placebo group, 16 in the 20 mcg group, and 19 in the 40 mcg group. In these patients, there were no statistically significant differences or trends between treatment groups for patients with ≥ 1 AE or any specific AE, except for: in the 20 mcg group, a decrease in the frequency of pain, and an increase in frequency of headache; in the 40 mcg group, an increase in the frequency of nausea and infection. The finding of nausea in the 40 mcg group is supported by other data. The other findings are not supported by other data, and may have been due to chance.

3.5 Vital Signs

In the phase 2/3 clinical trials, there were no consistent statistically significant differences or trends between the placebo, 20 mcg, and 40 mcg groups in routine measurements of sitting diastolic blood pressure, systolic blood pressure, or pulse rate. Vital signs at intervals after dosing with study drug were obtained only in study GHAM, in 19 women treated with placebo injection and 17 treated with LY333334. In the 40 mcg group compared to the placebo group, there were no statistically significant differences or trends in sitting or standing diastolic or systolic blood pressure, but there were statistically significant differences or trends of increased sitting and standing pulse rate within 6 hours after dosing with study drug. The largest mean increase in standing pulse rate, at 1 hour after dosing, was 5 beats per minute, in the 40 mcg group compared to the placebo group. One hour after injection, the range of standing pulse rates in the placebo group was 47-100 beats per minute and the range in the LY333334 group was 68-104 beats per minute.

3.6 Electrocardiograms

No electrocardiograms were obtained in the phase 2/3 clinical trials.

A phase 4 commitment has been made to obtain blood pressure, heart rate and ECG data before and at 0.5 and 2 hours after initial and subsequent dosing of osteoporosis patients with 20 mcg of LY333334.

3.7 Laboratory Safety Variables

The results from analysis of laboratory safety variables were similar in studies GHAC, GHAF, GHAH, and GHAJ. The findings from study GHAC for 20 mcg compared to placebo are presented here, because study GHAC was the largest clinical trial, and 20 mcg is the dose proposed for marketing. In study GHAC, the most comprehensive laboratory safety evaluations were at baseline, months 1, 6, and 12, and endpoint, and these evaluations are emphasized here.

Study GHAC: LY333334 20 mcg Compared to Placebo

Serum Calcium: The 4-6 hour postdose serum calcium was increased throughout the study, in the 20 mcg group compared to the placebo group ($p < 0.01$). The median increase was 0.08-0.12 mmol/L.

Hypercalcemia was defined as > 2.64 mmol/L. There were 44 (8.1%) patients with 1 episode and 16 (3.0%) with ≥ 2 episodes in the 20 mcg group, compared to 7 (1.3%) patients with 1 episode and 1 (0.2%) with ≥ 2 episodes in the placebo group ($p = 0.001$). The range of serum calcium levels in these episodes was 2.65-2.90 mmol/L. The majority of the 60 patients in the 20 mcg group with hypercalcemia episodes were identified within 150 days after randomization. The hypercalcemia was associated with: adjustment of calcium supplements in 39 (7.2%) patients in the 20 mcg group, compared to 3 (0.6%) in the placebo group ($p = < 0.001$); adjustment of study drug in 15 (2.8%) patients in the 20 mcg group, compared to 3 (0.6%) in the placebo group ($p = 0.004$); and study discontinuation for 1 (0.2%) patient in the 20 mcg group, compared to 1 (0.2%) in the placebo group ($p = 1.00$).

Urine Calcium: 24 hour urine calcium excretion was increased at months 1, 6, and 12, in the 20 mcg group compared to the placebo group ($p = 0.005$, < 0.001 , & 0.030 , respectively). The median increase was 0.50 mmol at month 1, 0.76 mmol at month 6, and 0.30 mmol at month 12. At endpoint, when most patients had been off study drug for about 5 weeks, the 24 hour urine calcium excretion was decreased, in the 20 mcg group compared to the placebo group ($p = 0.124$). The median decrease was 0.20 mmol/L.

Hypercalciuria was defined as a 24 hour urine calcium excretion >7.5 mmol. There were 96 (17.7%) patients with 1 episode and 26 (4.8%) with ≥ 2 episodes in the 20 mcg group, compared to 101 (18.6%) patient with 1 episode and 14 (2.6%) with ≥ 2 episodes in the placebo group ($p=0.460$). The maximum 24 hour urine calcium excretion in these episodes was reported as ≥ 11.00 mmol/day in the 20 mcg and placebo groups. The highest levels of 24 hour urine calcium excretion in these groups, during the study, were 20.2 mmol/day and 19.4 mmol/day in the placebo and 20 mcg groups, respectively. The hypercalciuria was associated with: adjustment of calcium supplements in 44 (8.1%) patients in the 20 mcg group, compared to 27 (5.0%) in the placebo group ($p=0.037$); adjustment of study drug in 16 (3.0%) patients in the 20 mcg group, compared to 7 (1.3%) in the placebo group ($p=0.061$); and study discontinuation for 1 (0.2%) patient in the 20 mcg group, compared to 3 (0.6%) in the placebo group ($p=0.624$).

Serum Uric Acid: Serum uric acid was increased at months 1, 6, and 12, in the 20 mcg group compared to the placebo group ($p<0.01$). The median increase was 36.3-54.0 mcmol/L. At endpoint, when most patients had been off study drug for about 5 weeks, it was still increased ($p<0.001$). The median increase was 13.3 mcmol/L.

There were 15 (2.8%) patients with elevations of serum uric acid above the upper limit of normal, in the 20 mcg group compared to 4 (0.7%) in the placebo group ($p=0.017$).

Serum Total Alkaline Phosphatase: Serum total alkaline phosphatase was increased at months 1, 6, and 12, in the 20 mcg group compared to the placebo group ($p<0.001$). The median increase was 3.00-10.00 U/L. At endpoint, when most patients had been off study drug for about 5 weeks, the increase was subsiding ($p=0.155$). The median increase at endpoint was 2.00 U/L.

There were 8 (1.5%) patients with serum total alkaline phosphatase above the upper limit of normal, in the 20 mcg group compared to 5 (0.9%) in the placebo group ($p=0.399$).

Serum Magnesium: Serum magnesium was decreased at month 1, 6, and 12, in the 20 mcg group compared to the placebo group ($p<0.001$). The median decrease was 0.06-0.07 mmol/L. At endpoint, when most patients had been off study drug for about 5 weeks, it was still decreased ($p=0.009$). The median decrease was < 0.01 mmol/L.

There were 4 (0.7%) patients with serum magnesium below the lower limit of normal, in the 20 mcg group compared to 2 (0.4%) in the placebo group ($p=0.409$).

Leukocyte Count and Differential: The leukocyte count and segmented neutrophil counts were increased at months 1, 6, and 12, in the 20 mcg group compared to the placebo group ($p<0.001$). The median increase in leukocytes was 0.45-0.60 GI/L, and the median increase in segmented neutrophils was 0.44-0.53 GI/L ($p<0.001$). There were no statistically significant differences or trends in the band or lymphocyte counts (in the 20 mcg group compared to the placebo group). The monocyte count was increased at month 1, 6, and 12 ($p<0.05$). The median increases were 0.01- 0.03 GI/L. The eosinophil count was decreased at month 1 ($p=0.086$). The median decrease was 0.01 GI/L. The basophil count was increased at month 12 ($p=0.056$). The median increase was by <0.01 GI/L. At endpoint, when most patients had been off study drug for about 5 weeks, there were no statistically significant differences or trends in the leukocyte, segmented neutrophil, monocyte, eosinophil, or basophil counts, in the 20 mcg group compared to the placebo group.

There was not a statistically significant difference or trend in the frequency of leukocyte counts above the upper limit of normal, in the 20 mcg group compared to the placebo group. The frequency of leukocyte counts below the lower limit of normal was 6.9 % in the 20 mcg group, compared to 11.2% in the placebo group ($p=0.016$). There were no statistically significant differences or trends in the frequency of abnormal values for the segmented neutrophil, band, lymphocyte, monocyte, eosinophil, or basophil counts, in the 20 mcg group compared to the placebo group.

Parathyroid Hormone (1-84): Of the blood samples obtained for measuring PTH (1-84), 89.1% in the 20 mcg group and 71.7% in the placebo group were below the level of quantitation. 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.

LY333334 Antibodies: 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 in the 20 mcg group, compared to 1 (0.2%) in the placebo group ($p<0.05$). 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.

Other Variables: For the variable listed below, there were no statistically significant differences or trends between the 20 mcg group and the placebo group in the frequency of abnormal values, and there were only minor differences in the medians or distributions of values, although these may have met criteria for a statistically significant difference or trend:

Serum phosphorus and 24 hour urine phosphorus excretion; serum glucose, cholesterol and triglycerides; serum alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, and total bilirubin; serum creatinine, creatinine clearance, and serum urea nitrogen; serum sodium, potassium bicarbonate, and chloride; urine specific gravity, pH, color, protein, glucose, ketones, bilirubin, urobilinogen, blood , nitrites, and microscopic examination; hemoglobin, hematocrit, mean cell volume/hemoglobin/hemoglobin concentration, and platelet count; creatine phosphokinase; and serum albumin and total protein.

4. Findings in Post-treatment Follow-up Study and Safety Update

4.1 Post-treatment Follow-up Study GHBJ

Study GHBJ is an observational post-treatment follow-up study of 1930 (77.6%) of the 2486 patients who participated in the phase 3 studies GHAC, GHAF, GHAH, GHAL, GHAU, GHAV, and GHAI (Table 1). The demographic and other characteristics of the patients were similar between treatment groups at baseline in the contributing studies. Investigational drugs are not used. Patients are given supplements of calcium and vitamin D, and the investigators may treat them with any drug used for osteoporosis.

Most patients in the phase 3 studies were discontinued due to sponsor's decision when Lilly stopped the studies in December 1998. The first evaluation in study GHBJ was about 6 months after study drug was discontinued (first patient visit in May 1999), and the second evaluation was about 12 months after the first. The main safety variables are physical examinations, vital signs, AEs, and laboratory tests of hematology, clinical chemistry, and creatinine clearance. The planned duration is 5 years.

The analyses of study GHBJ focus on the patients from studies GHAC, GHAI, GHAF, and GHAH. In these studies, the median duration of treatment with study drug ranged from about 11-19 months, and the median time from first study drug treatment to first evaluation in study GHBJ ranged from about 18-27 months. Results are presented for the treatment period, the follow-up period, and the total.

The main findings from study GHBJ are discussed in section 4.2 below.

4.2 Safety Update

The Safety Update to the NDA includes follow-up information on deaths, AEs, and laboratory safety variables for patients who were in the clinical studies, and reports from recently completed or ongoing clinical pharmacology and animal studies.

The Lilly safety database was searched through 5 February 2001 for any reports of death, osteosarcoma, or coronary artery disease in patients who had been in the clinical studies. Deaths are discussed below. No reports of osteosarcoma or previously unknown coronary disease were found. The additional follow-up data are from study GHBJ, through 9 February 2001 for SAEs, and 7 December 2000 for other data.

4.2.1 Deaths

A total of 42 patients who were in the clinical studies are known to have died, including 20 who died during the studies and 22 who died after discontinuation. The occurrence of death during the studies is discussed above (see section 3.4.1.1). The discussion here includes all deaths. Table 2 shows a list of the deaths by gender, age, and cause.

Of the 42 patients, 35 were in study GHAC, 5 were in study GHAJ, 1 was in study GHAH, and 1 was in study GHAL (Table 2). The death rates by treatment group are the number of deaths/number of patients in a group.

Combining data from studies GHAC and GHAJ accounts for 40 (95%) of the deaths and provides a valid comparison between placebo and the two LY333334 groups. The total death rates during or after discontinuation from these studies were: 10/691 (1.4%) in the placebo group, 15/692 (2.2%) in the 20 mcg group, and 15/691 (2.2%) in the 40 mcg group ($p=0.550$).

The 0.8% higher rates of death in the LY333334 groups compared to the placebo group appear to be due to confounding by age in study GHAC, where the mean ages in years at baseline were: 69.0 in the placebo group, 69.5 in the 20 mcg group, and 69.9 in the 40 mcg group ($p=0.10$). In study GHAC, the percentages of patients 70 years of age or older were: 40.7% in the placebo group, 44.5% in the 20 mcg group, and 46.0% in the 40 mcg group. Adjustment of the death rates for age reduced the 0.8% difference referred to above.

Figure 1 shows survival curves by treatment group for the patients in studies GHAC and GHAJ from randomization through post-treatment follow-up in study GHBJ (These are not age-adjusted).

4.2.2 Cancer

No osteosarcomas have been reported for any patient treated with LY333334. However, an increase in osteosarcoma in the patients treated with LY333334 would have to be very large to be reliably detected in the available data, since the incidence of osteosarcoma in untreated women and men 50 years of age or older is about 4 cases/million persons/year.

One 64 year old man who was treated with 40 mcg for about 13 months in study GHAJ developed Paget's disease of the pelvis. This disorder was diagnosed with scintigraphy and x-rays about 2 months after the study ended, and classified as a SAE. No Paget's disease was found

on scintigraphy in the month before LY333334 treatment began. The investigator assessed the event as possibly related to LY333334 treatment. Lilly assessed the event as probably coincidental.

Paget's disease is associated with an increased risk of osteosarcoma. Initially, Paget observed the development of sarcomas in 5 of 23 patients with osteitis deformans.¹ Since then, reports in the literature since then have described osteosarcomas in 0.7-5.0% of patients with Paget's disease, with the lower frequencies being in studies which followed both asymptomatic and symptomatic patients.²⁻⁵ Paget's disease may also be associated with osteoporosis, according to one study, which reported histories of osteoporosis in about 18% of women with Paget's disease compared to 9% of women of similar age who did not have the disease.⁶ About 1% of people 55 years of age or older have Paget's disease to an extent that is detectable on x-rays, primarily in the pelvis, according to data from the First (1971-75) National Health and Nutrition Examination Survey. The findings were similar for women and men, and for black and white patients. The disease was more common in the northeastern states than in other states.⁷

The NDA analyses of cancer discussed in section 3.4.1.2 above were based on serious AEs with a "reason serious" of cancer. The Safety Update presents more comprehensive analyses based on a search for AEs with terms indicative of (1) non-skin cancer, and (2) skin cancer or other neoplasm (whether malignant, benign or not clearly specified). These analyses focus on the patients from studies GHAC and GHAJ, and provide results for both the treatment period in the clinical trials and the follow-up period in study GHBJ.

The numbers of patients from studies GHAC and GHAJ with non-skin cancer AEs during the treatment in the clinical trials were: 19 (2.7%) in the placebo group, 10 (1.4%) in the 20 mcg group, and 6 (0.9%) in the 40 mcg group ($p=0.021$). The decrease in the LY333334 groups is largely due to a decrease in breast cancer in study GHAC, as discussed in section 3.4.1.2 above. There were no statistically significant differences or trends for other cancers. For the follow-up period in study GHBJ, the numbers of patients from studies GHAC and GHAJ with non-skin cancer AEs were: 15 (2.8%) in the placebo group, 12 (2.2%) in the 20 mcg group, and 5 (1.0%) in the 40 mcg group ($p=0.100$). The trend of a decrease in the LY333334 groups was not due to breast cancer or any other specific cancer.

The numbers of patients from studies GHAC and GHAJ with skin cancer or other neoplasia AEs during the treatment period in the clinical trials were:

48 (6.9%) in the placebo group, 39 (5.6%) in the 20 mcg group, and 51 (7.4%) in the 40 mcg group ($p=0.403$). For the follow-up period in study GHBJ, the numbers of patients from studies GHAC and GHAJ with skin cancer or other neoplasm AEs were: 32 (5.9%) in the placebo group, 44 (7.9%) in the 20 mcg group, and 51 (9.8%) in the 40 mcg group ($p=0.061$). The trend of an increase in the LY333334 groups was due to increases in the frequency of neoplasm ($p=0.019$), skin nodule ($p=0.038$), and breast neoplasm ($p=0.091$). The findings for the 36 patients with neoplasm AEs are difficult to interpret, because they largely represent a lower frequency of neoplasm in the placebo group during the follow-up period in study GHBJ, as compared to the treatment period in studies GHAC and GHAJ, rather than a higher frequency in the LY333334 groups during the follow-up period. In the 16 patients with skin nodules, the nodules were mostly in the hands or wrists, and 7 were in patients with arthritis. The 11 patients with breast neoplasm AEs included 4 patients with nodules, and 1 patient with each with cystic mass, breast mass, calcification, breast neoplasm (nos), breast mass benign, intertrigo under the breast; and not specified.

The decreases and increases in cancer other neoplasia that have been found in patients treated with LY333334 compared to placebo do not seem biologically plausible and may be due to chance.

4.2.3 Any Serious Adverse Event

The numbers and percentages of patients with ≥ 1 SAE during the follow-up period in study GHBJ, according to contributing study, were:

	<u>Placebo</u>	<u>20 mcg</u>	<u>40 mcg</u>	<u>P-value</u>
GHAC	49 (11.8%)	73 (16.7%)	54 (13.1%)	0.099
GHAJ	11 (8.7%)	19 (15.7%)	16 (15.0%)	0.195
	<u>HRT</u>			
GHAF	7 (7.2%)		1 (1.1%)	0.034
	<u>Alendronate</u>			
GHAH	4 (7.5%)		1 (1.9%)	0.176

In the patients from study GHAC, the numbers with pneumonia as a SAE during the follow-up period were: 1 (0.2%) in the placebo group, 4 (0.9%) in the 20 mcg group, and 7 (1.7%) in the 40 mcg group ($p=0.097$). There were no other statistically significant differences or trends between treatment groups for any specific SAE during the follow-up period, for the patients from study GHAC, or the patients from studies GHAJ, GHAF, or GHAH.

4.2.4 Discontinuations Due to Adverse Events

Five patients discontinued the follow-up study due to AEs: memory loss, asthma, gastrointestinal carcinoma (n=2), and breast carcinoma.

4.2.5 Adverse Events of Any Severity

For the patients from each of studies GHAC, GHAJ, GHAF, and GHAH, a screening evaluation was done on the data from study GHBJ which identified AEs with a total incidence ≥ 4 and a statistically significant difference between treatment groups during the treatment period, the follow-up period, or the total.

Only the follow-up period will be discussed here.

In the patients from studies GHAC and GHAJ (with both 20 mcg and 40 mcg doses of LY333334), the screening process identified back pain, hypesthesia, and malaise as decreased in both LY333334 groups compared to the placebo group. Cardiovascular disorder and anemia were increased in both LY333334 groups. Sinusitis, glaucoma and bradycardia, were increased in the 40 mcg group, with little or no increase in the 20 mcg group. Increased salivation, depression, and amnesia were increased in the 20 mcg group, with no increase in the 40 mcg group. In study GHAF (with only 40 mcg), bursitis and hypertonia were decreased, and insomnia was increased, in the 40 mcg group compared to the HRT group. In study GHAH (with only 40 mcg), there were no findings.

Most of the screening findings were of limited relevance to use of the 20 mcg dose or appeared to be due either to enrollment bias in the patient composition of study GHBJ compared to that of the contributing clinical studies, or chance.

In the patients from study GHAC, the numbers with anemia as an AE were: 1 (0.2%) in the placebo group, 11 (2.5%) in the 20 mcg group, and 11 (2.7%) in the 40 mcg group ($p=0.013$). This finding is supported by a statistically significant, small (<1%) decrease in median hemoglobin, in the LY333334 groups compared to the placebo group. However, the anemia finding could be due to enrollment bias, since it represents a lower frequency of anemia in the placebo group during the follow-up period in study GHBJ than was found during the treatment period in study GHAC, rather than a higher frequency in the LY333334 groups. Of the 23 cases of anemia, 20 were reported as mild and 3 as moderate.

The finding for cardiovascular disorder, in the patients from study GHAC, was investigated in-depth by grouping cardiovascular system AE terms related to common forms of cardiovascular disease: congestive heart failure, coronary artery disease, any arrhythmia, supraventricular arrhythmia, ventricular arrhythmia, and extracardiac thrombosis. This investigation showed no statistically significant differences or trends between treatment groups for any of these disorders except coronary artery disease: 17 (4.1%) in patients from the placebo group, 34 (7.8%) in patients from the 20 mcg group, and 20 (4.9%) in patients from the 40 mcg group ($p=0.046$). This finding may be due to chance, since there is no difference between the placebo and 40 mcg groups. Also, the baseline frequency of patients with a history of myocardial infarction or angina pectoris was somewhat higher in the 20 mcg group compared to the placebo and 40 mcg groups, although no direct evidence was provided that the patients with these conditions at baseline were the patients with coronary artery disease AEs in the follow-up period.

There were no statistically significant differences or trends between treatment groups, during the follow-up period, for urinary tract disorder, kidney calculus, kidney pain, or hematuria, in the patients from studies GHAC, GHAJ, GHAF, and GHAH.

4.2.6 Laboratory Safety Variables

The laboratory safety variables were evaluated in study GHBJ by comparing the treatment groups from each contributing study for the change from baseline in that study to the second study GHBJ evaluation. The findings from study GHAC patients for 20 mcg compared to placebo are presented here, because study GHAC was the largest clinical trial, and 20 mcg is the dose proposed for marketing. The 40 mcg dose and the other studies are considered when adding useful information.

In the patients from study GHAC, for 20 mcg compared to placebo, there were statistically significant decreases in median hemoglobin, hematocrit, erythrocyte count, and eosinophil count (each $<1\%$), and a statistically significant increase in median serum creatinine ($<2\%$).

Abnormally high serum creatinine (>101 $\mu\text{mol/L}$) was found in 17 (3.9%) patients in the 20 mcg group compared to 7 (1.7%) in the placebo group ($p=0.055$), and the findings for 40 mcg were similar. In the 17 patients in the 20 mcg group, the median creatinine was 110 $\mu\text{mol/L}$ and the range was 104-137; in the 7 patients in the placebo group, the median was 109 and the range was 104-115. The patients with abnormally high serum creatinine are being evaluated further.

The frequency of 4-6 hour postdose hypercalcemia during study GHAC was not related to the frequency of abnormally high serum creatinine during study GHBJ. There was a proportionally similar increase in the frequency of abnormally high serum creatinine in the patients from study GHAJ, in the LY333334 groups compared to the placebo group, but this was based on much smaller numbers of patients, and may have been due to chance. ($p>0.1$). There were no statistically significant differences or trends between treatment groups in the patients from any of the studies for measured creatinine clearance.

Serum total alkaline phosphatase was decreased by about 2% in the 20 mcg group compared to the placebo group ($p=0.063$), and the findings for 40 mcg were stronger. There were statistical trends for serum potassium, total protein, and albumin, but these were $<1\%$ different between the 20 mcg group and the placebo group, and the findings for 40 mcg were not supportive. There were no other statistically significant differences or trends between the 20 mcg group and the placebo group.

LY333334 antibody binding activity returned to baseline in 68 (59.1%) of the 115 patients treated with LY333334 who had post-treatment tests, and declined in most of the others. Of the 21 patients with post-treatment increases, 18 had binding activity <350 BU.

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Table 1

Clinical Studies of LY333334 with Patients in Follow-up Study GHBJ

Prior Study	Placebo	Prior Study Treatment						Total Enrolled in B3D-MC-GHBJ	Prior Study Enrollment	Percent of Prior Study Enrollment in B3D-MC-GHBJ
		PTH20	PTH40	HRT	HRT/ PTH40	ALEN	No TRT			
B3D-MC-GHAC	414	436	412				1262	1637	77.09%	
B3D-MC-GHAJ	127	121	107				355	437	81.24%	
B3D-MC-GHAF				97	94		191	247	77.33%	
B3D-MC-GHAH			52		53		105	146	71.92%	
B3D-MC-GHAL			3				3	6	50.00%	
B3D-MC-GHAU		4	2				10	13	76.92%	
B3D-MC-GHAV			3				4	6	66.67%	
Total	541	561	579	97	94	53	1930	2486*	77.63* 77.44 %	

* All B3D-MC-GHAL patients were previously enrolled in B3D-MC-GHAC.

Abbreviations: PTH20 = LY333334 20 µg/day; PTH40 = LY333334 40 µg/day; HRT = Hormone Replacement Therapy; ALEN = alendronate 10 ~~mg~~µg/day;

TRT = treatment.

Table 2

Deaths During Participation in Clinical Studies of LY333334

Patient Number	Previous Study	Sex	Age at Baseline (years)	Dose ($\mu\text{g}/\text{d}$)	Randomization to Last Dose (days)	Randomization to Death (days)	Cause of Death
GHAC-244-6003	GHAC	F	78	Placebo	281	296	Myocardial infarct
GHAC-281-1449	GHAC	F	76	Placebo	424	452	Cardiovascular disorder/ Myocardial infarct
GHAC-282-1791	GHAC	F	77	Placebo	442	443	Shock/ Myocardial infarct
GHAC-747-5143	GHAC	F	66	Placebo	88	89	Lung disease/Aspiration
GHAC-031-7832	GHAC	F	85	20 μg	538	540	Myocardial infarct
GHAC-156-2100	GHAC	F	68	20 μg	427	451	Pancreatitis
GHAC-244-0418	GHAC	F	70	20 μg	537	551	Pneumonia
GHAC-281-1459	GHAC	F	68	20 μg	178	179	Heart arrest/ Hypertension
GHAC-282-1574	GHAC	F	65	20 μg	216	217	Suicide
GHAC-745-5070	GHAC	F	76	20 μg	450	450	Unknown
GHAJ-203-4500	GHAJ	M	77	20 μg	238	239	Laryngeal cancer
GHAJ-760-5226	GHAJ	M	84	20 μg	46	103	Lung cancer/Pneumonia
GHAC-008-7173	GHAC	F	83	40 μg	58	60	Stroke
GHAC-157-2224	GHAC	F	66	40 μg	447	512	Lung cancer
GHAC-203-6281	GHAC	F	84	40 μg	459	490	Anemia/Arteritis
GHAC-203-6288	GHAC	F	76	40 μg	538	570	Bladder cancer
GHAC-725-5549	GHAC	F	66	40 μg	434	434	Pneumonia
GHAC-756-4770	GHAC	F	74	40 μg	73	168	Pneumonia/Lung cancer
GHAH-206-7609	GHAH	F	74	40 μg	313	313	Unknown
GHAL-156-2204	GHAL ^a	F	74	40 μg	78	78	Unknown

^a Patient initially treated in placebo group in Study B3D-MC-GHAC, then entered Study B3D-MC-GHAL.

Table 2-Concluded

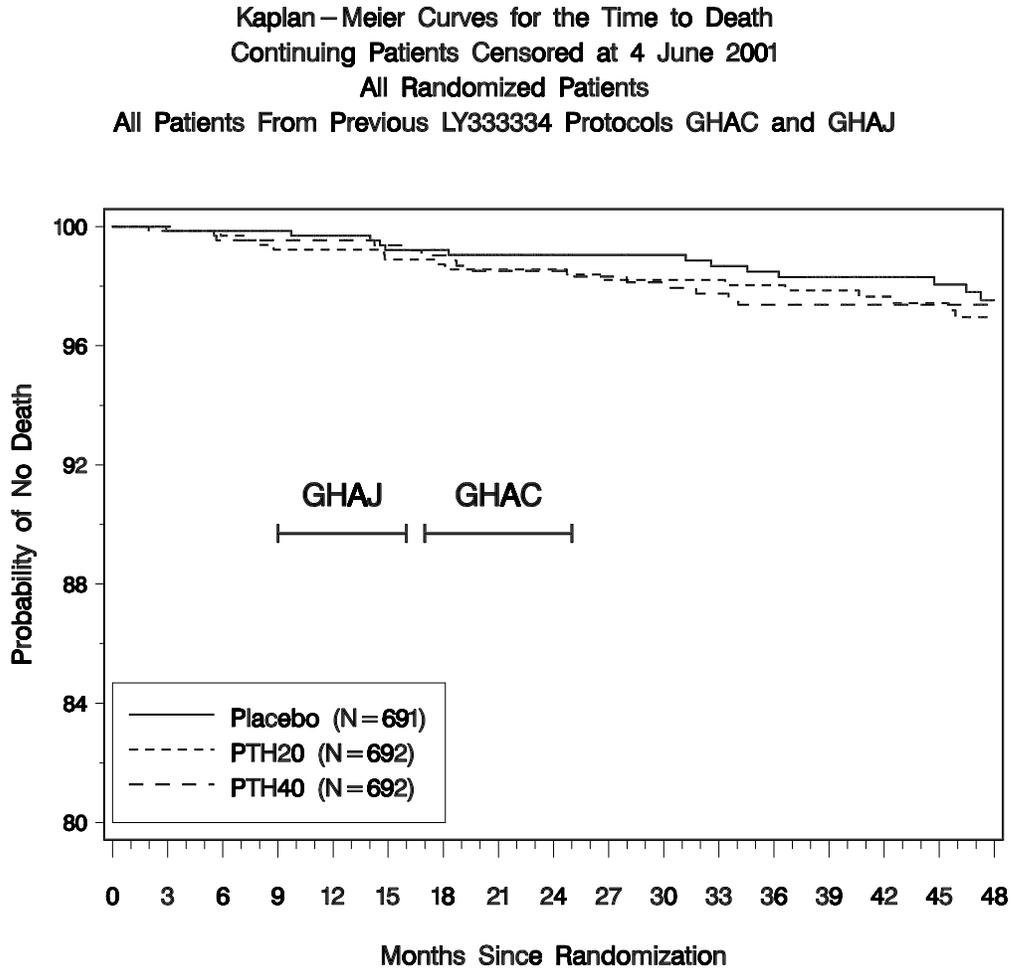
Deaths Subsequent to Participation in Clinical Studies of LY333334

Patient Number	Previous Study	Sex	Age at Baseline (years)	Dose ($\mu\text{g}/\text{d}$)	Random-ization to Last Dose (days)	Random-ization to Death (days)	Cause of Death
GHAC-150-3869	GHAC	F	66	Placebo	181	427	Breast cancer
GHBJ-015-0251	GHAC	F	75	Placebo	596	1439	Emphysema
GHBJ-040-0614	GHAC	F	75	Placebo	553	1362	Liver cancer
GHBJ-043-0655	GHAC	F	71	Placebo	251	1104	Myocardial infarct/ Lung fibrosis
GHBJ-147-1703	GHAC	F	63	Placebo	545	992	Suicide
GHBJ-148-1810	GHAC	F	82	Placebo	562	1415	Septic shock
GHBJ-282-2913	GHAC	F	65	Placebo	512	950	Lung cancer
GHBJ-963-9607	GHAC	F	74	Placebo	658	1052	Pancreatic cancer
GHBJ-993-9903	GHAJ	M	72	Placebo	329	557	Bronchopneumonia/ Coronary disease
GHAC-244-5925	GHAC	F	84	20 μg	665	811	Congestive heart failure
GHAC-705-5671	GHAC	F	75	20 μg	605	1293	Pulmonary edema
GHAC-725-5554	GHAC	F	65	20 μg	196	267	Metastatic cancer/ Gastric tumor
GHBJ-150-1839	GHAC	F	78	20 μg	669	1386	Breast cancer
GHBJ-157-1267	GHAC	F	71	20 μg	597	1015	Arteriosclerosis
GHBJ-282-2926	GHAC	F	76	20 μg	507	1397	Congestive heart failure/Hypertension
GHBJ-725-7331	GHAC	F	79	20 μg	626	1237	Stroke
GHBJ-746-7538	GHAC	F	59	20 μg	657	1115	Myocardial infarct
GHBJ-747-7571	GHAJ	M	59	20 μg	372	753	Aortic aneurysm
GHAC-010-1172	GHAC	F	81	40 μg	698	852	Cardiac arrest/ Hypertension
GHAC-282-1580	GHAC	F	72	40 μg	81	172	Sepsis/Stroke
GHAC-746-5095	GHAC	F	76	40 μg	579	589	Myocardial infarct
GHAC-852-4453	GHAC	F	77	40 μg	115	967	Lung or colon cancer
GHBJ-013-0210	GHAC	F	68	40 μg	677	1021	Septic shock
GHBJ-244-2440	GHAC	F	77	40 μg	553	765	Cardiac arrest/ Left ventricular dysfunction
GHBJ-282-2919	GHAC	F	69	40 μg	526	914 ^a	Unknown
GHBJ-747-7597	GHAJ	M	67	40 μg	269	556	Myocardial infarct
GHBJ-855-8629	GHAC	F	75	40 μg	651	1037	Aortic aneurysm

^a Date of last hospital discharge; death occurred within 3 months (date of death unknown).

Figure 1

Survival or patients in studies GHAC and GHAJ, from Randomization Through Post-Treatment Follow-up in study GHBJ



LOG–RANK p–value= 0.780

WILCOXON p–value= 0.713

Horizontal lines indicate when randomized studies stopped and follow up period began.
Program in RMPB3DSBJV2.SASPGM(AEGC.J1RB)
Source: Eli Lilly ClinTrace Database 4 June 2001

Appendix

Findings in Preclinical and Phase 1 Clinical Studies

1. Preclinical Pharmacology and Toxicology Studies

1.1 Hypotension and Tachycardia in Rats, Dogs, and Monkeys

LY333334 decreased blood pressure and increased heart rate in single-dose studies of rats given 23-1000 mcg/kg and dogs given 6 mcg/kg. In a 1 year study of monkeys given daily doses of 0.5-10 mcg/kg, heart rate increased modestly in the treated animals and decreased in the controls. In dogs, LY333334 increased the left ventricular inotropic state. In male monkeys treated with LY333334, the PQ and QT intervals on electrocardiograms did not change appreciably from baseline, whereas these intervals increased in the controls. No electrocardiogram effects were reported for dogs or female monkeys. The blood pressure and heart rate effects of LY333334 were dose-dependent and maximal in the 2 hours after injection. In rats, the no-observed-effect level was estimated to be 4.3 mcg/kg, which corresponds on average to about 3.1X the human exposure at a daily dose of 20 mcg; the exposure multiple ranges from about 1.4-3.6, depending on how it is calculated. In male monkeys, the differences between treated animals and controls in heart rate (increased), and the PQ and QT intervals (decreased), were statistically significant at 25 weeks but not at 48 weeks.

1.2 Renal Histopathology in Monkeys

LY333334 induced renal histopathology in monkeys treated for 3 months with daily doses of 2-40 mcg/kg or for 1 year with daily doses of 0.5-10 mcg/kg. In a 4 month study designed to evaluate reversibility, 1 of 8 monkeys treated with daily doses of 40 mcg/kg showed signs of renal failure after 78 days of treatment. Renal function in this monkey returned to nearly normal after LY333334 was discontinued. In the other monkeys, the renal histopathology was not associated with altered renal function, and partially reversed after LY333334 was discontinued. In the 3 month and 1 year studies, the severity of renal histopathology was directly related to the magnitude and duration of hypercalcemia. Renal histopathology was not found in an 18 month study in which daily doses of 1-5 mcg/kg were given to oophorectomized female monkeys estimated to be over 9 years of age. These monkeys were fed a diet containing 0.3% calcium, whereas the monkeys with renal histopathology after LY333334 treatment were fed a diet containing 0.7% calcium. Based

on an estimated average daily food intake of 25 g/kg, the monkeys in the 18 month study had a daily calcium intake of about 75 mg/kg. A postmenopausal woman taking a calcium supplement has a daily calcium intake of about 30 mg/kg.

1.3 Osteosarcomas in Rats

LY333334 induced osteosarcomas and other proliferative bone lesions in rats treated for 2 years with daily doses of 5-75 mcg/kg. The tumors were found by external palpation after about 17 months of treatment in the 75 mcg/kg group and after about 20 months in the 5-30 mcg/kg groups. When LY333334 serum levels measured at 6, 12, and 18 months of treatment of the rats were averaged and compared to serum levels in postmenopausal women treated with daily doses of 20 mcg, the AUC values in the rats were about 3.0-58 times higher and the C_{max} values were about 8.8-136 times higher. The multiples at 6-12 months were higher and those at 18 months were lower, compared to the average. The predictive value of the osteosarcoma finding in rats is unclear because of differences between the rat carcinogenicity model and the intended clinical use of LY333334 in the treatment of osteoporosis.

2. Phase 1 Clinical Studies

2.1 Description of Studies

Eleven completed clinical pharmacology studies were included in the NDA, of which 3 were placebo-controlled. Two more placebo-controlled studies have since been completed and 1 is in progress.

The 11 completed studies in the NDA enrolled 206 patients, including 175 healthy patients and 31 patients with chronic renal insufficiency or hypertension. About 94% of the patients were Caucasian, 90% were 50-85 years of age, and 56% were women. In total, 659 doses of LY333334 were given: 16 patients received 16 doses of 5-15 mcg, 42 patients received 42 doses of 20 mcg, 192 patients received 543 doses of 30-40 mcg, and 57 patients received 58 doses of 60-100 mg (some patients were treated at more than 1 dose level). In the studies of 40 mcg, patients received 1-14 doses; in the studies of other dose levels, patients received 1 dose. Eight studies tested LY333334 alone, and 3 studies tested LY333334 alone and with concomitant use of: hydrochlorothiazide in healthy patients (10 women, 10 men); furosemide in healthy patients (4 women, 5 men) and patients with chronic renal insufficiency (7 women, 10 men); and atenolol or a calcium antagonist (diltiazem, nifedipine, felodipine or nisoldipine) in hypertensive patients (14 women). One of the

studies completed subsequent to the NDA enrolled patients with mild or moderate heart failure (5 men, 8 women) and tested a 20 mcg dose, and the other enrolled healthy patients (24 men, 25 women) and also tested a 20 mcg dose. Patients in all of these studies were treated with LY333334 during inpatient observation. The safety evaluations included solicitation of adverse events (AEs), physical examinations, measurement of vital signs, and laboratory tests of routine safety variables and serum calcium and phosphorus. Additional testing was done as required by each study protocol. In some studies, 12-lead surface electrocardiograms were done, and in some 24 hour urine calcium excretion was measured.

Findings from the 11 completed studies in the NDA are discussed below. The results from the 2 studies completed subsequently do not change the conclusions.

2.2 Adverse Events

The analysis of clinical AEs focused on events that began within 24 hours after dosing with study drug and were considered by the investigators to be treatment-related. A review of the other AEs revealed no important additional findings. Most of the AEs actually began within about 4 hours after dosing.

There were no deaths. There was 1 serious AE: a patient who had lightheadedness, nausea, vomiting, orthostatic hypotension, and leukocytosis after a 75 mcg dose of LY333334 was kept overnight for observation, which led to the AE being called serious. Three patients were discontinued or withdrew from studies due to AEs: 2 had dizziness with nausea or vomiting, and orthostatic hypotension, after 60 mcg and 75 mcg doses of LY333334, and 1 had nausea and vomiting after a 40 mcg dose.

For LY333334 administered alone, there were no AEs in patients given 5-15 mcg. There were 10 AEs in patients given 20 mcg, including 1 case of orthostatic hypotension. At higher doses, the most common AEs were headache, dizziness, nausea, and vomiting, and the most important were orthostatic or other hypotension and tachycardia. In patients given 30-40 mcg, there were 105 AEs, including 3 cases of orthostatic hypotension, 4 of other hypotension, and 3 of tachycardia. In patients given 60-100 mcg, there were 76 AEs, including 1 case of orthostatic hypotension, 3 of other hypotension, and 2 of tachycardia. Considering the numbers of patients and doses at the different dose levels, there was a direct relationship between LY333334 dose and the frequency of headache, nausea, and dizziness. There was also a direct, but less strong,

relationship between dose and the frequency of orthostatic or other hypotension, and tachycardia. No cardiac arrhythmias were associated with the AEs. Patients with orthostatic hypotension were treated by having them lie down, which improved blood pressure and symptoms. Full recovery occurred within a few hours. In one patient intravenous fluids were given. Some patients with orthostatic hypotension were rechallenged with the same or higher dose without incident.

For LY333334 administered with hydrochlorothiazide, furosemide, atenolol or calcium channel antagonists, the types of AEs were similar to those reported for LY333334 alone. However, the frequency of these AEs is difficult to evaluate due to the small numbers of patients.

2.3 Hemodynamics

Serial supine and standing blood pressure and pulse rate measurements before and in a 6 hour period after dosing were combined across studies for 5 LY333334 doses: 0 mcg (n=65), 5-15 mcg (n=16), 20 mcg (n=42), 30-40 mcg (n=192), and 60-100 mcg (n=58). Results were expressed as changes from baseline. At LY333334 doses of 20 mcg or lower, the findings were similar to the findings for 0 mg, except that the average change from baseline in standing pulse was 3 bpm higher in the 20 mcg group than in the 0 mcg group ($p < 0.05$). At doses over 20 mcg, there were statistically significant, dose-related decreases in supine and standing diastolic blood pressure, and increases in supine and standing pulse rate, in the LY333334 groups compared to the 0 mcg group. Repeat measurements after 14 days of dosing with 40 mcg showed continuation of these effects. Using an algorithm for orthostatic hypotension based on blood pressure, pulse, and symptoms, a total of 49 patients were found to have had a total of 56 episodes. The numbers of patients with episodes/numbers of patients treated with LY333334 were 0/16 for 5-15 mcg, 2/42 (6%) for 20 mcg, 36/192 (19%) for 30-40 mcg, and 11/57 (19%) for 60-100 mcg ($p = 0.065$).

Patient with orthostatic hypotension and tachycardia generally had smaller decreases in blood pressure than patients without tachycardia. The frequency of orthostatic hypotension in patients given 40 mcg of LY333334 appeared to be similar in healthy patients and patients with chronic renal insufficiency or hypertension, although the small numbers of patients in the latter 2 groups make the comparisons difficult to interpret.

2.4 Electrocardiograms

ECGs after dosing with LY333334 were obtained from 49 healthy patients who received single doses and 7 chronic renal insufficiency patients who received 2 doses each. The ECGs were taken before and at 0.83, 3.75, 5.25, and 24 hours after dosing. Data were obtained for 0, 20, 40, and 80 mcg of LY333334.

Compared with 0 mcg, all 3 active doses reduced the RR interval at 0.83 and 3.75 hours after dosing. For 20 mcg compared to 0 mcg, the mean RR change from baseline in milliseconds was -41.9 at 0.83 hours and -60.2 at 3.75 hours ($p < 0.05$). After 3.75 hours, the difference between active doses and 0 mcg was statistically significant only for 80 mcg.

The reductions in RR intervals were accompanied by changes in QT intervals. These were corrected for the increased heart rates with the formulas of Fridericia and Bazett. Using these formulas, and comparing 20 mcg to 0 mcg, the mean corrected QT at 3.75 hours after dosing was decreased by 3.6-8.0 milliseconds at 3.75 hours and 13.2-16.7 milliseconds at 5.25 hours. ($p < 0.05$).

ECG data obtained at intervals after repeated dosing with LY333334 were not available for evaluation.

Additional ECG data from 49 healthy patients and 13 patients with heart failure treated with single doses of 20 mcg of LY333334 were submitted after the NDA. The findings were similar to those described above.

2.5 Laboratory Tests

Serum Calcium: LY333334 increased serum calcium. The serum calcium levels generally peaked at about 3-4 hours after dosing with 5-15 mcg and 5-8 hours after dosing with 20-100 mcg. Across the 10 studies with serial measurements after dosing, a total of 25 patients had at least 1 level that was above both the upper limit of normal and exceeded the highest pretreatment level. The elevated serum calcium levels ranged from 2.54-2.79 mM (10.2-11.2 mg/dL). The frequency of elevations was directly related to the dose of LY333334, but did not appear to increase with repeated dosing. None of the elevations was associated with symptoms of hypercalcemia.

Urine Calcium: LY333334 decreased urine calcium excretion for 6-8 hours after dosing; subsequently, the rate of excretion was similar to or higher than occurred with placebo. There were no statistically significant differences or trends in 24 hour urine calcium excretion for 20, 40, or 80 mcg compared to placebo.

Phosphorus and Magnesium: LY333334 20-40 mcg decreased serum phosphorous and increased urine phosphorus, but the measurements returned to pretreatment levels within 9 hours after dosing. Across the 10 studies with serial measurements, 25 patients had mild hypophosphatemia (0.55-0.87 mM or 1.7-2.7 mg/dL). LY333334 also decreased serum magnesium. The lowest level was 0.62 mM (1.5 mg/dL), and was within 0.3 mg/dL of the lower limit of normal.

Hepatic and Renal Function: Serum tests of hepatic or renal function were above the upper limit of normal in the following numbers of healthy patients treated with LY333334: alanine aminotransferase (ALT/SGPT), n=8; aspartate aminotransferase (AST/SGOT), n=11; alkaline phosphatase, n=11; total bilirubin, n=5; urea nitrogen, n=25; and creatinine, n=11. All of the transaminase elevations were less than 2 times the upper limit of normal. The alkaline phosphatase elevations were less than 25% above the upper limit of normal, except in 4 patients, 3 of whom had elevations before treatment, and 1 of whom had an elevation in only 1 of 20 measurements. All of the bilirubin elevations were less than 20 % above the upper limit of normal, and none were associated with abnormal transaminase or alkaline phosphatase levels. The urea nitrogen elevations were less than 27 mg/dL, except in 3 patients with elevations in the range of 27-34 mg/dL that returned to normal at next blood draw. The creatinine elevations were less than 12% above the upper limit of normal. (Patients with chronic renal insufficiency were excluded from the tabulations.)

Hematology: Hemoglobin levels were below the lower limit of normal in 32 healthy patients treated with LY333334 and hematocrit levels were below the lower limit of normal in 39 patients, although some of these patients were mildly anemic before treatment. Leukocyte and neutrophil counts were increased in healthy patients treated with LY333334 but the changes were within normal limits.

Drug-Drug and Drug-Disease Interactions: The calcium response to a 40 mcg dose of LY333334 was the main variable tested for evidence of drug-disease or drug-drug interactions. In patients with chronic renal insufficiency compared to healthy patients, the serum ionized calcium response was decreased, although the total calcium response was similar. Also, the 24 urine calcium excretion was 60-65% lower in the chronic renal

insufficiency patients. In patients with hypertension treated with atenolol or a calcium channel antagonist, the serum calcium response was similar to the response in healthy patients. In healthy patients treated with hydrochlorothiazide, the serum response was similar to the response in patients not treated with that drug, but the 24 hour urine calcium excretion was about 15% lower ($p < 0.05$). In healthy patients and patients with chronic renal insufficiency, treated with furosemide, there were small differences in serum calcium and 24 hour urine calcium excretion, compared to otherwise similar patients not treated with furosemide. The combination did not increase the average maximum serum calcium above the level seen with LY333334 alone, although there was some increase in 24 urine calcium excretion. These findings were based on small numbers of patients.

Pharmacokinetics: Pharmacokinetic studies of LY333334 showed that men had 20-30% lower total systemic exposure than women ($p < 0.01$). The pharmacokinetic variables did not appear to be significantly influenced by age, smoking, or alcohol consumption. Clearance was not related to weight, but the volume of distribution increased with weight in both women and men, such that the peak serum level increased with decreasing weight. Also, the volume of distribution was about 20-30% higher when LY333334 was injected in the thigh compared to the abdomen, so that injection in the thigh produced lower peak serum levels. In the clinical trials, the difference between women and men in total systemic exposure was not associated with any clear difference in the relationship of LY333334 dose to the occurrence of adverse events.

LY333334 Metabolism: LY333334 is primarily metabolized by hepatic Kupffer cells, which cleave the molecule into fragments that are mainly cleared by the kidney. Hepatocytes do not appear to have an important role, suggesting that hepatotoxicity is unlikely, and that hepatic impairment should not have a clinically important effect of systemic exposure. Also, maximum serum levels and total systemic exposure to LY333334 did not differ significantly between healthy patients and patients with chronic renal insufficiency, although there was a small correlation between total systemic exposure and creatinine clearance.