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 a 2-year study of rats treated from weanling age with daily doses of 5-75 mcg/kg. The incidence of osteosarcoma was dose-related and reached 45% in the highest dose group. 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 Cmax 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. Further work is in progress to evaluate the effect of LY333334 on the incidence of osteosarcoma in rats when treatment is begun at an older age (See Pharmacology Review).

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 and a digoxin interaction study have since been completed.

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 mcg (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, another enrolled healthy patients (24 men, 25 women) and also tested a 20 mcg dose, and a third enrolled healthy patients (2 men, 13 women), and tested a 20 mcg dose with and without concomitant digoxin. 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 3 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, calcium channel antagonists, or digoxin, 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 mcg, 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 after14 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. In patients with mild to moderate heart failure, 20 mcg of LY333334 did not appear to have clinically important effects on supine or standing blood pressure, heart rate, or electrocardiographic intervals. However, the numbers of patients with chronic renal insufficiency, hypertension, and heart failure were small.

2.4 Electrocardiograms

ECGs after dosing with LY333334 were obtained from 49 healthy patients single doses and 7 chronic renal insufficiency patients who received 2 doses each. The ECGs were done before and at intervals of 0.83, 3.75, 5.25, and 24 hours after dosing. Data were obtained for 0, 20, 40, and 80 mcg of LY333334. ECGs at intervals after repeated dosing with LY333334 were not obtained.

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 reduced by 3.6-8.0 milliseconds at 3.75 hours and 13.2-16.7 milliseconds at 5.25 hours.($p<0.05$).

In 49 healthy patients and 13 patients with mild to moderate heart failure, treated with single doses of 20 mcg, the findings were similar to those described above. In 15 healthy patients, a single dose of 20 mcg did not appear to interact with the effects of digoxin on cardiac function as measured by the time from the ECG Q wave to echocardiographic closure of the aortic valve, heart rate, and other secondary endpoints.

A cardiology consult was obtained concerning the ECG changes. A copy is attached to the hardcopy of this review. The main recommendations were: (1) to evaluate the clinical trial data for episodes of arrhythmia or adverse events that might represent arrhythmia, and (2) to obtain further ECG data after repeated dosing with LY333334. The clinical trial data

were examined and the LY333334 groups and placebo groups showed similar frequencies of reported arrhythmias and acute cardiovascular events such as sudden death, myocardial infarction, syncope, and hypotension. The issues were discussed within the Division and a decision was made to request further ECG data after repeated dosing with LY333334 in a phase 4 study.

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 hepatoxicity 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.

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Appendix II

Study GHAC in Women and Study GHAJ in Men

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

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1. Study GHAC: Effects of LY333334 in the Treatment of Postmenopausal Women with Osteoporosis

1.1 Study Design

Study GHAC was a randomized, double-blind, placebo-controlled, parallel-group clinical trial of LY333334 conducted at 99 centers in 17 countries between December 1996 and December 1998, when it was stopped by Lilly. The patients were 1637 women 42-85 years of age who were at least 5 years postmenopausal and had at least 1 moderate or 2 mild atraumatic vertebral fractures.

The patients were randomized to placebo (n=544), 20 mcg (n=541), or 40 mcg (n=552). All patients received 1000 mg of calcium and 400-1200 IU of vitamin D per day. The planned duration of treatment was 3 years. The actual duration ranged from less than 1 month to 26 months; most patients were treated for 18-23 months.

The primary efficacy endpoint was the proportion of patients with new vertebral fractures. Other efficacy endpoints included: proportion of patients with nonvertebral fractures; BMD (spine, hip, wrist, and total body); 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 population 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; serum calcium and albumin 4-6 hours after dosing with study drug; urinalysis; 24 hour urine calcium, phosphorus, and creatinine excretion; creatinine clearance; fasting triglycerides; 25 hydroxyvitamin D; PTH (1-84); and LY333334 antibodies. Bone biopsies were done and are discussed in the review of efficacy.

The primary aim of Study GHAC was to fulfill regulatory guidelines for licensure of a drug for osteoporosis. These required demonstration of a statistically significant reduction in the proportion of patients with new vertebral fractures, in a randomized, double-blind, controlled study. The main elements in designing this type of study are the proportions of patients in the control group and experimental group who are expected to sustain new vertebral fractures, and the numbers of patients in the two groups that are needed to show the difference in new vertebral fracture rates at the stated levels of statistical significance and power.

Vertebral fractures were selected for study because they occur frequently enough to be investigated in a study of reasonable size, and because their rate of occurrence decreases with treatment over a reasonable period of time.

At the time the study was being planned, there was evidence that about 18-20% of patients with established osteoporosis (low bone mass and at least 1 vertebral fracture) would sustain a new fracture within 3 years. These were considered to be the patients most likely to benefit from the rapid increases in bone mass that had been reported for PTH treatment. In addition, since these patients had demonstrable disease (a vertebral fracture), they were considered more likely to accept an injection regimen than patients with low bone mass but no fractures.

The term "vertebral fracture" was defined as a radiographic deformity. Since most patients who sustain this kind of fracture do not have the disability associated with a non-vertebral fracture, risk to patients in the study was kept at a minimum. Any patient who sustained more than 1 new moderately severe vertebral fracture was withdrawn from the study.

The study was planned to have 4 phases: a calcium and vitamin D run-in phase of 2 weeks to 6 months (visits 0-3), an injection run-in phase of 2 weeks (visits 3-4), a treatment phase of 3 years (visits 4-17), and an optional randomized extension phase of about 2 years (visits 17-21). However, the study was stopped in December 1998 due to the finding of osteosarcoma in a rat carcinogenicity study, after about 19 months of treatment with LY333334 (see Appendix 1). The clinical investigators were advised to have all patients complete an 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 77.1% of the eligible patients enrolled.

The schedule of study visits and other events is presented in Table 1 on pages 45-48.

Table 1 Schedule of Study Events

Activity	Calcium/Vit D		Injection	Treatment		
Visit--Visits that may be office or telephone visits are designated with (tele)	0, 1	2 (tele)	3	4	5	6
Month (unless otherwise indicated)	-6 to -1	*	-2 weeks	0	1	3
Informed consent document signed	X[a]			X[b]		
Screening number assigned	X[a]					
Review of inclusion/exclusion criteria	X[a]			X		
Patient number assigned	X					
Medical history	X	●		X		
Sitting blood pressure, pulse	X		X	X	X	X
Concomitant medication reporting	X	X	X	X	X	X
Patient education regarding injections	X		X			
Record of adverse event reporting		X	X	X	X	X
Physical examination				X		
Height[c], weight				X		
Assessment of habits: smoking, alcohol, caffeine				X		
Assessment of dietary calcium				X		
Patient assigned to treatment group				X		
Laboratory Assessments						
Hematology, clinical chemistry, urinalysis	X			X[d]	X	
Serum calcium and albumin (4-6 hours postdose)	X			X	X	X
TSH, PTH (1-84)	X					
FSH, serum estradiol	X[e]					
25-hydroxyvitamin D	X			X		
24-hour urine calcium, creatinine, phosphorus			X[f]		X	
PTH(1-84) postscreening, subset				X		
1,25-dihydroxyvitamin D, subset				X	X	X
Biochemical markers of bone metabolism, subset				X	X	X
Fasting triglycerides, subset				X	X	X
LY333334 antibodies				X		X
LY333334 serum concentrations/weight, subset					X	X
Technical Assessments						
Lateral thoracic and lumbar spinal x-ray films	X[a,g]			X[h,i]		
AP thoracic and lumbar spinal x-ray films	X[a,j]			X[h,k]		
PA lumbar spine BMD			X[l]	X[l]		X[m]
Hip BMD			X[l]	X[l]		
Total body and radial BMD, subset				X[n]		
Bone biopsy, subset				X		
Miscellaneous						
Health-related quality of life				X		
Medical resource utilization				X		
Patient stipend for bone biopsy, subset				X		

Table 1-continued. Schedule of Study Events

	Treatment Phase						
Visit--Visits that may be office or telephone visits are designated with (tele)	7	8 (tele)	9	10 (tele)	11	12 (tele)	13
Month (unless otherwise indicated)	6	9	12	15	18	21	24
Activity							
Informed consent document signed							
Screening number assigned							
Review of inclusion/exclusion criteria							
Patient number assigned							
Medical history							
Sitting blood pressure, pulse	X		X		X		X
Concomitant medication reporting	X	X	X	X	X	X	X
Patient education regarding injections							
Record of adverse event reporting	X	X	X	X	X	X	X
Physical examination			X				X
Height[c], weight			X				X
Assessment of habits: smoking, alcohol, caffeine			X				X
Assessment of dietary calcium							
Patient assigned to treatment group							
Laboratory Assessments							
Hematology, clinical chemistry, urinalysis	X		X				X
Serum calcium and albumin (4-6 hours postdose)	X		X		X		X
TSH, PTH (1-84)							
FSH, serum estradiol							
25-hydroxyvitamin D			X				X
24-hour urine calcium, creatinine, phosphorus	X[o]		X[o]				X[o]
PTH(1-84) postscreening, subset			X				
1,25-dihydroxyvitamin D, subset	X		X				X
Biochemical markers of bone metabolism, subset	X		X				X
Fasting triglycerides, subset	X		X				X
LY333334 antibodies			X				X
LY333334 serum concentrations/weight, subset	X		X		X		X
Technical Assessments							
Lateral thoracic and lumbar spinal x-ray films							X
AP thoracic and lumbar spinal x-ray films							
PA lumbar spine BMD	X[m]		X		X		X
Hip BMD			X				X
Total body and radial BMD, subset			X				X
Bone biopsy, subset			X[p]				X[p]
Miscellaneous							
Health-related quality of life			X				X
Medical resource utilization	X		X		X		X
Patient stipend for bone biopsy, subset			X[p]				X[p]

Table 1 – continued. Schedule of Study Events

	Treatment Phase				
Visit--Visits that may be office or telephone visits are designated with (tele)	14 (tele)	15	16 (tele)	17	Early Discontinuation
Month (unless otherwise indicated)	27	30	33	36	
Activity					
Informed consent document signed, extension				X	
Screening number assigned					
Review of inclusion/exclusion criteria					
Patient number assigned					
Medical history					
Sitting blood pressure, pulse		X		X	X
Concomitant medication reporting	X	X	X	X	X
Patient education regarding injections					
Record of adverse event reporting	X	X	X	X	X
Physical examination				X	X
Height[c], weight				X	X
Assessment of habits: smoking, alcohol, caffeine				X	X
Assessment of dietary calcium				X	X
Patient assigned to treatment group, extension				X	
Laboratory Assessments					
Hematology, clinical chemistry, urinalysis				X	X
Serum calcium and albumin (4-6 hours postdose)		X		X	X
TSH, PTH (1-84)					
FSH, serum estradiol					
25-hydroxyvitamin D				X	X
24-hour urine calcium, creatinine, phosphorus				X[o]	X
PTH(1-84) postscreening, subset				X	X
1,25-dihydroxyvitamin D, subset				X	X
Biochemical markers of bone metabolism, subset				X	X
Fasting triglycerides, subset				X	X
LY333334 antibodies				X	X
LY333334 serum concentrations/weight, subset		X		X	X
Technical Assessments					
Lateral thoracic and lumbar spinal x-ray films				X	X
AP thoracic and lumbar spinal x-ray films					
PA lumbar spine BMD				X	X
Hip BMD				X	X
Total body and radial BMD, subset				X	X
Bone biopsy, subset					X
Miscellaneous					
Health-related quality of life				X	X
Medical resource utilization		X		X	X
Patient stipend for bone biopsy, subset					X

Table 1 – concluded. Schedule of Study Events

Abbreviations: Calcium/Vit D = calcium and vitamin D run-in phase; Injection = injection run-in phase; TSH = thyroid-stimulating hormone; FSH = follicle-stimulating hormone; PTH = parathyroid hormone; BMD = bone mineral density; AP = anterior-posterior; PA = posterior-anterior.

* = Optional visit midpoint between the calcium and vitamin D run-in phase and the injection run-in phase.

[a] To be performed at Visit 0.

[b] At some study sites, a single informed consent document may be used for both the calcium and vitamin D run-in and injection run-in phases and the treatment phase of the study. At these study sites, patients would only need to sign the informed consent document at Visit 0.

[c] Height measurements will be made via [redacted] stadiometer or other suitable stadiometer at approximately the same time of day throughout the study. Three separate measurements will be made, and the average of the three measurements will be recorded on the clinical report form.

[d] To be obtained within 1 calendar month prior to randomization.

[e] Performed in hysterectomized patients, ovariohysterectomized patients, and patients younger than 45 years of age.

[f] To be performed after a minimum of 2 weeks of calcium and vitamin D supplementation and prior to randomization.

[g] A historical lateral spinal x-ray film establishing a previous vertebral fracture may be used for entry into the calcium and vitamin D run-in phase.

[h] To be obtained within 2 calendar months prior to randomization.

[i] Required if a historical lateral spinal x-ray film establishing a previous vertebral fracture was used for entry into the calcium and vitamin D run-in phase, or if study x-ray films at Visit 0 were obtained more than 2 calendar months prior to randomization.

[j] Not required if a historical lateral spinal x-ray film was used for entry into the calcium and vitamin D run-in phase.

[k] Required if not performed at Visit 0.

[l] One or two BMDs may be obtained at this visit. One hip or one lumbar spine BMD is required prior to entry into the injection run-in phase if the patient has fewer than 2 moderate vertebral fractures or has previously been taking bisphosphonates or fluorides. A total of two hip and two lumbar spine BMDs must be obtained within 1 month prior to randomization.

[m] Performed in a subset of patients.

[n] It is required that two baseline BMDs be obtained within 1 month prior to randomization.

[o] May be collected up to 1 calendar month prior to the scheduled visit.

[p] Patients who had a bone biopsy performed at the randomization visit (Visit 4) will have a bone biopsy performed at Month 12 or Month 24. The timing of the follow-up bone biopsies will be determined after enrollment closes.

1.2 Baseline Characteristics of Patients

The inclusion criteria were:

- 30-85 years of age, ambulatory, and postmenopausal for at least 5 years due to permanent cessation of ovarian function (natural, surgical, or chemotherapy-induced menopause);

- at least 1 moderate or 2 mild atraumatic vertebral fractures, and a at least 7 evaluable nonfractured vertebrae. Fractures were evaluated by a visual semiquantitative method, in which a mild vertebral fracture corresponded to a decease of about 20% in anterior, central, or posterior vertebral height (T-4 to L-4) compared to adjacent vertebrae, and a moderate fracture corresponded to a

decrease of about 25%. Patients with histories of traumatic fractures were eligible only if they also had at least 1 moderate or 2 mild atraumatic vertebral fractures and at least 7 evaluable nonfractured vertebrae. In patients with fewer than 2 moderate fractures and in patients previously treated with therapeutic doses of bisphosphonates or fluorides, the hip or lumbar spine BMD was required to be at least 1.0 standard deviation (SD) below the average BMD for young, healthy women;

- Laboratory values for serum calcium, PTH(1-84), and urine calcium were within normal limits, and the laboratory value for 25-hydroxyvitamin D was between the lower limit of normal and three times the upper limit. Normal was defined by the central laboratory reference range.

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

- fractures in areas of bone affected by diseases other than osteoporosis, metabolic bone disorders other than postmenopausal osteoporosis, or any disease which affects bone metabolism;

- carcinoma (except excised superficial lesions), urolithiasis or nephrolithiasis, sprue, inflammatory bowel disease, malabsorption syndrome, any indication of poor intestinal absorption of calcium, or significantly impaired hepatic or renal function;

- bisphosphonates, fluorides (except fluoridated water and topical dental treatments), calcitriol, calcitriol analogs or agonists, calcitonins, antacids containing calcium or aluminum, estrogens, progestins, androgens or other anabolic steroids, corticosteroids, heparins, coumarins, 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).

Women with other chronic medical conditions were included, and about 30-50% of the women enrolled had secondary conditions in the body as whole, or in the cardiovascular, digestive, musculoskeletal, or nervous groupings of conditions defined by the COSTART (Coding Symbol and Thesaurus for Adverse Reaction Terminology) dictionary.

Table 2 on this page and page 51 summarizes demographic and other characteristics of the patients at baseline.

The majority of patients were Caucasian (98.7%), nonsmokers (83.0%), and used caffeine (84.3%); 37.3% used alcoholic beverages. Patients in both LY333334 groups had mean ages about 1 year older than the patients in the placebo group (p=0.099).

Table 2 Baseline Characteristics of Patients

Characteristic	Placebo (N=544)	PTH20 (N=541)	PTH40 (N=552)	Total (N=1637)	P-Value
Age, years (mean ± SD)	68.97 ± 7.02	69.53 ± 7.07	69.86 ± 6.84	69.46 ± 6.98	0.099
Origin, n (%)					0.878
Caucasian	538 (98.9)	535 (98.9)	543 (98.4)	1616 (98.7)	
East/Southeast Asian	3 (0.6)	3 (0.6)	2 (0.4)	8 (0.5)	
Hispanic	2 (0.4)	1 (0.2)	4 (0.7)	7 (0.4)	
African Descent	1 (0.2)	0	1 (0.2)	2 (0.1)	
Western Asian	0	1 (0.2)	1 (0.2)	2 (0.1)	
Other	0	1 (0.2)	1 (0.2)	2 (0.1)	
Body mass index (kg/m^2) (mean ± SD)[a]	26.61 ± 4.77	26.71 ± 4.20	26.54 ± 4.23	26.62 ± 4.41	0.814
Height (cm) (mean ± SD)[b]	157.37 ± 6.34	156.95 ± 6.53	157.37 ± 6.75	157.23 ± 6.54	0.490
Weight (kg) (mean ± SD)[c]	65.87 ± 12.56	65.75 ± 11.22	65.77 ± 11.42	65.80 ± 11.74	0.983
Current smoker, n (% Yes)	102 (18.8)	89 (16.5)	88 (15.9)	279 (17.0)	0.421
Alcohol, n (% Yes)	198 (36.4)	203 (37.5)	209 (37.9)	610 (37.3)	0.872
Caffeine, n (% Yes)	456 (84.3)	460 (85.2)	456 (83.4)	1372 (84.3)	0.712
Previous osteoporosis drug user, n (% Yes)	81 (14.9)	84 (15.5)	72 (13.0)	237 (14.5)	0.479
Dietary calcium (g/day) (mean ± SD)[d]	0.76 ± 0.44	0.77 ± 0.44	0.76 ± 0.45	0.76 ± 0.44	0.937
Years postmenopausal (mean ± SD)[e]	20.94 ± 8.50	21.46 ± 8.67	21.81 ± 8.20	21.41 ± 8.46	0.273
Hysterectomy status, n (% Yes)	129 (23.8)	125 (23.1)	119 (21.6)	373 (22.9)	0.682
Hysterectomy type					0.511
2 ovaries removed	61 (47.3)	57 (45.6)	51 (42.9)	169 (45.3)	
0, 1 ovary removed	57 (44.2)	51 (40.8)	58 (48.7)	166 (44.5)	
Unknown	11 (8.5)	17 (13.6)	10 (8.4)	38 (10.2)	

Table 2-concluded. Baseline Characteristics of Patients

Characteristic	Placebo (N=544)	PTH20 (N=541)	PTH40 (N=552)	Total (N=1637)	P-Value
Baseline vertebral BMD (mean ± SD)[f]	0.82 ± 0.17	0.82 ± 0.17	0.82 ± 0.17	0.82 ± 0.17	> 0.990
Baseline number of vertebral fractures, n (%)[g]					0.522
0	54 (10.4)	45 (8.8)	54 (10.1)	153 (9.8)	
1	144 (27.8)	159 (31.1)	169 (31.6)	472 (30.2)	
2	128 (24.7)	128 (25.0)	125 (23.4)	381 (24.3)	
3	75 (14.5)	67 (13.1)	81 (15.1)	223 (14.2)	
4	59 (11.4)	49 (9.6)	45 (8.4)	153 (9.8)	
5	28 (5.4)	31 (6.1)	21 (3.9)	80 (5.1)	
6	13 (2.5)	20 (3.9)	25 (4.7)	58 (3.7)	
7	6 (1.2)	7 (1.4)	10 (1.9)	23 (1.5)	
8	9 (1.7)	5 (1.0)	3 (0.6)	17 (1.1)	
9	1 (0.2)	0	2 (0.4)	3 (0.2)	
10	1 (0.2)	1 (0.2)	0	2 (0.1)	
Body Surface Area (mean ± SD)	1.69 ± 0.17	1.69 ± 0.16	1.69 ± 0.16	1.69 ± 0.16	0.969

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

[a] 28 patients were excluded from the body mass index analysis because of missing values.

[b] 26 patients were excluded from the height analysis because of missing values.

[c] 16 patients were excluded from the weight analysis because of missing values.

[d] 95 patients were excluded from the dietary calcium analysis because of missing values.

[e] 189 patients were excluded from the years postmenopausal analysis because of missing values.

[f] 55 patients were excluded from the baseline vertebral BMD analysis because of missing values.

[g] 72 patients were excluded from the baseline number of vertebral fracture analysis because of missing values.

1.3 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 75% of the study drug . The percentages of patients who took at least 50% of the study drug were 97.8% in the placebo group, 95.9% in the 20 mcg group, and 95.3% in the 40 mcg group.

Table 3 on page 52 shows the numbers of patients by treatment group and duration of treatment. Most patients were treated for 18-23 months, including 70.6% in the placebo group, 69.6% in the 20 mcg group, and 65.6% in the 40 mcg group. The patient-years of treatment were 798.4 for placebo, 779.2 for 20 mcg, and 774.2 for 40 mcg.

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

	Number of Months Completed									
Number of Patients	0 to 2	3 to 5	6 to 8	9 to 11	12 to 14	15 to 17	18 to 20	21 to 23	24 to 26	Total
Placebo	18	23	16	7	15	79	257	127	2	544
PTH20	24	24	14	16	10	76	250	125	0	539
PTH40	34	27	19	15	21	72	235	127	2	552
Total	76	74	49	38	46	227	742	379	4	1635[a]

Abbreviations: PTH20 = LY333334 20 µg/day; PTH40 = LY333334 40 µg/day.

[a] Two of the 1,637 patients randomly assigned to treatment are not included in this table: 1) the date of last dose was unreported; 2) the date of last dose was reported in error (reported as 11 December 1999, but actually 11 December 1998). Both of these patients were randomly assigned to LY333334 20 µg/day.

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1.4 Patient Disposition

A total of 9347 women were screened for the study, of whom 1637 (17.5%) were enrolled and randomized to placebo (n=544), 20 mcg (n=541), or 40 mcg (n=552); all patients received 1000 mg/day of calcium and 400-1200 IU/day of vitamin D. Of the 7710 women excluded from the study, 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, the reason for 1145 (80.8%) was that they 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 $\geq$1 vertebral fractures on x-ray.

Table 4 on page 54 shows the reasons for study discontinuation for the 1637 patients who were randomized. Two reasons for discontinuation, sponsor's decision and adverse event (AE), showed statistically significant differences between treatment groups. Due to Lilly's decision to stop the study, the most common reason for discontinuation was sponsor's decision. In total, 1295 (79.1%) of the patients discontinued for this reason, including 447 (82.2%) in the placebo group, 433 (80.0%) in the 20 mcg group, and 415 (75.2%) in the 40 mcg group (p=0.014). A total of 126 (7.7%) patients discontinued due to AEs, including 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). There were no statistically significant differences or trends between treatment groups for other reasons for discontinuation.

Patients with an increase in clinical laboratory serum calcium or urinary calcium above the upper limit of normal may have had the calcium dose reduced or stopped, or the LY333334 dose reduced by half or stopped. Any patient with side effects likely attributable to study drug such as nausea or dizziness may have had the LY333334 dose reduced by half or discontinued. Of the 1637 randomized patients, 113 (6.9%) had the dose reduced because of hypercalcemia and/or hypercalciuria and 46 (2.8%) had the dose of reduced because of nausea, dizziness, or other reasons. The numbers of patients with dosage reductions by treatment group were: 11 (2.0%) in the placebo group, 43 (7.9%) in the 20 mcg group, and 105 (19.0%) in the 40 mcg group (p<0.001).

Table 4 Reasons for Patient Discontinuation

Reasons Discontinued	PLACEBO (N=544) n (%)	PTH20 (N=541) n (%)	PTH40 (N=552) n (%)	TOTAL (N=1637) n (%)	P-VALUES# P_PCHI	P_MHCHI	_EXACT_
Sponsor's decision	447(82.2)	433(80.0)	415(75.2)	1295(79.1)	0.014	0.004	0.015
Adverse event	32(5.9)	35(6.5)	59(10.7)	126(7.7)	0.005	0.003	0.006
Patient decision	32(5.9)	45(8.3)	40(7.2)	117(7.1)	0.296	0.384	0.296
Exclusion medication	7(1.3)	6(1.1)	4(0.7)	17(1.0)	0.644	0.358	0.622
Death	4(0.7)	6(1.1)	6(1.1)	16(1.0)	0.781	0.555	0.818
Significant lab values	4(0.7)	2(0.4)	8(1.4)	14(0.9)	0.143	0.197	0.165
Protocol entry criteria not met	4(0.7)	4(0.7)	2(0.4)	10(0.6)	0.655	0.427	0.677
Unable to contact patient (lost to follow-up)	3(0.6)	2(0.4)	5(0.9)	10(0.6)	0.512	0.450	0.625
Patient moved	2(0.4)	4(0.7)	3(0.5)	9(0.5)	0.710	0.696	0.719
Physician decision	2(0.4)	2(0.4)	5(0.9)	9(0.5)	0.381	0.227	0.529
Lack of efficacy, progressive disease	5(0.9)	0(0.0)	2(0.4)	7(0.4)	0.065	0.160	0.058
Noncompliance	1(0.2)	1(0.2)	2(0.4)	4(0.2)	0.788	0.549	1.000
Other	1(0.2)	1(0.2)	1(0.2)	3(0.2)	1.000	0.992	1.000

P-VALUES ARE FROM THE FOLLOWING TESTS:
P_PCHI: PEARSON'S CHI SQUARE TEST
P_MHCHI: MANTEL-HAENSZEL TEST FOR CORRELATION WITH DOSE
EXACT: FISHER'S EXACT TEST

RMP.B3DSGHAC.SASPGM(RDS002CT) PTH-CTG 29APR00
Data from RMP.SAS.B3DM.MCGHACSW.SUBMISS

1.5 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."

1.5.1 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 315 (19.2%) patients reported at least 1 SAE: 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).

1.5.1.1 Deaths

Sixteen (1.0%) patients died during the study: 4 (0.7%) in the placebo group, 6 (1.1%) in the 20 mcg group, and 6 (1.1%) in the 40 mcg group (p=0.781). The listed 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 pneumonia, pancreatitis, death not otherwise specified; and suicide; in the 40 mcg group, cerebrovascular accident, iron deficiency anemia, pneumonia (n=2), bladder neoplasm, carcinoma of lung. None of the

deaths appeared to be related to study drug. For further information see Table 2 and Figure 1 on pages 31-33.

1.5.1.2 Any Serious Adverse Event

There were 197 different SAEs (i.e., SAE terms). Breast cancer, hernia, and pain were the only SAEs with statistically significant differences or trends between treatment groups. For breast cancer, there were: 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). For hernia, there were: none in the placebo group, 5 (0.9%) in the 20 mcg group, and 4 (0.7%) in the 40 mcg group (p=0.095). For pain, there were: 2 (0.4%) in the placebo group, 6 (1.1%) in the 20 mcg group, and 1 (0.2%) in the 40 mcg group (p=0.091). Interpretation of these findings is not clear.

1.5.2 Discontinuations Due to Adverse Events

A total of 126 (7.7%) patients discontinued the study due to AEs: 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). 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).

1.5.3 Adverse Events of Any Severity

A total of 1396 (85.3%) patients reported at least 1 AE: 437 (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). There was a statistically significant decrease in the frequency of patients with at least 1 AE in the 20 mcg group compared to the placebo group (p=0.047), which was mainly due to a decrease in back pain. There was not a statistically significant difference or trend between the 40 mcg group and the placebo group; although there was a decrease in back pain, there were offsetting increases in nausea and headache. 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 (23.2%), back pain (18.4%), surgical procedure (16.2%), accidental injury (12.9%), nausea (11.6%), headache (9.8%), arthralgia (9.4%), abdominal pain (9.3%), flu syndrome (8.8%), and asthenia (8.7%). Of these, there were statistically significant differences or trends between treatment groups for back pain, nausea, and headache (see below).

Table 5 on page 58 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. There was a decrease in back pain in both LY333334 groups compared to the placebo group: 123 (22.6%) in the placebo group 91 (16.8%) in the 20 mcg group, and 87 (15.8%) (p=0.007). Nausea and headache occurred at similar frequency in the placebo and 20 mcg groups but were increased in the 40 mcg group. For nausea, there 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 headache, there 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). These findings are substantial and supported by other information about the effects of LY333334.

Eight other shown AEs in Table 5 were increased in the LY333334 groups compared to the placebo group: leg cramps, cyst, nail disorder, injection site reaction, tooth caries, emphysema, hypokalemia, and skin benign neoplasm. Three AEs were decreased in the LY333334 groups compared to the placebo group: diabetes mellitus, epistaxis, and breast carcinoma. Two AEs showed inconsistency in the LY333334 groups compared to the placebo group: syncope and dry eyes. The findings for these 8 AEs are discussed further in the review of AEs by body system (see Section 1.5.4).

A total of 450 different Coding Symbol and Thesaurus for Adverse Reaction Terminology (COSTART) terms were reported by at least 1 patient. Of these, the 213 AE terms that were reported by at least 5 patients each were analyzed for treatment group differences. Of the 213 AE terms analyzed, 188 (88.3%) showed no statistical differences between groups at the alpha = 0.10 level. The other 25 AE terms did show statistical differences between groups. Table 4, discussed above, presents findings for the 16 of these 25 AE terms that were reported by at least 1% of patients in any of the 3 treatment groups. Of the other 9 AE terms, 4 were increased, 4 were decreased, and 1 showed inconsistency in the LY333334 groups compared to placebo. The terms with an increase in the LY333334 groups were injection site pain, congestive heart failure, ataxia, and urinary urgency. Those with a decrease were chills, cerebrovascular disorder, iron deficiency anemia, and cataract (not otherwise specified). Bradycardia showed inconsistency. The findings for these 9 AE terms are discussed further in the review of AEs by body system (see Section 1.5.4).

For accidental injury, the numbers of patients 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). This finding was just short of meeting the p-value criterion for Table 5.

Table 5 Adverse Events in at Least 1% of Patients in Any Treatment Group With Statistical Differences Between Groups at alpha = 0.10

	Placebo N=544		PTH20 N=541		PTH40 N=552		Total N=1637			PTH20	PTH40	PTH20
Event Classification	n	%	n	%	n	%	n	%	Overall	vs Pbo	vs Pbo	vs PTH40
Back Pain	123	(22.6)	91	(16.8)	87	(15.8)	301	(18.4)	0.007	0.017	0.004	0.635
Nausea	41	(7.5)	51	(9.4)	98	(17.8)	190	(11.6)	<0.001	0.264	<0.001	<0.001
Headache	45	(8.3)	44	(8.1)	72	(13.0)	161	(9.8)	0.008	0.934	0.011	0.008
Leg Cramps	6	(1.1)	17	(3.1)	13	(2.4)	36	(2.2)	0.069	0.020	0.112	0.426
Cyst	5	(0.9)	9	(1.7)	17	(3.1)	31	(1.9)	0.029	0.277	0.011	0.125
Syncope	9	(1.7)	17	(3.1)	4	(0.7)	30	(1.8)	0.011	0.109	0.155	0.004
Nail Disorder	2	(0.4)	7	(1.3)	17	(3.1)	26	(1.6)	0.001	0.093	0.001	0.044
Diabetes Mellitus	8	(1.5)	2	(0.4)	2	(0.4)	12	(0.7)	0.048	0.058	0.054	a
Epistaxis	7	(1.3)	4	(0.7)	1	(0.2)	12	(0.7)	0.100	0.368	0.032	0.172
Injection Site Reaction	1	(0.2)	2	(0.4)	9	(1.6)	12	(0.7)	0.009	a	0.012	0.037
Tooth Caries	1	(0.2)	7	(1.3)	2	(0.4)	10	(0.6)	0.042	0.033	a	0.088
Breast Carcinoma	7	(1.3)	1	(0.2)	1	(0.2)	9	(0.5)	0.017	0.034	0.032	a
Dry Eyes	3	(0.6)	0	(0.0)	6	(1.1)	9	(0.5)	0.052	a	0.326	0.015
Emphysema	0	(0.0)	2	(0.4)	7	(1.3)	9	(0.5)	0.014	a	0.008	0.100
Hypokalemia	1	(0.2)	6	(1.1)	1	(0.2)	8	(0.5)	0.041	0.057	a	0.055
Skin Benign Neoplasm	1	(0.2)	1	(0.2)	6	(1.1)	8	(0.5)	0.047	a	0.061	0.062

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.

[a] Combined incidence rate less than 5 and Pearson's chi-square p-value not calculated.

1.5.4 Adverse Events by Body System

The body as a whole showed a statistically significant decrease in the proportion of patients reporting at least 1 AE in the 20 mcg group compared to the placebo group, mainly due to the previously discussed reduction in back pain. The digestive system showed a statistically significant increase in the proportion of patients reporting at least 1 AE in the 40 mcg group compared to the placebo group, mainly due to the previously discussed increase in nausea. There were no statistically significant differences or trends between treatment groups in the proportion of patients with at least 1 AE in any of the other body systems.

1.5.4.1 Body as a Whole

Of the 12 body systems, body as a whole had the highest number of patients reporting at least 1 AE: 1064 (65.0%) of the 1637 patients in the study. The numbers of patients in the 3 treatment groups reporting at least 1 AE were: 373 (68.6%) in the placebo group, 324 (59.9%) in the 20 mcg group, and 367 (66.5%) in the 40 mcg group (p=0.007). The difference between the placebo group and 20 mcg group was statistically significant (p=0.003); the difference between the placebo group and 40 mcg group was not (p=0.462).

In the 20 mcg group compared to the placebo group, there were decreases in back pain, accidental injury, and chills. Back pain and accidental injury are discussed in Section 1.5.3 above. For chills, the numbers of patients were 5 (0.9%) in the placebo group, none in the 20 mcg group, and 2 (0.4%) in the 40 mcg group (p=0.065). Interpretation of this finding is not clear.

In the 40 mcg group compared to the placebo group, there were also a decrease in back pain, but there was less decrease in accidental injury and chills that in the 20 mcg group, and there were statistically significant increases or trends in headache, injection site reaction or pain, and cyst.

The increases in headache and injection site reaction or in the 40 mcg group appear to be real effects of LY333334. Headache is discussed in Section 1.5.3 above. For injection site reaction, the numbers of patients were: 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). For injection site pain, the numbers of patients were: 1(0.2%) in the placebo group, none in the 20 mcg group, and 4 (0.7%) in the 40 mcg group (p=0.078).

For cyst, the numbers of patients were: 5 (0.9%) in the placebo group, 9 (1.7%) in the 20 mcg group, and 17 (3.1%) in the 40 mcg group (p=0.029). The specific types of cysts grouped under the general term cyst were: 5 sebaceous cysts, 4 ganglion cysts, 3 cutaneous cysts, 3 hepatic cysts, 3 ovarian cysts, 2 popliteal cysts, 2 renal cysts, and 1 each of benign breast cyst, cyst drainage, vaginal wall cyst abscess, brain cyst, mucoid cyst, wound seroma, conjunctival cyst, nasal cyst, and cyst on upper lip. Although a biologically plausible explanation for this finding is not apparent, the statistical association is moderately strong and there is some evidence of dose-response.

There were no other AEs in the body as a whole with statistically significant differences or trends between treatment groups.

1.5.4.2 Cardiovascular System

The numbers of patients reporting at least one AE in the cardiovascular system were: 149 (27.4%) the placebo group, 144 (26.6%) the 20 mcg group, and 147 (26.6%) in the 40 mcg group (p=0.947).

Syncope was potentially important because the clinical pharmacology studies of LY333334 showed hemodynamic effects, including orthostatic hypotension. 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). There were no statistically significant differences or trends between either the 20 mcg or 40 mcg group and the placebo group, although the difference between the 20 mcg group and the 40 mcg group was statistically significant (p=0.004). Syncope is discussed further in section 1.5.5.8 below.

Three other AEs showed trends between treatment groups. For bradycardia, the numbers of patients were: 3 (0.6%) in the placebo group, none in the 20 mcg group, and 5 (0.9%) in the 40 mcg group (p=0.097). For congestive heart failure, the numbers of patients were: none in the placebo group, 2 (0.4%) in the 20 mcg group, and 5 (0.9%) in the 40 mcg group (p=0.069). For cerebrovascular disorder, the numbers of patients were: 4 (0.7%) in the placebo group, 1 (0.2%) in the 20 mcg group, and none in the 40 mcg group (p=0.072). Before randomization, there was a higher prevalence of myocardial ischemia in the LY333334 groups compared to the placebo group: none in the placebo group, 3 (0.6%) in the 20 mcg group, and 6 (1.1%) in the 40 mcg group (p=0.052). Also, there was also a lower prevalence of cerebrovascular disease in the LY333334 groups compared to the placebo group: 5 (0.9%) in the

placebo group, 1 (0.2%) in the 20 mcg group, and 1 (0.2%) in the 40 mcg group (p=0.099). Thus, the LY333334 groups may have been at higher risk that the placebo group for cardiac disease and lower risk of cerebrovascular disease, due to the baseline imbalance. However, the cardiac and cerebrovascular AEs occurred in too few patients to draw firm conclusions.

There were no other AEs in the cardiovascular system with statistically significant differences or trends between treatment groups.

1.5.4.3 Digestive System

The numbers of patients reporting at least 1 AE in the digestive system were: 171 (31.4%) in the placebo group, 169 (31.2%) in the 20 mcg group, and 207 (37.5%) in the 40 mcg group (0.044). The difference between the placebo group and the 40 mcg group was statistically significant (p=0.035); the difference between the placebo group and the 20 mcg group was not (p=0.945).

Nausea in the 40 mcg group accounted for the statistically significant finding above. For nausea, the numbers of patients 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, the numbers of patients 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). Nausea appears to have been a real effect of LY333334 at the 40 mcg dose.

There were statistically significant differences between treatment groups for tooth caries. The numbers of patients were: 1 (0.2%) in the placebo group, 7 (1.3%) in the 20 mcg group, and 2 (0.4%) in the 40 mcg group (p=0.042). Interpretation of this finding is not clear.

There were no other AEs in the digestive system with statistically significant differences or trends between treatment groups.

1.5.4.4 Endocrine System

The numbers of patients reporting at least 1 AE in the endocrine system were: 14 (2.6%) in the placebo group, 8 (1.5%) in the 20 mcg group, and 10 (1.8%) in the 40 mcg group (p=0.410).

For diabetes mellitus, the numbers of patients were: 8 (1.5%) in the placebo group, 2 (0.4%) in the 20 mcg group, and 2 (0.4%) in the 40 mcg group (p=0.048). Interpretation of this finding is not clear.

There were no other AEs in the endocrine system with statistically significant differences or trends between treatment groups.

1.5.4.5 Hemic and Lymphatic System

The numbers of patients reporting at least 1 AE in the hemic and lymphatic system were: 45 (8.3%) in the placebo group, 39 (7.2%) in the 20 mcg group, and 40 (7.2%) in the 40 mcg group (p=0.753).

There were no AEs in the hemic and lymphatic system with statistically significant differences or trends between treatment groups.

1.5.4.6 Metabolic and Nutritional Disorders

The numbers of patients reporting at least 1 AE in the area of metabolic and nutritional disorders were: 84 (15.4%) in the placebo group, 72 (13.3%) in the 20 mcg group, and 66 (12.0%) in the 40 mcg group (p=0.237).

For hypokalemia, the numbers of patients were: 1 (0.2%) in the placebo group, 6 (1.1%) in the 20 mcg group, and 1 (0.2%) in the 40 mcg group (p=0.041). For iron deficiency anemia, the numbers of patients were: 5 (0.9%) in the placebo group, none in the 20 mcg group, and 2 (0.4%) in the 40 mcg group (p=0.065). Interpretation of these findings is not clear.

There were no other AEs in the metabolic and nutritional disorders with statistically significant differences or trends between treatment groups.

1.5.4.7 Musculoskeletal System

The numbers of patients reporting at least 1 AE in the musculoskeletal system were: 145 (26.7%) in the placebo group, 147 (27.2%) in the 20 mcg group, and 149 (27.0%) in the 40 mcg group (p=0.981).

For leg cramps, the numbers of patients 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 cramps, the numbers of patients were: 2 (0.4%) in the placebo group, 2 (0.4%) in the 20 mcg group, and none in the 40 mcg group. Leg cramps are discussed further in Section 1.5.5.7 below.

There were no other AEs in the musculoskeletal system with statistically significant differences or trends between treatment groups.

1.5.4.8 Nervous System

The numbers of patients reporting at least 1 AE in the nervous system were: 144 (26.5%) in the placebo group, 158 (29.2%) in the 20 mcg group, and 167 (30.3%) in the 40 mcg group (p=0.361).

For dizziness, the numbers of patients 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, the numbers of patients 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). It is possible that LY333334 may increase the comparatively rare occurrence of severe dizziness without a statistically significant increase or trend in the frequency of dizziness in general.

For ataxia, the numbers of patients were: none in the placebo group, 2 (0.4%) in the 20 mcg group, and 5 (0.9%) in the 40 mcg group (p=0.069). Interpretation of this finding is not clear.

There were no other AEs in the nervous system with statistically significant differences or trends between treatment groups.

1.5.4.9 Respiratory System

The numbers of patients reporting at least 1 AE in the respiratory system were: 170 (31.3%) in the placebo group, 161 (29.8%) in the 20 mcg group, and 153 (27.7%) in the 40 mcg group (p=0.437).

For emphysema, the numbers of patients were: none in the placebo group, 2 (0.4%) in the 20 mcg group, and 7 (1.3%) in the 40 mcg group (p=0.014). There were 11 patients in the 40 mcg group with emphysema at randomization compared to 5 in the placebo group, and 4 of the 9 emphysema events during the trial were in patients with preexisting disease.

For epistaxis, the numbers of patients were: 7 (1.3%) in the placebo group, 4 (0.7%) in the 20 mcg group, and 1 (0.2%) in the 40 mcg group (p=0.100). Interpretation of this finding is not clear.

There were no other AEs in the respiratory system with statistically significant differences or trends between treatment groups.

1.5.4.10 Skin and Appendages

The numbers of patients reporting at least 1 AE in the skin and appendages were: 94 (17.3%) in the placebo group, 96 (17.7%) in the 20 mcg group, and 117 (21.2%) in the 40 mcg group (p=0.192).

For nail disorder, the numbers of patients were 2 (0.4%) in the placebo group, 7 (1.3%) in the 20 mcg group, and 17 (3.1%) in the 40 mcg group (p=0.001). The specific terms grouped under the general term nail disorder included nail fungus, brittle nails, ingrown nails, and paronychia. Although a biologically plausible explanation for this finding is not apparent, the statistical association is strong and there is evidence of dose-response.

For skin benign neoplasm, the numbers of patients were: 1 (0.2%) in the placebo group, 1 (0.2%) in the 20 mcg group, and 6 (1.1%) in the 40 mcg group (p=0.047). The specific AE terms under the general term skin benign neoplasm included nevi and verrucae. Interpretation of this finding is not clear.

There were no other AEs in the skin and appendages with statistically significant differences or trends between treatment groups.

1.5.4.11 Special Senses

The numbers of patients reporting at least 1 AE in the special senses were: 71 (13.1%) in the placebo group, 67 (12.4%) in the 20 mcg group, and 89 (16.1%) in the 40 mcg group (p=0.161).

For dry eyes, the numbers of patients were: 3 (0.6%) in the placebo group, none in the 20 mcg group, and 6 (1.1%) in the 40 mcg group (p=0.052). For cataract nos, the numbers of patients were: 5 (0.9%) in the placebo group, none in the 20 mcg group, and 2 (0.4%) in the 40 mcg group (p=0.065). Interpretation of these findings is not clear.

There were no other AEs in the special senses with statistically significant differences or trends between treatment groups.

1.5.4.12 Urogenital System

The numbers of patients reporting at least 1 AE in the urogenital system were: 99 (18.2%) in the placebo group, 96 (17.7%) in the 20 mcg group, and 96 (17.4%) in the 40 mcg group (p=0.940).

For breast cancer, the numbers of patients were: 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). For urinary urgency, the numbers of patients were: none in the placebo group, 1 (0.2%) in the 20 mcg group, and 4 (0.7%) in the 40 mcg group (p=0.078). Interpretation of these findings is not clear.

There were no other AEs in the urogenital system with statistically significant differences or trends between treatment groups.

15.5 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 the study, related laboratory findings, or other clinical or non-clinical experience.

1.5.5.1 Back Pain

The numbers of patients reporting 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, the numbers of patients 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 were consistent with the decreased incidence and severity of vertebral fractures in the LY333334 groups compared to the placebo group.

1.5.5.2 Accidental Injury

The numbers of patients reporting 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, the numbers were: 13 (2.4%) in the placebo group, 4 (0.7%) in the 20 mcg group, and 6 (1.1%) n the 40 mcg group (p=0.051). Most of the specific terms grouped under the general term accidental injury described falls and fractures. Because LY333334 decreased vertebral and nonvertebral fractures, and back pain, there is some plausibility in the trend toward a decrease in severe accidental injury. However, more information is needed from other clinical trials to determine whether this is a consistent finding.

1.5.5.3 Nausea

The numbers of patients reporting 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, the numbers of patients 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). For study discontinuation due to nausea, the numbers of patients were: 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).

Nausea occurred earlier in the LY333334 groups that in the placebo group (p<0.001). These findings mainly reflected an increase in nausea during the first few weeks of the study in the 40 mcg group although there was also a small increase in the 20 mcg group.

However, there were no statistically significant differences or trends between treatment groups for nausea as a serious AE, for AEs indicating serious upper GI pathology (such as esophagitis, gastritis, duodenal ulcer, stomach ulcer, or peptic ulcer), or for the use of medications indicating upper GI pathology (such as H2-antagonists or proton pump inhibitors).

Thus, LY333334 appears to have increased the frequency of nausea that was not medically serious. The increase was mainly in the 40 mcg group. A dose-dependent increase in nausea was also seen in the Phase 1 and 2 studies, where LY333334 doses from 5-100 mcg were given.

1.5.5.4 Headache

The numbers of patients reporting 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, the numbers of patients 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). Headache occurred earlier in the LY333334 groups than the placebo group (p=0.003). LY333334 appears to have increased the frequency of headache that was not severe. The increase was only in the 40 mcg group. A dose-dependent increase in headache was also seen in the Phase 1 and 2 studies, where LY333334 doses from 5-100 mcg were given.

1.5.5.5 Gout and Arthralgia

Gout and arthralgia were reviewed because there were statistically significant increases in uric acid in the LY333334 groups compared to the placebo group. At months 1, 6, and 12, uric acid was increased 36.3-54.0 mcmol/L in the 20 mcg group compared to the placebo group (p<0.01), and 55.0-69.5 mcmol/L in the 40 mcg group compared to the placebo group (p<0.01).

The numbers of patients reporting gout were: 3 (0.6%) in the placebo group, 1 (0.2%) patient in the 20 mcg group, and 2 (0.4%) in the 40 mcg group (p=0.607). For arthralgia, the numbers of patients were: 49 (9.0%) in the placebo group, 56 (10.4%) in the 20 mcg group, and 49 (8.9%) in the 40 mcg group (p=0.654). For severe arthralgia, the numbers of patients were: 7 (1.3%) in the placebo group, 5 (0.9%) in the 20 mcg group, and 7 (1.3%) in the 40 mcg group (p=0.821). LY333334 does not appear to have increased the frequency of gout or arthralgia.

1.5.5.6 Dizziness and Vertigo

Dizziness and vertigo were reviewed because the clinical pharmacology studies of LY333334 showed hemodynamic effects, including orthostatic hypotension. In study GHAC, patients were required to stay at the study sites for at least 3 hours after the first dose of study drug, as a precaution.

The numbers of patients reporting 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 dizziness (p=0.144). For severe dizziness, the numbers of patients 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). For vertigo, the numbers of patients 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 no statistically significant differences or trends between treatment groups for dizziness or vertigo as serious AEs, or for study discontinuation due to dizziness or vertigo. Also, dizziness or vertigo due to the hemodynamic effects of LY333334 might be expected to increase the risk of accidental injury and nonvertebral fractures, whereas these events were decreased in the LY333334 groups compared to the placebo group.

Interpretation of the finding for severe dizziness is not clear. It is possible that LY33333 may have increased frequency of symptomatically severe dizziness, without increasing the frequency of dizziness as a serious AE, as a reason for study discontinuation, or as a cause of accidental injury.

1.5.5.7 Leg Cramps

There was a trend toward an increase in the reporting of leg cramps for the LY333334 groups compared to the placebo group. The numbers of patients: 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 the numbers of patients were: 2 (0.4%) in the placebo group, 2 (0.4%) in the

20 mcg group, and none in the 40 mcg group. Data from other clinical trials support the conclusion that LY333334 increases the frequency of mild or moderate leg cramps in women.

There was a decrease in serum magnesium of about 6.7-11.1% in the LY333334 groups compared to the placebo group, but this did not appear to correlate with the leg cramps.

1.5.5.8 Syncope

Syncope was reviewed because of the hemodynamic effects of LY333334, which included orthostatic hypotension.

The numbers of patients reporting 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 was due to the decrease in syncope in the 40 mcg group compared to the 20 mcg group, rather than to the differences between the LY333334 groups and the placebo group.

Table 6 on pages 70-72 provides information about the patients with syncope AEs. No patterns were found in the specific AE terms or other associated AEs which suggested that LY333334 caused the events.

The numbers of patients with syncope as a serious AE were: 4 (0.7%) in the placebo group, 5. (0.9%) in the 20 mcg group, and 1 (0.2%) in the 40 mcg group (p=0.260). One patient in the 20 mcg group was discontinued from the study due to syncope; the investigator later concluded that the event was not related to study drug. There were no other discontinuations due to syncope. The numbers of patients for whom syncope had a serious outcome were: 4 in the placebo group, 5 in the 20 mcg group, and 1 in the 40 mcg group. Injury occurred in 2 patients in the placebo group, 1 in the 20 mcg group, and none in the 40 mcg group.

Eleven of the syncope episodes had identifiable causes not related to study drug: 3 in the placebo group, 7 in the 20 mcg group, and 1 in the 40 mcg group. In the placebo group, 1 episode appeared related to extreme heat, 1 to a vasovagal reaction immediately after study drug injection, and 1 to a transient ischemic attack. In the 20 mcg group, 2 episodes appeared related to phlebotomy or surgery, 2 to preexisting cardiac disease, 1 to epilepsy, 1 to the use of sublingual nitroglycerin, and 1 to preexisting anemia and podiatric treatment. In the 40 mcg group, 1episode appeared related to the syndrome of inappropriate antidiuretic hormone secondary to new diuretic treatment. The remaining episodes did not have readily apparent causes, according to the investigators.

The episodes of syncope did not appear to be related to electrolyte abnormalities. Serum magnesium was low only 1 patient, who had a level of 0.50 mmol/L (normal: 0.60-1.25 mmol/L). Serum calcium was high in 3 patients and low in 3 patients; the highest and lowest levels in these patients were 2.92 mmol/L and 1.97 mmol/L, respectively (normal: 2.05-2.64 mmol/L). Serum potassium was low in only 1 patient, who had a level of 3.2 mmol/L (normal range 3.3-5.5 mmol/L). Low serum sodium due to the syndrome of inappropriate antidiuretic hormone was found in 1 patient, who had a value of 124 mmol/L (normal range 134-150 mmol/L).

The first occurrence of syncope ranged from 1 day to over 18 months after randomization, and the events were evenly distributed across that time. A Kaplan-Meier plot showed statistically significant differences between treatment groups (log-rank p=0.012, Wilcoxon p=0.011). The rates of occurrence were low in all 3 groups, and the 3 curves did not separate in a clear way. The frequency of episodes in the placebo group was constant through the study, reflecting the underlying occurrence of syncope in the patient population. The 20 mcg group showed an increase in episodes after about 4 months that continued through the study. The frequency of episodes was consistently lower over time in the 40 mcg group than in the placebo and the 20 mcg groups.

If LY333334 increased the risk of syncope by acute hemodynamic effects, the increased risk should have been clearest soon after treatment began, and should have shown a dose-response. Also, if LY333334 increased the risk of syncope by chronic effects, the increased risk should have persisted as long as treatment continued. Neither an acute nor chronic causal effect seems plausible, because the syncope episodes occurred at about the same rate over time, and all but 2 of the patients in the LY333334 groups who had syncope had only 1 episode, even though they continued treatment.

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Table 6 Syncope Adverse Events

Patient Number	Tx	Severity	Serious?	Onset (months)	Duration (days)	Actual Term	Other Concurrent Adverse Events	Electrolyte Abnormalities
Placebo Group								
008-7171	0	Moderate	Yes	0.5	2	Syncope	Heat related	—
019-7459	0	Severe	Yes	12.0	1	Syncope	Vasovagal injection reaction	—
040-1093	0	Mild	No	18.2	1	Loss Of Consciousness Due To Fall	—	—
168-2507	0	Mild	No	16.2	1	Loss Of Consciousness	—	—
282-1788	0	Mild	No	12.2	1	Faint	—	—
740-2195	0	Moderate	Yes	2.6	1	Syncope	Possible transient ischemic attack	—
747-5143	0	Severe	Yes	2.9	1	Fainted	—	—
853-4420	0	Mild	No	13.7	1	Fainting Spell	—	—

Abbreviations: Tx = Treatment group (0 = placebo, 20 = LY333334 20 µg/day, 40 = LY333334 40 µg/day); L = low; H = high.

Table 6-continued. Syncope Adverse Events

Patient Number	Tx	Severity	Serious?	Onset (months)	Duration (days)	Actual Term	Apparent Cause	Electrolyte Abnormalities
LY333334 20-µg/day Treatment Group								
015-7338	20	Mild	No	19.2	12	Fainting Spells	—	—
019-7451	20	Moderate	No	5.1	1	Fainting Spells	—	—
043-0669	20	Mild	No	0.1	24	Fainting	—	K, Mg (L)
143-2589	20	Moderate	No	2.7d	1	Collapse Vasomotor	—	—
148-3857	20	Mild	No	19.4	1	Syncope	—	—
150-3873	20	Mild	No	9.2	1	Syncope	—	—
150-3873	20	Mild	No	20.7	1	Syncope	—	—
157-2146	20	Moderate	Yes	3.3	1	Loss Of Consciousness	Epilepsy	
282-1669	20	Severe	Yes	16.7	1	Syncope	Preexisting cardiac insufficiency	Ca (L)
507-3047	20	Mild	No	2.5	1	Syncope	—	—
507-3047	20	Mild	No	17.0	1	Syncope	Vasovagal reaction to phlebotomy	—
705-5669	20	Mild	No	8.9	1	Syncope	—	—
740-2183	20	Moderate	Yes	0.2	1	Syncope	Administration of sublingual nitroglycerin	Ca (L)
743-2717	20	Mild	Yes	3.7	1	Syncope	Preexisting atrial fibrillation	—
746-5107	20	Severe	Yes	0.5	1	Syncope	Preexisting anemia and podiatric treatment	—
851-0329	20	Mild	No	18.5	1	Lipothymia	Associated with biopsy of breast carcinoma	—
853-4345	20	Mild	No	12.5	1	Loss Of Consciousness	—	—

Abbreviations: Tx = Treatment group (0 = placebo, 20 = LY333334 20 µg/day, 40 = LY333334 40 µg/day); L = low; H = high.

Table 6-concluded. Syncope Adverse Events

Patient Number	Tx	Severity	Serious?	Onset (months)	Duration (days)	Actual Term	Other Concurrent Adverse Events	Electrolyte Abnormalities
LY333334 40-µg/day Treatment Group								
013-7289	40	Severe	Yes	11.7	1	Fainting	Syndrome of Inappropriate Antidiuretic Hormone (SIADH)	Na (L)
038-1031	40	Moderate	No	14.8	1	Syncope	—	Ca (H)
281-1415	40	Moderate	No	14.7	1	Faint	—	Ca (L)
Patients Who Did Not Experience Loss of Consciousness								
748-5219	0	Moderate	No	6.9	1	Swooning	—	—
023-7576	20	Moderate	No	3.6	1	Near Syncope	Abnormal EEG	—
868-4632	20	Severe	No	5.0	1	Near-Blackout Spell	—	Ca (H)
851-0355	40	Mild	No	5.1	1	Vagal Reaction	—	Ca (H)

Abbreviations: Tx = Treatment group (0 = placebo, 20 = LY333334 20 µg/day, 40 = LY333334 40 µg/day); L = low; H = high.

1.5.5.9 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: 2 in the placebo group (both kidney calculus), 6 in the 20 mcg group (1 kidney and ureter calcification, 2 kidney calculus, 3 kidney pain), and 2 in the 40 mcg group (1 kidney calcification, 1 kidney pain) (p=0.192).

1.5.5.10 Cancer

Cancer was reviewed because LY333334 caused osteosarcoma a 2-year rat oncogenicity study.

There were no reports of osteosarcoma. The numbers of patients reporting ≥1 cancer AE were: 21 (3.9%) in the placebo group, 8 (1.5%) in the 20 mcg group, and 11 (2.0%) in the 40 mcg group (p=0.028). This finding was mainly due to a decrease in breast cancer in the LY333334 groups: 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). Interpretation of this finding is not clear. For all other cancer, excluding breast cancer, the numbers of patients were: 16 (2.9%) in the placebo group, 7 (1.3%) in the 20 mcg group, and 10 (1.8%) in the 40 mcg group (p=0.142).

1.5.6 Subgroup Analyses of Adverse Events

Possible subgroup-by-treatment-group interactions were evaluated for: subgroups of patients reporting back pain, nausea, headache, dizziness, leg cramps, syncope, all cancer, and breast cancer; and for subgroups of patients defined by the site of study drug injection, the use of digitalis glycosides, the presence of congestive heart failure, and tertiles of age (545 patients less than 66.6, 546 patients 66.7-72.9, and 546 patients 73 years of age or older).

1.5.6.1 Back pain

A total of 301 patients reported back pain. The subgroups evaluated for possible subgroup-by-treatment-group were defined by categories of age, number of baseline vertebral fractures, BMD response categories, and the occurrence of new vertebral fractures. No statistically significant interactions were found.

In general, patients with new vertebral fractures during the study had more back pain AEs than patients without new vertebral fractures. The

difference was larger in the placebo group (45.35 vs. 19.6%) than the 20 mcg group (22.7% vs. 16.6%) or the 40 mcg group (21.1% vs. 15.6%).

In the placebo group, back pain occurred more often in the subgroup of patients with less than 10% increase in lumbar spine BMD than in the subgroup with more than 10% increase (23.8% vs. 13.8%).

In the LY333334 groups compared to the placebo group, there were statistically significant decreases in back pain in the subgroup of patients with new vertebral fractures and the subgroup with less than 10% BMD increase (p=0.046 and p=0.029, respectively); there were no statistically differences between treatment groups in the subgroup without new vertebral fractures and the subgroup with BMD increase of 10% or more.

1.5.6.2 Nausea

A total of 190 patients reported nausea. The subgroups evaluated for possible subgroup-by-treatment-group interactions were defined by categories of age, study drug dose reduction, and elevation of the 4-6 hour postdose serum calcium.

In the top and bottom age tertiles, nausea was increased in the LY333334 groups compared to the placebo group, whereas in the middle tertile nausea occurred more frequently in the placebo group than in the LY333334 groups (p=0.049). No other statistically significant interactions were found. Across the 3 treatment groups, nausea was associated with an increased frequency of study drug dose reductions.

1.5.6.3 Headache

A total of 161 patients reported headache. The subgroups evaluated for possible subgroup-by-treatment group interaction were defined by categories of age, study drug dose reduction, and elevation of the 4-6 hour postdose serum calcium. No statistically significant interactions were found. In general, headache was more common in younger patients than in older ones.

1.5.6.4 Dizziness

A total of 127 patients reported dizziness. The subgroups evaluated for possible subgroup-by-treatment-group interactions were defined by categories of age, baseline antihypertensive drug use, concomitant thiazide use, baseline sitting systolic blood pressure, baseline sitting

diastolic blood pressure, study drug dose reduction, and elevation of the 4-6 hour postdose serum calcium.

A statistically significant interaction was found for subgroups of patients defined by 4-6 hour postdose total serum calcium (p=0.041). In patients with no elevations of 4-6 hour postdose total serum calcium, the percentage with dizziness was higher in the 40 mcg group compared to the other treatment groups, whereas in patients with at least 1 elevation of 4-6 hour postdose total serum calcium, the percentage with dizziness was lower in the 40 mcg group compared to the other groups. No other statistically significant interactions were found.

1.5.6.5 Leg Cramps

A total of 36 patients reported leg cramps. The subgroups evaluated for possible subgroup-by-treatment-group interactions were defined by categories of age, baseline dietary and serum calcium tertiles, concomitant estrogen and thiazide use, serum magnesium tertiles at 1 year, study drug dose reduction, and elevation of the 4-6-hour postdose serum calcium.

The proportion of patients in the 20 mcg group with leg cramps was highest in the bottom and middle tertiles of baseline dietary calcium, and lowest for the top tertile (p=0.011). No other statistically significant interactions were found.

1.5.6.6 Syncope

A total of 30 patients reported syncope. The subgroups evaluated for possible subgroup-by-treatment-group interactions were defined by categories of age, baseline antihypertensive drug use, concomitant thiazide use, baseline sitting systolic blood pressure, baseline sitting diastolic blood pressure, and study drug dose reduction. No statistically significant interactions were found. However, a treatment group difference was found in the lowest age tertile, where the percentages of patients with syncope were 0.5% for the placebo group, 3.9% for the 20 mcg group, and 1.2% for the 40 mcg group (p=0.040); there were no statistically significant treatment group differences in the other 2 age tertiles. Syncope was more common in patients with low baseline blood pressure than patients with higher baseline blood pressure, in all 3 treatment groups.

1.5.6.7 Cancer

A total of 40 patients had cancer as an AE. The subgroups for which possible subgroup-by-treatment group interactions were evaluated included age tertiles, baseline smoking status, and previous estrogen or hormone replacement therapy. No statistically significant interactions were found for these subgroups.

1.5.6.8 Breast Cancer

A total of 9 patients had breast cancer as an AE. The subgroups evaluated for which possible subgroup-by-treatment-group interactions were defined by categories of age, body mass index, baseline smoking status, previous estrogen or hormone replacement therapy, and concomitant estrogen use. No statistically significant interactions were found. Of the 9 patients with breast cancer, 7 were in the bottom age tertile, 8 had a body mass index of less than 30, only 1 was a previous estrogen or hormone replacement therapy user, and none were using concomitant estrogen.

1.5.6.9 Site of Injection

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. Reported AEs were analyzed separately for patients who injected in the abdomen and those who injected in the thigh. AEs in the two groups were similar to the overall results, and there were no clinically significant differences between sites of injection for any AE. The pharmacokinetic differences between injection in the thigh and abdomen that were seen in the clinical pharmacology studies did not appear to cause differences in AEs.

1.5.6.10 Use of Digitalis Glycosides

There were 55 patients who used digitalis glycosides during the study. There were no apparent differences in the pattern of AEs between patients who did and did not use digitalis glycosides. Patients who used digitalis glycosides did not appear to develop treatment-related arrhythmias or other cardiovascular AEs.

1.5.6.11 Congestive Heart Failure

There were 48 patients who reported congestive heart failure during the study. There were no apparent differences in the pattern of AEs between patients with and without congestive heart failure. Patients with congestive heart failure did not appear to develop treatment-related cardiovascular AEs.

1.5.6.12 Age

Possible treatment group interactions with age were evaluated for subgroups of patients defined by tertiles of age. There were 545 patients less than 66.6, 546 patients 66.7-72.9, and 546 patients 73.0 or older. The AEs in these subgroups were generally similar to the AEs overall.
In the oldest subgroup, cystitis, fever, pruritis, and weight loss were decreased in the LY333334 groups compared to the placebo group (p=0.008, 0.017, 0.042, and 0.007, respectively); there were no statistically significant treatment group differences for these 4 AEs in the 2 younger subgroups.

The statistically significant increase in nail disorder in the LY333334 groups compared to the placebo group that is discussed above, in Section 1.5.4.10, was present in the 2 older subgroups but not the youngest.

Sweating was increased in the LY333334 groups compared to the placebo group in the youngest subgroup (p=0.032) but not the two older ones . Hypertension was decreased in the 40 mcg group compared with the other two treatment groups in the youngest subgroup (p=0.051); no treatment group differences were found for hypertension in the 2 older subgroups.

1.5.7 Summary of Adverse Events

A total of 1637 postmenopausal women with osteoporosis were randomly assigned to placebo, LY333334 20 mcg/day, or LY333334 40 mcg/day; all patients received 1000 mg of calcium and 400-1200 IU of vitamin D per day. Of the 1637 patients, 1121 (68.5%) received placebo or LY333334 for 18-23 months. A majority of the patients returned for their study closeout visits over a period of 4 months after stopping study drug; these patients completed up to 27 months of follow-up after randomization.

Sixteen patients died during the study: 4 (0.7%) in the placebo group, 6 (1.1%) in the 20 mcg group, and 6 (1.1%) in the 40 mcg group (p=0.781). The causes of death appear to have been unrelated to treatment group. A total of 315 (19.2%) patients reported at least 1 serious AE: 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). Breast cancer was the only serious AE with a statistically significant difference between treatment groups: 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). Interpretation of this finding is not clear because the numbers of patients were small and many AE comparisons were made.

A total of 126 (7.7%) patients discontinued the study because of AEs: 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). Nausea was the only specific AE that showed a statistically significant differences between treatment groups as a reason for discontinuation.

A total of 1396 (85.3%) of the 1637 patients reported at least 1 AE: 437 (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). There was a statistically significant decrease in the proportion of patients with at least 1 AE in the 20 mcg group compared to the placebo group (p=0.047), which was mainly due to a decrease in back pain. There was not a statistically significant difference or trend between the 40 mcg group and the placebo group; although there was a decrease in back pain in the 40 mcg group, there were offsetting increases in nausea and headache.

The 10 most common AEs and the percentages of the 1637 patients with these AEs were pain (23.2%), back pain (18.4%), surgical procedure (16.2%), accidental injury (12.9%), nausea (11.6%), headache (9.8%), arthralgia (9.4%), abdominal pain (9.3%), flu syndrome (8.8%), and asthenia (8.7%). Of these, there were statistically significant differences or trends between treatment groups for back pain, nausea, and headache.

There were 16 AEs which occurred in at least 1% of patients in at least 1 of the 3 treatment groups and show statistical differences between groups at the alpha=0.10 level. There was a decrease in back pain in both LY333334 groups compared to the placebo group: 123 (22.6%) in the placebo group, 91 (16.8%) in the 20 mcg group, and 87 (15.8%) (p=0.007). Nausea and headache occurred at similar frequency in the placebo and 20 mcg groups but were increased in the 40 mcg group. For nausea, there 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 headache, there 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). These findings are substantial and supported by data from other clinical trials. Eight other AEs were increased in both LY333334 groups compared to the placebo group: leg cramps, cyst, nail disorder, injection site reaction, tooth caries, emphysema, hypokalemia, and skin benign neoplasm. Three AEs were decreased in both LY333334 groups compared to the placebo group: diabetes mellitus, epistaxis, and breast carcinoma. Two AEs showed inconsistency in the LY333334 groups compared to the placebo group: syncope and dry eyes. The finding for leg cramps was based on substantial numbers of patients and is supported by the other clinical trials. The findings for cyst and nail disorder were also based on substantial numbers, but are not supported by the other clinical trials; however, the other trials were smaller and shorter in duration than study GHAC. Interpretation of the findings for the other disorders with an increase or decrease in both LY333334 groups is not clear because the numbers of patients were small and many comparisons were made.

There were 450 different Coding Symbol and Thesaurus for Adverse Reaction Terminology (COSTART) terms reported by at least 1 patient in the study. Of these, 213 were reported by at least 5 patients and were analyzed for treatment group differences. Of the 213 terms analyzed, 188 (88.3%) showed no statistical differences between groups at the alpha = 0.10 level. The remaining 25 terms showed statistical differences between groups. The 16 of these that occurred in at least 1% of patients in at least 1 of the 3 treatment groups have been discussed above. Of the other 9, 4 were increased and 4 were decreased, and 1 showed inconsistency in the LY333334 groups compared to placebo. The terms with an increase in the LY333334 groups were injection site pain, congestive heart failure, ataxia, and urinary urgency. The terms with a decrease were chills, cerebrovascular disorder, iron deficiency anemia, and cataract nos. Bradycardia showed inconsistency. Interpretation of these findings is not clear because the numbers of patients were small and many comparisons were made.

Analysis of AEs by body system and for subgroup-by-treatment-group interactions did not reveal substantial findings beyond those described above.

1.6 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 after dosing with study drug were not specified in the study protocol. 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.

No electrocardiograms were obtained.

1.7 Clinical Laboratory Evaluation

1.7.1 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; fasting triglycerides; 25-hydroxyvitamin D; PTH (1-84); and LY333334 antibodies.

1.7.2 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.

1.7.3 Calcium and Phosphorus

1.7.3.1 Serum Calcium

Serum calcium and albumin were measured 4-6 hours after the injection of study drug at baseline (visit 4), months 1, 3, 6, 12, and 18 (visits 5, 6, 7, 9, and 11), and the early discontinuation or study closeout visit. They were also measured as part of general chemistry, without specification of time since study drug injection, at baseline (visit 4), months 1, 6, and 12 (visits 5, 7, and 9), and the early discontinuation or study closeout visit.

The albumin levels were considered to be normal for the study population, and adjusting the calcium measurements for the albumin levels increased variability in the data but did not change the average calcium results or interpretation of the findings. Unadjusted calcium levels were therefore used in the safety evaluation. "Serum calcium" means serum total calcium in the discussion below.

There was a statistically significant, dose-dependent, increase in the peak postdose serum calcium, which occurred about 4 hours after each dose of LY333334 (see Section 1.7.3.2 for pharmacodynamics). The median 4-6 hour postdose serum calcium during the study was 0.08-0.12 mmol/L higher in the 20 mcg group ($p<0.01$), and 0.12-0.17 mmol/L higher in the 40 mcg group ($p<0.01$), compared to the placebo group.

Also, there were statistically significant increases in the numbers of patients with serum calcium elevations above the upper limit of normal in the LY333334 groups compared to the placebo group. Table 7 on page 82

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. The differences between treatment groups at each visit were statistically significant ($p<0.001$)

Of the patients with 4-6 hour postdose hypercalcemia, the majority in the 20 mcg group were identified within 150 days after randomization, and the majority in the 40 mcg group were identified within 300 days after randomization, as shown in Figure 1 on page 83.

Table 7 Number of Patients with 4-6 Hour Postdose Hypercalcemia by Month/Study Visit, Calcium Level, and Treatment Group

	Month 1 (Visit 5) n	Month 3 (Visit 6) n	Month 6 (Visit 7) n	Month 12 (Visit 9) n	Month 18 (Visit 11) n
Placebo Group (N=544)					
2.64-2.70	1	0	1	1	0
2.70-2.76	0	0	1	1	0
2.76-2.81	0	1	0	1	0
2.81-2.85	0	0	0	0	1
Total	1	1	2	3	1
LY333334 20-µg/day Treatment Group (N=541)					
2.64-2.70	12	9	13	11	6
2.70-2.76	1	4	10	3	1
2.76-2.81	2	0	4	2	0
2.81-2.85	1	0	0	0	0
2.85-2.90	0	1	0	0	0
Total	16	14	27	16	7
LY333334 40-µg/day Treatment Group (N=552)					
2.64-2.70	19	26	23	25	11
2.70-2.76	12	12	12	9	3
2.76-2.81	5	7	10	12	1
2.81-2.85	2	6	4	3	0
2.85-2.90	1	3	0	1	1
2.90-2.95	1	3	1	1	0
2.95-3.0	0	3	1	0	1
3.0 and up	1	1	1	2	1
Total	41	61	52	53	18

Abbreviation: n = number of patients with serum calcium within the specified range; N = number of patients randomly assigned to each treatment group.

Figure 1 Time to First 4-6 Hours Postdose Hypercalcemia by Treatment Group

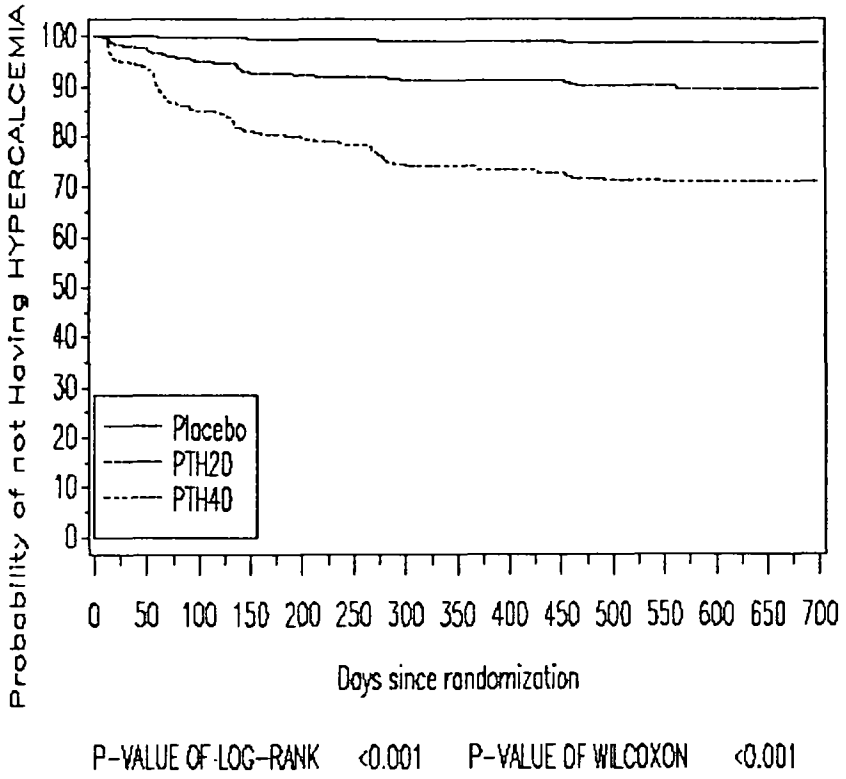


Table 8 on page 84 shows that a total of 221 patients had at least 1 episode of hypercalcemia (at a scheduled study visit or other time): 8 (1.5%) in the placebo group, 60 (11.1%) in the 20 mcg group, and 153 (27.7%) in the 40 mcg group (p<0.001). Seventy patients had at least 2 consecutive episodes: 1 (0.2%) in the placebo group, 16 (3.0%) in the 20 mcg group, and 53 (9.6%) in the 40 mcg group (p<0.001).

Table 8 also describes the management of the 221 patients with at least episode of hypercalcemia. The calcium supplements were reduced for 3 (0.6%) in the placebo group, 39 (7.2%) in the 20 mcg group, and 102 (18.5%) in the 40 mcg group (p<0.001). Study drug was reduced for 3 (0.6%) in the placebo group, 15(2.8%) in the 20 mcg group, and 62 (11.2%) in the 40 mcg group (p<0.001). Study drug was discontinued for 1 (0.2%) in the placebo group, 1 (0.2%) in the 20 mcg group, and 9 (1.6%) in the 40 mcg group (p=0.003).

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

	Placebo N=544 n (%)	PTH20 N=541 n (%)	PTH40 N=552 n (%)	Total N=1637 n (%)
Patients with ≥1 elevated serum calcium	8 (1.5)	60 (11.1)	153 (27.7)	221 (13.5)
Patients with ≥2 consecutive elevated serum calcium	1 (0.2)	16 (3.0)	53 (9.6)	70 (4.3)
Patients with calcium supplement adjustments related to elevated serum calcium	3 (0.6)	39 (7.2)	102 (18.5)	144 (8.8)
Patients with study drug adjustments related to elevated serum calcium	3 (0.6)	15 (2.8)	62 (11.2)	80 (4.9)
Patients who discontinued study drug due to elevated serum calcium	1 (0.2)	1 (0.2)	9 (1.6)	11 (0.7)

Abbreviations: PTH20 = LY333334 20 µg/day; PTH40 = LY333334 40 µg/day; N = number of patients randomly assigned to each treatment group; n = number of patients in each treatment group with elevated serum calcium on repeat laboratory testing, or who had study drug adjustments or discontinuation of study drug due to these elevations.

There were no statistically significant differences or trends between treatment groups in 24-hour postdose serum calcium except at 6 months, when in comparison to baseline the median was decreased in the placebo group by 0.04 mmol/L ($p<0.001$), increased in the 20 mcg group by 0.02 mmol/L ($p>0.05$), and increased in the 40 mcg group by 0.03 mmol/L ($p<0.001$). For the differences between the LY333334 groups and the placebo group, $p<0.001$.

1.7.3.2 Pharmacodynamic Analysis of Postdose Serum Calcium

Figure 2 on pages 85-86 shows serum calcium versus time since last dose of study drug for the 3 treatment groups. The graph includes all results for which the time of last dosing and the time of sample collection were recorded. Because the graph covers all study visits, there are several measurements from each patient. The density of results is greatest in the 4-6 hour postdose interval because the study protocol specified serum calcium measurement in this interval for all patients at all visits.

As shown in Figure 2, serum calcium in both LY333334 groups peaked at about 4 hours postdose and returned toward baseline within a few hours. Both the number and magnitude of the serum calcium elevations were greater in the 40 mcg group than in the 20 mcg group. By 24 hours postdose, the distribution of calcium levels was similar for the 3 treatment groups, with no statistically significant differences.

Figure 2 Serum Calcium by Time Since Last Dose of Study Drug
Placebo Group

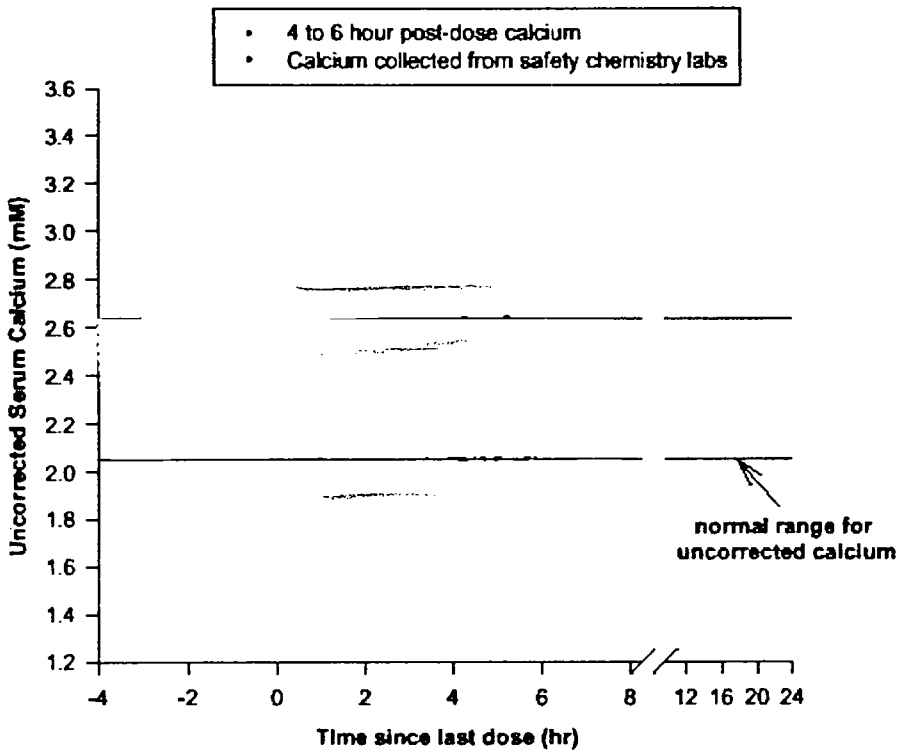


Figure 2-continued. Serum Calcium by Time Since Last Dose of Study Drug
20 mcg Group

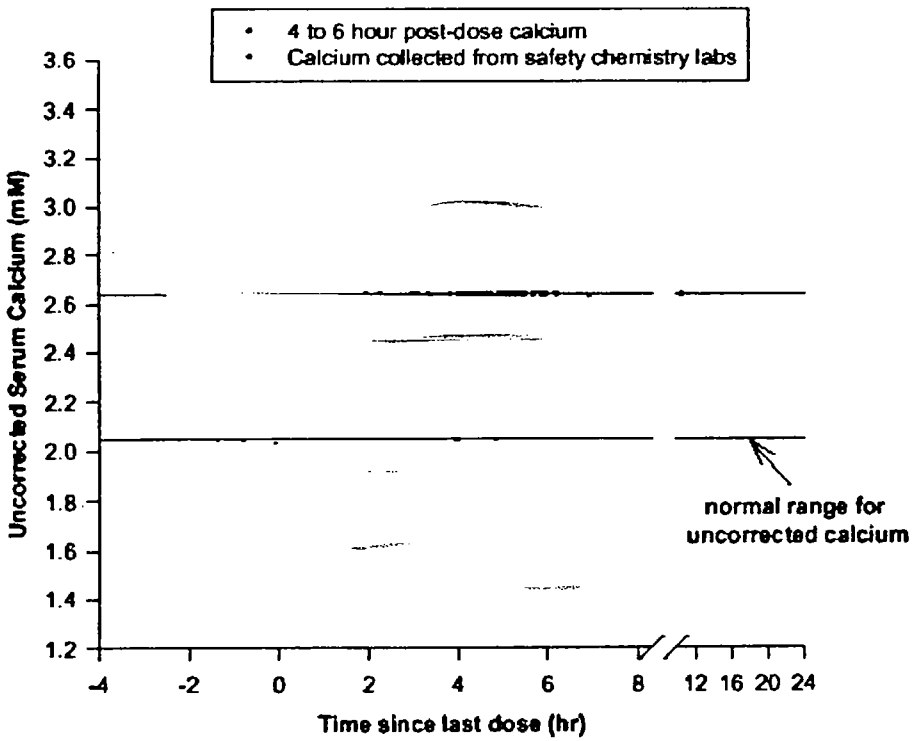
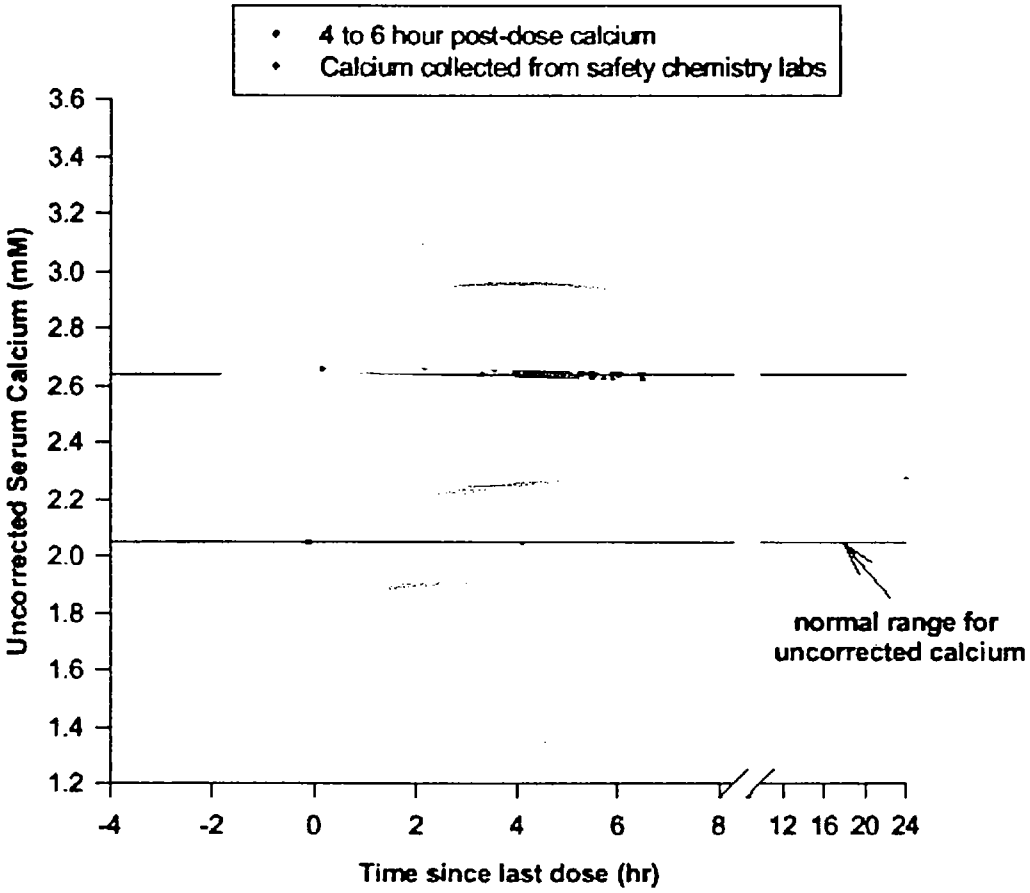


Figure 2-concluded. Serum Calcium by Time Since Last Dose of Study Drug
40 mcg Group



1.7.3.3 Change in Serum Calcium Calibrator by

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1.7.3.4 Serum Phosphorus

Serum phosphorus was measured at baseline (visit 4), months 1,6, and 12 (visits 5, 7, and 9), and the early discontinuation or study closeout visit.

In the 20 mcg group compared to the placebo group, the median serum phosphorus at month 6 was decreased by 0.04 mmol/L (p=0.036). In the 40 mcg group compared to the placebo group, the median serum phosphorous was decreased at month 6 by 0.04 mmol/L (p=0.049), and was increased at endpoint by 0.04 mmol/L (p=0.001).

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

1.7.3.5 Urine Calcium and Phosphorus

Urine calcium and phosphorus excretion were measured in 24 hour urine collections at baseline (visit 3, about 2 weeks before visit 4), months 1, 6 and 12 (visits 5, 7, and 9), and the early discontinuation or study closeout visit.

1.7.3.5.1 Urine Calcium

In the placebo group, there was an increase of about 0.10 mmol over baseline in the median 24 hour urine calcium excretion throughout the study, with a statistical trend at month 6 (p=0.098); there were no other statistically significant results or trends. This finding is consistent with effects of the calcium and vitamin D supplements.

In the 20 mcg group 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); it was decreased by 0.20 mmol at endpoint (p=0.124), when most of the patients had been withdrawn from study drug for a median of 6 weeks. In the 40 mcg group compared to the placebo group, the median 24 hour urine calcium excretion was increased at month 1 by 0.30 mmol (p=0.341) and at month 6 by 0.40 mmol (p=0.003); it was decreased at month 12 by 0.75 mmol (p=0.669), and decreased by 0.50 mmol at endpoint (p<0.001), when most of the patients had been withdrawn from study drug for a median of 6 weeks.

Table 9 on this page shows the numbers of patients with 24 hour hypercalciuria at scheduled study visits according to month/study visit, calcium level, and treatment group. There were no statistically significant differences or trends between treatment groups.

Table 9 Number of Patients With 24 Hour Hypercalciuria by Month/Study Visit, Calcium Level, and Treatment Group

Urine Calcium (mmol/day)	Month 1 (Visit 5) n	Month 6 (Visit 7) n	Month 12 (Visit 9) n
Placebo Group (N=544)			
7.5-8.0	13	8	9
8.0-8.5	7	13	12
8.5-9.0	6	8	3
9.0-9.5	3	2	5
9.5-10.0	4	4	2
10.0-10.5	1	0	3
10.5-11.0	4	0	2
11.0 and up	5	8	11
Total	43	43	47
LY333334 20-µg/day Treatment Group (N=541)			
7.5-8.0	12	17	16
8.0-8.5	9	8	11
8.5-9.0	6	10	1
9.0-9.5	7	2	2
9.5-10.0	4	6	8
10.0-10.5	3	3	2
10.5-11.0	1	3	3
11.0 and up	7	11	9
Total	49	60	52
LY333334 40-µg/day Treatment Group (N=552)			
7.5-8.0	14	6	5
8.0-8.5	3	10	5
8.5-9.0	7	11	5
9.0-9.5	7	11	3
9.5-10.0	7	2	1
10.0-10.5	4	3	0
10.5-11.0	0	4	5
11.0 and up	10	11	7
Total	52	58	31

Abbreviations: N = number of patients randomly assigned to each treatment group; n = number of patients in each treatment group with elevated urine calcium levels at each visit.

According to the study protocol, any patient with a 24 hour urine calcium excretion over 8.75 mmol and a urine calcium/creatinine ratio over 1.0 mmol/mmol was required to have the urine test repeated. If the second value was also elevated, the investigator was to adjust the dose of study drug or the calcium and vitamin D supplement and repeat the test, in an effort to keep the 24 hour urine calcium excretion below 8.75 mmol.

Table 10 on this page shows that a total of 354 patients had at least 1 episode of 24 hour hypercalciuria (at a scheduled study visit or other time): 115 (21.1%) in the placebo group, 112 (22.6%) in the 20 mcg group, and 117 (21.2%) in the 40 mcg group (p=0.976). Sixty-two patients had at least 2 consecutive episodes: 14 (2.6%) in the placebo group, 26 (4.8%) in the 20 mcg group, and 22 (4.0%) in the 40 mcg group (p=0.150).

Table 10 also describes the management of the 354 patients with at least 1 episode of 24 hour hypercalciuria. The calcium supplements were reduced for 27 (5.0%) in the placebo group, 44 (8.1%) in the 20 mcg group, and 48 (8.7%) in the 40 mcg group (p=0.038). Study drug was reduced for 7 (1.3%) in the placebo group, 16(3.0%) in the 20 mcg group, and 20 (3.6%) in the 40 mcg group (p=0.045). Study drug was discontinued for 3 (0.6%) in the placebo group, 1 (0.2%) in the 20 mcg group, and 2 (0.4%) in the 40 mcg group (p=0.607).

(Table 10 may overestimate the number of study drug adjustments due to 24 hour hypercalciuria, because the reasons for adjustment were not recorded, and the adjustments could be made for several reasons, including increased 4-6 hour postdose serum calcium, increased 24 hour urine calcium excretion, or symptoms such as nausea or headache.)

Table 10 Number of Patients with at Least 1 and at Least 2 Consecutive Episodes of 24 Hour Hypercalciuria by Treatment Group; Management of Hypercalciuria Patients

	Placebo N=544 n (%)	PTH20 N=541 n (%)	PTH40 N=552 n (%)	Total N=1637 n (%)
Patients with ≥1 elevated urine calcium	115 (21.1)	122 (22.6)	117 (21.2)	354 (21.6)
Patients with ≥2 consecutive elevated urine calciums	14 (2.6)	26 (4.8)	22 (4.0)	62 (3.8)
Patients with calcium supplement adjustments related to elevated urine calcium	27 (5.0)	44 (8.1)	48 (8.7)	119 (7.3)
Patients with study drug adjustments related to elevated urine calcium	7 (1.3)	16 (3.0)	20 (3.6)	43 (2.6)
Patients who discontinued study drug due to elevated urine calcium	3 (0.6)	1 (0.2)	2 (0.4)	6 (0.4)

Abbreviations: PTH20 = LY333334 20 µg/day; PTH40 = LY333334 40 µg/day; N = number of patients randomly assigned to each treatment group; n = number of patients in each treatment group with elevated urine calcium on repeat laboratory testing, or who had study drug adjustments or discontinuation of study drug due to these elevations.