

#### B.2.8.5.4 Other efficacy outcomes

Height: Inexplicably, this pre-specified secondary efficacy objective was reported as a safety outcome. There were no statistically significant between-group differences in height at baseline (mean for all 3 groups was 173 cm). At endpoint, patients in the placebo, 20 µg, and 40 µg groups had a mean decrease of 1.90, 2.20, and 3.25 mm, respectively. All within-group comparisons with baseline were statistically significant ( $p < 0.001$  for all 3 comparisons). However, there were no statistically significant between-group differences in height change at endpoint; nor were there significant differences between groups at any visit.

Fractures: These were not part of the efficacy evaluation. The trial was not powered to detect treatment-related differences in fracture occurrence at any skeletal site.

The sponsor obtained baseline radiographs of the spine, but follow-up radiographs were not planned, precluding any assessment of vertebral fractures. Unlike GHAC, the presence of a specified number of evaluable vertebrae was not an entry criterion. Non-vertebral fractures were confirmed (x-ray or radiologist's written report) when they occurred throughout the trial.

As shown in the next table, there were very few incident non-vertebral fractures in this trial. The table shows the number of patients reporting at least one non-vertebral fracture, by anatomic location, in GHAJ. There were no significant

**Table GHAJ. 12.110. Nonvertebral Fracture Results**  
All Randomly Assigned Patients  
B3D-MC-GHAJ

	Placebo (N = 147)	PTH20 (N = 151)	PTH40 (N = 139)
Radius	0	1	0
Ankle	0	1	0
Ribs	1	1	0
Other	3	0	1
Total Patients*	3	2	1

between-group differences in the numbers of patients reporting fractures.

#### B.2.9 GHAJ: Summary and Conclusions

This pivotal Phase 3 study was designed to support an indication for LY333334 in the treatment of men with idiopathic osteoporosis or osteoporosis associated with primary hypogonadism. GHAJ was a randomized, double-blind, placebo-controlled, parallel, multi-center (37

study sites in 11 countries) trial that was originally designed to run for two years. The primary efficacy outcome was per cent change in lumbar spine BMD following two years of treatment with LY333334 (20 µg/day or 40 µg/day) or PBO. Other outcome variables included % change in BMD at several non-vertebral skeletal sites, % changes in bone turnover biomarkers, loss of height, and changes in Health-Related Quality of Life scores. The trial was not intended to detect treatment group differences in fracture rates. Therefore, achievement of efficacy and safety goals will lead to an indication for “treatment to increase bone mass in men with osteoporosis,” rather than a blanket “treatment” indication. The situation is essentially the same as for alendronate, which was recently approved for treatment to increase bone mass in men with osteoporosis. At the time of this review, there are no prospective randomized placebo-controlled clinical trial data that demonstrate fracture reduction efficacy (vertebral or non-vertebral) for any agent in the treatment of osteoporotic men.

Patients in GHAJ were ambulatory, aged 31-84 years, and in generally good health except for primary osteoporosis, defined by lumbar spine or hip BMD T-score  $\leq -2.0$ . Individuals were excluded if they had metabolic bone disease, any disease that can secondarily affect bone physiology, any disorder of mineral metabolism (including hypercalciuria, hyper- or hypoparathyroidism, abnormal 25-hydroxyvitamin D levels, urolithiasis, nephrolithiasis), and recent or concurrent use of any drug that can significantly affect bone structure or metabolism. Significant alterations of hepatic or renal function (Cr  $> 2.0$  mg/dl) were also reasons for exclusion. Hypogonadal patients taking replacement androgens at stable doses could remain on their regimens.

Four hundred thirty-seven men (age 31-84 years) with lumbar spine or hip BMD T-scores  $\leq -2.0$  SD were randomized (in a 1:1:1 schedule) to receive PBO or either 20 µg or 40 µg/day of LY333334. Ninety-nine percent of the patients were Caucasian. The mean age was 58.6 years (range 31-84). The mean body weight was 75.71 kg (range, 47.6 to 128.9 kg). The mean BMI was 25.15 kg/m<sup>2</sup>. Overall, 49 % of the patients were hypogonadal and 51% were classified as idiopathic. Fifty-nine percent of patients had a previous non-vertebral fracture. About 30 % were classified as smokers, and 70% used alcohol. The three treatment groups did not differ in any of these baseline variables.

As in GHAC, all patients were supplemented with calcium, 1000 mg, plus vitamin D, 400-1200 IU/day, throughout the trial.

Because of premature study termination, patients received treatment with active drug or placebo for about 300 days. Eighty-two per cent of enrolled patients discontinued due to the sponsor's decision to terminate the study. The proportions of patients who discontinued for this reason did not differ

significantly between the 20 µg group (81.5%) and placebo (88.4%). In the 40 µg group, there was an increase in early discontinuation rate due mainly to adverse events and patient decision. This led to a smaller proportion of patients who discontinued due to sponsor's decision (74.1%;  $\chi^2$  p=0.008 for 40 µg vs placebo).

Data from the 437 patients contributed to the primary efficacy analysis, and nearly all of the secondary analyses, using the ITT approach with LOCF. Data from a subset of 251 patients who were taking LY333334, 20 or 40 µg/day, were used for the population pharmacokinetic studies.

Despite the premature termination of the trial, the primary efficacy goal was clearly met. Treatment of men with primary osteoporosis (idiopathic or due to primary hypogonadism) for 11 months with LY333334 resulted in statistically significant placebo-subtracted increases in lumbar spine BMD of 5.19% at Month 12 and 5.35% at endpoint in the 20 µg/day group, and 8.21% at Month 12 and 8.51% at endpoint in the 40 µg/day group (p<0.001 for all comparisons vs placebo). Statistically significant differences from placebo were seen in both groups as early as 3 months after beginning treatment. A responder analysis showed that over 50% of patients treated with 20 µg of LY333334/day had increases in lumbar spine BMD that were  $\geq$  5%. In the 40 µg group, 70.5% of patients had spinal BMD increases of 5% or more, and over 40% had increases that were in excess of 10% over baseline (about 15% of the 20 µg group had spinal BMD increases of over 10 %).

The robust and statistically significant increase in lumbar spine BMD was observed regardless of choice of endpoint time for the analysis (Visit 6 or Visit 7). However, the choice of endpoint affected the statistical significance of secondary BMD results. Using the 12-month endpoint with LOCF, there were statistically significant placebo-subtracted increases in BMD at the total hip, femoral neck, and whole body. Other sites at the hip (trochanter, intertrochanter, Ward's triangle) showed no statistically significant increase in BMD, compared to placebo. Again, the distal 1/3 radius and the ultra-distal radius showed no significant changes in BMD, compared with PBO. Using the study endpoint with LOCF, statistical significance was maintained only at the femoral neck. As indicated above, I find no *a priori* reason not to use the Visit 7 (endpoint) data with LOCF for the analytical data set, since this set includes final values for all patients. I have summarized the outcomes for the 20 µg group, using the two endpoints, in the following (reviewer's) table:

<b>SKELETAL SITE</b>	<b>PLACEBO-SUBTRACTED % BMD INCREASE, MONTH-12 DATA</b>	<b>PLACEBO-SUBTRACTED % BMD INCREASE, ENDPOINT DATA</b>	<b>TREATMENT COMPARISON (20 µg vs PLACEBO) MONTH-12 DATA</b>	<b>TREATMENT COMPARISON (20 µg vs PLACEBO) ENDPOINT DATA</b>
LUMBAR SPINE	5.19	5.35	p<0.001	p<0.001
TOTAL HIP	0.73	0.63	p<0.040	NS
FEMORAL NECK	1.08	1.24	p<0.038	p<0.029
TROCHANTER	0.30	0.24	NS	NS
INTERTROCHANTER	0.72	0.57	NS	NS
WARD'S TRIANGLE	1.77	1.76	NS	NS
WHOLE BODY	0.83	0.76	p<0.039	NS
ULTRADISTAL RADIUS	0.13	-0.19	NS	NS
DISTAL RADIUS	-.029	-.031	NS	NS

Much larger, and statistically significant (relative to placebo), increases in BMD were found in the 40 µg group at all the above skeletal sites except for the trochanter (trend with p=0.06), ultradistal, and distal radius at both study endpoints. The results are similar to those presented at Month 12 (see sponsor's table above). Given the lower systemic exposure of men to LY333334, it is possible that 20 µg is sub-optimal dose for treatment of male osteoporosis. The 40 µg dose produced an increase in mainly non-serious adverse events, and it is possible that future studies will establish an intermediate dose (e.g., 25-30 µg/day) as the optimal regimen for men.

It should be emphasized that we do not yet know the degree to which these LY333334-induced increases in BMD can be translated into fracture prevention efficacy in men.

The BMD responses at the lumbar spine at 11 months were similar to those that were found in response to alendronate, in a similar osteoporotic male population, at 24 months. The spine BMD increases in response to LY333334 appeared somewhat earlier than with alendronate. Of interest, an additional analysis showed that the increase in bone mineral content (BMC) at the lumbar spine was accompanied by enlargement in bone mineral area (BMA) at that site. Thus the increases in lumbar spine BMD that followed LY333334 treatment may underestimate the increases in the lumbar spine mineral space (i.e., the size of the vertebral space and the content of mineral in that space). In this ancillary analysis, there were no meaningful changes in BMA at other skeletal sites.

At some non-vertebral skeletal sites (e.g., the trochanter), the effects of LY333334 20 µg appear to be inferior to those that followed treatment with alendronate.

The sponsor performed an analysis of treatment-by-subgroup interactions for six pre-specified subgroups [age, BMI, baseline vertebral BMD, previous non-vertebral fracture, baseline free testosterone, and osteoporosis type (idiopathic or hypogonadal)]. There was no significant interaction on BMD at any of the five skeletal sites listed (BMD efficacy at the spine, hip, femoral neck, whole body, and wrist), with two exceptions. There were interactions of spine BMD efficacy with BMI ( $p=0.017$ ) and with baseline vertebral BMD ( $p=0.072$ ). The interaction between therapy and baseline BMD tertile was significant, but each dose of LY333334 had a statistically significant effect on spine BMD regardless of baseline tertile. Similarly, there was a significant interaction between therapy and baseline BMI tertile, but both LY333334 doses had significant therapeutic effects in patients in all three BMI tertiles.

Changes in biomarkers of bone formation and resorption were a secondary endpoint. Consistent with the anabolic action of LY333334, there were substantial and statistically significant increases in BSAP and PICP that were evident after 1 month of treatment. In the 20  $\mu\text{g}$  group, PICP peaked at 1 month after treatment (34% over baseline) and declined following this, to 13% below baseline at study end. BSAP also rose promptly and was 28.8% above baseline at study end. More substantial increases in both formation markers were found in the 40  $\mu\text{g}$  group. For BSAP, at all visits, the 20  $\mu\text{g}$  group had greater median percent change than in placebo, and the 40  $\mu\text{g}$  group had higher levels than the 20  $\mu\text{g}$  group ( $p<0.001$  for each comparison at all visits).

There were somewhat delayed but even greater median per cent increases from baseline in urinary NTX and free deoxypyridinoline, both markers of bone resorption. At endpoint, the increases seen in the 20  $\mu\text{g}$  and 40  $\mu\text{g}$  LY333334 groups were statistically significantly different from baseline, from placebo, and from each other ( $p<0.001$  for all comparisons). The increases in the 40  $\mu\text{g}$  group were again greater than in the 20  $\mu\text{g}$  group. These changes are consistent with the coupling of the formation and resorptive processes, as well as the net increase in bone remodeling associated with LY333334 treatment.

There were also significant LY333334-associated increases in serum 1,25-dihydroxyvitamin D levels, consistent with the action of PTH on renal  $1\alpha$ -hydroxylase.

The overall pattern of bone biomarker responses is entirely different from that which has been repeatedly demonstrated with anti-resorptive agents.

With the latter, bone resorption markers decline following a few months of therapy. This is followed by a decline in formation markers.

A subgroup analysis (using the same six subgroups described above) of changes in each of the four biomarkers plus 1,25-dihydroxyvitamin D yielded five significant ( $p < 0.10$  for this analysis) interactions among the 30 comparisons. The major interaction was with osteoporosis type. Both doses of LY333334 increased BSAP in both eugonadal and hypogonadal patients. However, the 20  $\mu\text{g}$  dose failed to increase PICP in either group. Note that these interactions were for endpoint values, and by the last visit the PICP values had declined to below baseline (see above).

Changes in height constituted another secondary endpoint. Presumably, the hypothesis was that LY333334 treatment would diminish the height loss (relative to placebo) that is associated with osteoporosis, although this was not formally proposed. Height was measured at specified intervals with a stadiometer. At endpoint, all three treatment groups lost stature ( $p < 0.001$  for all within-group comparisons vs baseline). However, at endpoint, patients in the placebo, 20  $\mu\text{g}$ , and 40  $\mu\text{g}$  groups had mean decreases of 1.90, 2.20, and 3.25 mm, respectively. The between-group differences in height loss were not statistically different at endpoint or at any visit.

An analysis of five Health-related Quality of Life Indicators (another secondary endpoint) disclosed very little within- or between-group change, from baseline, in any of the measured parameters. Two of the HRQOL indicators were osteoporosis-specific.

An extensive population pharmacokinetic analysis disclosed the following major outcomes:

Following s.c. injection of a 20  $\mu\text{g}$  dose of LY333334, the median peak serum concentration of the drug was 121.2 pg/mL, and the median systemic exposure (estimated as AUC) was 208.6 pg.hr/mL. In most males, serum LY333334 concentrations will be            (the lower limit of quantitation with the sponsor's assay) by 2 hours after a 20  $\mu\text{g}$  dose.

The apparent volume of distribution (V/F) correlated with body weight. The predicted V/F decreased from 131 L for a 74.0 kg individual (the median value of the population) to 90 L for a patient weighing 48.2 kg, the population minimum value. When normalized to body weight, V/F was essentially the same across the range of weights in the population (approximately 1.8 L/kg). The effect of body weight on V/F does not alter AUC significantly, but it may affect  $C_{\text{max}}$ . The predicted  $C_{\text{max}}$  after injection of 20  $\mu\text{g}$  into the abdominal wall for a patient weighing 48.2 kg is 185.0 pg/mL; for a patient weighing 74.0 kg, the predicted peak concentration is 132.4 pg/mL. These effects of body weight on V/F, peak serum

concentrations were not likely to be clinically significant, based on concentration-time curves and clinical adverse event reports.

Injection site (thigh vs abdomen) affected V/F, which was approximately 30% higher in patients who injected the dose into the thigh, compared with the abdomen. This resulted in a  $C_{max}$  that was lower after injection into the thigh. However, as shown in the combined population pharmacodynamic analyses, the BMD and biomarker responses in patients injecting into the abdomen were essentially the same as those in patients injecting into the thigh. Therefore, site of injection does not result in a clinically important effect on the disposition of LY333334.

Creatinine clearance affected the clearance of LY333334. Over the seven-fold range of CL/cr that was present in the trial population (123.2 ml/min, measured by 24-hr urine collection) the estimated clearance of LY333334 changed two-fold (from 64.8 L/hr to 128.0 L/hr). A reduction in creatinine clearance from the population median of 123.2 ml/min to the population minimum of 64.8 ml/min resulted in a 31% decrease in clearance of the drug (from 93.9 to 64.8 L/hr). Changes in clearance of the drug are expected to affect systemic exposure. For a patient with CLcr of 123.2 mL/min the predicted AUC is 309 pg·hour/mL; for a CLcr of 64.8 mL/min, the corresponding AUC is 213 pg·hour/mL. Thus a 70% reduction in renal function would be predicted to increase systemic exposure by about 45-50%.

It is unlikely that the partial dependence of AUC on creatinine clearance over this range will be clinically meaningful. The addition of CLcr as a covariate in the final pk model resulted in only a small reduction in inter-patient variability of LY333334 clearance. In addition, for individuals in the lowest 5<sup>th</sup> percentile of CLcr values, there were no episodes of hypercalcemia or serious adverse events that were considered to be drug-related. In addition, exposure estimates from the final population pharmacokinetic model were used to identify patients in the 95<sup>th</sup> percentile for LY333334 AUC and  $C_{max}$ . For this subset of patients, none had a "drug-related" serious adverse event or a dosage reduction or discontinuation due to hypercalcemia or hypercalciuria while taking LY333334 20 µg/day. Among patients in this subset who were taking 40 µg/day, none had a drug-related serious adverse event and only one had a dosage reduction due to elevated serum and urine calcium. None of these patients discontinued due to hypercalcemia or hypercalciuria.

The effects of race/ethnicity could not be evaluated because 99% of the patients were Caucasian. The effects of severe hepatic dysfunction also could not be evaluated because patients with severe liver disease were excluded. Within the range of the trial population, there was no association between LY333334 clearance and serum bilirubin, ALT, AST, or GGTP.

There was also no significant association between smoking status or alcohol use and LY333334 clearance or V/F.

## **CONCLUSIONS**

- In men with idiopathic osteoporosis or osteoporosis associated with primary hypogonadism, treatment with LY333334 20 µg/day for 11 months resulted in substantial and statistically significant increases in lumbar spine BMD, relative to baseline and to placebo. The mean placebo-subtracted difference in BMD increase was 5.19-5.35% in the 20 µg group and 8.21-8.51% in the 40 µg group. A responder analysis showed that 54.6% of LY333334-treated patients in the 20 µg group had spinal BMD increases of 5% or more, compared to 9.8% in the placebo group.
- In this same population, treatment with LY333334 20 µg/day for 11 months resulted in placebo-subtracted increases in BMD of 1.08-1.24% at the femoral neck ( $p < 0.038$ ). Although there were numerical BMD increases at several other skeletal sites, none achieved statistical significance, using endpoint data. Using Month 12 data, there were statistically significant increases at the total hip and total body (placebo-subtracted differences of 0.73%,  $p < 0.040$ , and 0.83%,  $p < 0.038$ , respectively), in addition to the increases at the femoral neck. However, the instability of the latter results, as well as their dependence on an arbitrary data set, preclude claims of efficacy at these sites.
- LY333334 20 µg/day was effective in both hypogonadal and eugonadal patients. A subgroup analysis showed that LY333334 was effective in increasing BMD at the lumbar spine regardless of age, BMI, baseline vertebral BMD, serum free testosterone, and osteoporosis type (idiopathic or hypogonadal). This was also true of the 40 µg/day dose.
- At the lumbar spine, total hip, femoral neck, intertrochanter, and Ward's triangle, the LY333334 40 µg group had substantially and statistically significantly greater increases in BMD, compared to the 20 µg group. At the lumbar spine, the mean placebo-subtracted difference in BMD increase in this treatment group was 8.51% at study endpoint. In the responder analysis, 70.5% of patients in the 40 µg group had spinal BMD increases of 5% or more and over 40% had increases that were in excess of 10% (as opposed to about 15% of patients in the 20 µg group). Although it is difficult to compare results across the trials, it is worth noting that, in the 20 µg group, the BMD increases at the lumbar spine at about 11 months (5.35%) are somewhat less than were found in women at 12 months in GHAC (7.42% in the 20 µg group). Consistent with this, there were greater BMD increases in the 40 µg group in women at 12

months, compared to the 40 µg group in men at 11 months. This may relate to the lower systemic exposure to the drug in men. It is possible that an intermediate dose of LY333334 (e.g., 25-30 µg/day) would convey far greater benefit in men without increasing risk of adverse events.

- The response of bone biomarkers PICP, BSAP, NTX, and DPD, to LY333334 20 µg/day was consistent with the anabolic action of the drug, coupled to a secondary increase in the rate of bone turnover. The increase in remodeling is consistent with the known action of PTH on bone. The effects of 40 µg /day exceeded those of 20 µg. LY333334 treatment also increased the levels of circulating 1,25-dihydroxyvitamin D.
- There was no effect of LY333334 treatment on height loss.
- There was no effect of LY333334 treatment on the HRQOL indicators.
- Population pharmacokinetic analysis disclosed some variability in AUC or C<sub>max</sub>, depending on body weight, injection site, and creatinine clearance. However, the magnitude of the changes in these pharmacokinetic parameters, and the lack of associated alterations in pharmacodynamic responses and safety/tolerability outcomes, suggest that there is no need for dose adjustments based on body weight, creatinine clearance, or injection site. These considerations apply to the range of renal function present in the trial population. There were no discernible effects of elevated liver enzymes or bilirubin, or of alcohol intake or smoking status, on the clearance of LY333334. The effects of race/ethnicity could not be tested.
- The only currently approved drug for osteoporosis in men is alendronate. There are no head-to-head data with which to compare the efficacies of these two drugs for this indication. The overall efficacy of LY333334 20 µg/day appears to be slightly better than alendronate at the lumbar spine (BMD). Although we have no data past a median of 11 months exposure to LY333334, there is very little evidence that this dose (20 µg/day) of the drug has substantial or clinically meaningful beneficial effects at other skeletal sites, with the exception of the femoral neck. In contrast, alendronate increased BMD over placebo at the femoral neck, trochanter, total hip, and total body, with a numerical increase at Ward's triangle. Since we have no fracture efficacy data for either drug in men, it is difficult to conclude, on the basis of available data, that LY333334 20 µg/day offers any advantage over current therapy.

- While LY333334 20 µg produced no overt safety concerns during the trial (and very few adverse events in the 40 µg group), the unresolved issue of osteosarcoma risk should weigh in the decision regarding approvability of the drug for this indication. In this sense, the risk/benefit estimate for the use of LY333334 in men differs from that which applies to women. Possible courses of action in regulatory decisions have been presented.
- Major unresolved efficacy issues: determination of optimum dose, development of algorithm and mechanism for dose titration in individual patients, and determination of treatment duration. Other issues are the same as in women (long-term safety monitoring, determination of which osteoporotic patients should be treated, decision whether LY333334 should be second-line therapy, and determination if/when a bisphosphonate should be added to the regimen).

Other controlled phase 3 clinical studies:

The other two large Phase 3 studies employed an active control design. These were conducted to provide supportive data and are not included in proposed labeling.

Study B3D-MC-GHAF, Effects of LY333334 in postmenopausal women on estrogen and progestin therapy:

This was a Phase 3, multicenter, randomized, double-blind, parallel-design study comparing the effects of LY333334 plus HRT to HRT alone. All patients were supplemented with calcium plus vitamin D. The study enrolled 247 healthy postmenopausal women with a hip or lumbar spine BMD T-score < -1. The study demonstrated that LY333334, 40 µg/day for 15 months significantly increased BMD over that of the group treated with HRT only. This was true whether or not women had been treated with HRT prior to study. The increases in BMD, compared with HRT alone, were found at the spine, total hip, and femoral neck. Ultradistal radius and whole body BMD were significantly increased over values in the group receiving HRT alone only in subjects who had not been treated with HRT prior to study. As noted above, the utility of these data is limited by the inclusion of only a 40 µg dose of LY333334.

Study B3D-MC-GHAH, LY333334 compared with alendronate in postmenopausal women with osteoporosis:

This was a Phase 3, randomized, double-blind, double-dummy, parallel, multicenter study comparing the effects of alendronate 10 mg/day with those of

LY333334 in postmenopausal women with osteoporosis. The primary efficacy variable was change in BMD from baseline. One hundred forty-six postmenopausal women either hip or lumbar spine BMD t-scores < 2.5 were given LY333334 40 µg/day or alendronate 10 mg/day for up to 75.6 weeks. All patients were supplemented with calcium and vitamin D.

Results: Compared to baseline, the increases in BMD at the lumbar spine, total hip, and femoral neck were significantly greater in the LY333334 group than in the alendronate group. At some sites, the differences between the groups were quite dramatic. For example, the mean % increases at the lumbar spine were 12.21% in LY333334 vs 5.62% in ALN. Wide differences were also found at the femoral neck, total hip, and Ward's triangle. At the ultra-distal radius, the between-group differences did not differ. Of note, at the distal 1/3 radius (forearm), the BMD in the LY333334 group was significantly less than in the alendronate group and the difference was substantial: -3.43% in LY333334 vs -0.17% in ALN. The mean whole body BMD increased significantly in both treatment groups, but the between-group differences were not statistically significant.

Again, the clinical utility of these data is limited by the absence of a 20 µg group. It is likely that increasing the dose of LY333334 to 40 µg dramatically increases BMD in some areas (presumably those rich in trabecular bone), while decreasing BMD in others that contain substantial cortical components. In a male osteoporotic population, a comparison of alendronate to LY333334 40 µg would be quite informative.

### Non-controlled Phase 3 Clinical Studies

#### Study B3D-MC-GHBJ Extended follow-up of patients in LY333334 trials:

This is an ongoing multi-center two-year observational follow-up study of patients who participated in one of the following 7 clinical trials: GHAC, GHAF, GHAH, GHAJ, GHAL, GHAU, and GHAV. The first four trials have been described above. The last 3 enrolled very few patients for brief periods and did not contribute to the efficacy analyses. These trials are described in the NDA and in the integrated safety review. Nearly all the data generated in the follow-up study are derived from patients who participated in the trials GHAC, GHAF, GHAH, and GHAJ.

The primary objective of GHBJ is to collect additional safety data following cessation of treatment with LY333334. A secondary objective is to assess BMD responses following drug withdrawal. The planned duration of the study was two years, with an interim analysis following Visit 1. The median time from the treatment endpoint to Visit 1 was 6 months. Data from Visit 1 are included in the NDA.

Results: After the study drug was stopped, there was resolution of all clinical AEs and laboratory abnormalities. No new clinical or laboratory abnormalities that were judged to be drug-related appeared during the first 6 months of observation. Safety data are reviewed in detail in the Integrated Summary of Safety. Further safety data are pending.

Summary: The clinical development of LY333334 for the treatment of osteoporosis began with an extensive Phase 1-2 clinical pharmacology program that established dosing schedules for LY333334, based on efficacy and safety/tolerability. These studies provided a thorough understanding of the pharmacokinetics and pharmacodynamics of rhPTH (1-34) in humans. The clinical pharmacology program also reconfirmed the anabolic action of PTH on bone and differentiated this action from that of anti-resorptive agents. Finally, the phase 2 studies established 20 µg and 40 µg as the LY333334 doses for the subsequent phase 3 trials.

The two large pivotal Phase 3 trials clearly established the efficacy of LY333334 for the treatment of osteoporosis in postmenopausal women (BMD and fracture data) and showed that LY333334 increases spinal BMD in osteoporotic males. Despite the early termination of the GHAC (after a median of 19 months), the efficacy of LY333334, in preventing vertebral fractures and increasing spinal BMD in postmenopausal osteoporotic women exceeded that which has been demonstrated following treatment for 3-4 years with any known anti-resorptive drug. LY333334 increased BMD at other skeletal sites, but the increases were no greater than with other agents. Trial GHAC (postmenopausal osteoporosis) demonstrated that, despite the overall superiority of the 40 µg dose in promoting increases in BMD, the anti-fracture efficacy of the two doses were the same. This trial, together with results of the earlier phase 2 studies, established 20 µg/day as the indicated dose of LY333334 for treatment of postmenopausal osteoporosis.

In men, trial GHAJ showed that LY333334 20 µg/day for about 11 months substantially increased lumbar spine BMD. The increases were more rapid and substantial than with alendronate, the only other drug approved for this indication. However, LY333334 20 µg was generally ineffective at other skeletal sites, compared to placebo. This dose of LY333334 appeared to be inferior to alendronate at these non-vertebral sites. Far greater responses were found in response to LY333334 40 µg/day. Further work is required to establish a more effective dose of LY333334 for the treatment of osteoporosis in men.

Two supportive Phase 3 trials established superiority, in terms of increases in BMD, of LY333334, 40 µg/day, to either HRT alone or to alendronate alone. Unfortunately, the 20 µg dose of LY333334 was not included in these studies, limiting the utility of the results. The sponsor is

The overall safety/tolerability of LY333334 appeared to be acceptable for these indications, based on data from the clinical trials. Safety data were obtained from all patients who participated in any of the clinical trials. These data are reviewed in detail in the Integrated Summary of Safety. Adverse events were generally mild and included nausea, abdominal pain, headache, and orthostatic hypotension post-dose. Most of these AEs were not encountered with the 20 µg/day dose. Since 20 µg/day was as effective as 40 µg/day in reducing fractures, the dose for treatment of postmenopausal osteoporosis will be 20 µg/day. There has been no indication of neuromuscular complaints (often reported in patients with primary hyperparathyroidism) or renal toxicity due to either the 40 µg or the 20 µg dose of LY333334. No clinically significant hypercalcemia has been seen, although there were dose adjustments (in calcium supplementation) made as part of the protocol. No clinically meaningful immunological reactions to LY333334 have been reported. Data derived from the 6-month interim analysis of the 2-year follow-up study do not indicate that any drug-associated clinical or laboratory changes persist after discontinuation of LY333334. As discussed in the Safety Review, further work is required to resolve issues pertaining to potential cardiovascular responses to LY333334. In addition, a protocol for active post-marketing monitoring for osteosarcoma should be established if the drug is approved for either indication.

#### **VII. Integrated Review of Safety**

Please see attached Integrated Review of Safety, which was written by Bruce V. Stadel, MD, MPH.

#### **VIII. Assessment of Dosing/Regimen/Administration issues**

The clinical development program clearly established 20 µg/day as the indicated dose for women with osteoporosis. No dose adjustments are required, based on any demographic or clinical characteristics, within the limits of the trial populations. In men, the optimum dose has not been established. Based on results of GHAJ, it appears that men with severe osteoporosis could benefit from an intermediate dose of LY333334 (e.g., 30 µg/day). It is possible that the lower systemic exposure in men led to diminished efficacy.

## IX. Use in Special Populations

LY333334 is intended for the treatment of postmenopausal women with osteoporosis. The drug is also intended for the treatment of adult males with osteoporosis or osteoporosis associated with primary hypogonadism. The drug should not be used in pregnancy, in breastfeeding women, and in women of childbearing potential. Development of LY333334 for treatment of pediatric patients should be deferred until the osteosarcoma issue is settled.

LY333334 should not be given to patients with metabolic bone disease other than osteoporosis. In particular, patients with Paget's disease should not receive this drug.

- A. Gender:** See above.
- B. Pediatric Program** See above.
- C. Effects of age, race, ethnicity:** LY333334 is intended for use in adults. Extensive population pharmacokinetic/pharmacodynamic investigations disclosed no age group in which the drug was not effective or in which drug dose adjustments would be required. Nearly all patients were Caucasian; therefore, effects of race/ethnicity on the safety and efficacy of LY333334 are not known.
- D. Other populations:** The drug has not been investigated in populations other than Caucasian women with postmenopausal osteoporosis and adult men with primary osteoporosis.
- E. Pregnancy:** LY333334 should not be used in women of childbearing potential.
- F. Drug-disease and drug-drug interactions:** Extensive drug-disease interactions have not been studied. There is no indication that patients with mild renal failure require dose adjustments. This statement cannot be made with confidence about patients with more severe renal failure (ClCr < about 25 cc/min), because there were too few patients in this category. Similarly, patients with mild congestive heart failure and diminished hepatic blood flow did not appear to require LY333334 dose adjustments. I also believe that there were insufficient numbers of patients with significant degrees of heart failure to be confident regarding safety and efficacy of these doses of LY333334. In addition, the absence of EKGs during clinic visits limits the level of assurance. It should be pointed out that the sponsor has made no provision for a mechanism that would allow for dose adjustments, if such were required. The effects of hepatic failure on safety and efficacy of LY333334 have not been studied (it is believed that LY333334 is cleared by hepatic Kupffer cells, not by hepatocytes).

In general, drug-drug interaction studies were carried out on very few patients. Although there was a small study of interaction of LY333334 with digitalis, this study was inadequate to permit blanket statements about the

safety of these drugs when used concomitantly. Concomitant furosemide administration did not substantially alter the pharmacokinetic/pharmacodynamic actions of LY333334. Systematic studies of the interaction of LY333334 with digitalis have not been carried out. The concern here is not so much with interactions at the level of pharmacokinetics, but with possible effects of LY333334 and/or changing calcium levels with the actions and toxicities of concomitant medications.

## **X. Conclusions and Recommendations**

**In women with postmenopausal osteoporosis, LY333334, 20 µg for up to two years, is highly effective in reducing the incidence of morphometric vertebral fractures. The drug is also effective in reducing the incidence of extra-vertebral fractures when data from all such sites are pooled. However, the results are not as robust as in the spine. LY333334 was highly effective in increasing lumbar spine BMD, as well as BMD at several other skeletal sites. The effects of the 40 µg dose exceeded those of the 20 µg dose in increasing BMD, but the two doses did not differ in fracture efficacy. The overall effects at the lumbar spine appeared to exceed those of any known agent. The effects at peripheral sites were about the same as previously reported for other (anti-resorptive) drugs. The drug had no effect on height loss.**

**In adult men with idiopathic osteoporosis (with or without primary hypogonadism), LY333334, 20 µg for about 11 months, was highly effective in increasing lumbar spine BMD, but was ineffective, or only marginally effective, in increasing bone density at other skeletal sites. This dose of the drug appears to be inferior to alendronate (the only currently marketed drug for male osteoporosis) at these non-vertebral sites. There was no effect of either dose of LY333334 on height loss.**

**The 40 µg dose of the drug was superior to 20 µg at nearly all skeletal sites. If the drug is to be approved for this indication, it would seem sensible to demonstrate benefits that are at least on a par with established therapy, given the unresolved risk of osteosarcoma.**

**For both men and women, the lack of effect on height loss in the overall population is somewhat surprising, given the overall efficacy at the spine. Other, anti-resorptive, drugs have demonstrated reduction of height loss in the entire trial population, although the results have been inconsistent, and the treatment-related differences have been small. Analyses of height loss that are restricted to the subset of patients who fracture are flawed, as described above.**

**It should be emphasized that there are no fracture efficacy data from any controlled clinical trials in men. The degree to which these changes in**

lumbar spine BMD translate into fracture efficacy is unknown in men. In this regard, increases in BMD as a result of treatment (of either men or women) with an anabolic agent may be associated with long-term benefits that differ from those that accompany BMD changes resulting from anti-resorptive therapy. We do not have sufficient data to determine whether this is true.

Balanced against these benefits is the unknown risk of osteosarcoma. As discussed above, these results were extremely robust (occurring in up to 50% of rats treated with the drug); they were biologically plausible as well. The rat findings have also been observed in mice treated with a similar agent. The sponsor and their external consultants have stated that it is "unlikely" that the rodent findings are relevant to humans. Several reasons are given in support of this position. I have reviewed and discussed these in detail above. None are entirely reassuring. Osteosarcoma is a very high price to pay for treatment of a non-lethal disease.

The sponsor is conducting further experiments that are designed to determine whether LY333334 causes osteosarcomas when given for shorter periods later in the life of rats. It is my opinion that these experiments are extremely important. If the occurrence of tumors is shown to be restricted to animals treated from 6 weeks of age, this will lend some assurance of safety. On the other hand, if tumors occur in animals that began treatment at six months, then the sponsor cannot claim that these findings are caused by life-long exposure to the drug and/or that young animals are particularly vulnerable. The pharmacodynamic responses of the skeletons of older-treated animals will be informative as well. Osteosarcoma may occur without the exaggerated skeletal anabolism seen in the younger group.

If these additional animal experiments disclose significant vulnerability to tumor formation at an older age, particularly following shorter periods of treatment, then I would be reluctant to approve the drug (except possibly for short-term use in osteoporotic patients who are incapacitated by the disease). To many authorities, the assumed requirement for life-long drug exposure appeared to provide a framework for assessment of the clinical relevance of rodent osteosarcomas. In the event that these additional experiments negate these assumptions, then the entire issue should be revisited in a public forum. Of course, other mitigating information may become available in the near future.

In addition to these experiments, additional studies of tumor formation in other species, including the mouse, should be undertaken. I have strongly urged further investigation into the molecular and cellular bases of PTH-induced tumor formation. Perhaps such studies will yield some identifiable marker or mechanism that distinguishes rodent from human osteoblastic

osteosarcomas. The proposed monkey experiments are too small to address this concern adequately, as discussed above.

Based on these considerations, I consider that it would be unsafe and unwise to approve this drug before the ongoing rat experiments are completed, reviewed, and publicly discussed. Although no experiment of this type can resolve the issue of human risk completely, the additional data will provide a far more comprehensive picture of the tumor responses in rodents. The public, as well as practicing physicians, would certainly be better informed about this entire issue before deciding to use this drug.

Accordingly, my recommendation is:

**For treatment of postmenopausal osteoporosis**

**APPROVABLE, pending**

1. establishment of a system for long-term monitoring of osteosarcoma occurrence in patients treated with teriparatide,
2. submission and review of additional study of osteosarcoma occurrence in rodents (see discussions above and in the section on preclinical pharmacology/toxicology), and
4. agreement that the label will include a black box warning about osteosarcoma; the label should also emphasize that the drug is indicated only for patients with severe disease, for which available therapy has been, or is likely to be, inadequate from the standpoint of efficacy, safety, or tolerability.

**For the indication, treatment to increase bone mass in men with  
osteoporosis associated with  
primary hypogonadism**

**APPROVABLE, pending**

- completion of 1, 2, and 3 above, and
- agreement with the Division about dosing of teriparatide in men.

**BRUCE S. SCHNEIDER, MD  
MEDICAL OFFICER, DMEDP, ODE II**

## **XI. Appendix**

This section contains information regarding financial disclosure of investigators, examination of informed consent documents, and results of DSI investigations.

No irregularities were found in examination of informed consent documents. DSI investigations of two of the largest study sites also disclosed no irregularities.

Financial disclosure information was submitted for studies B3D-MC-GHAC and B3D-MC-GHAJ. Agreement was reached with the Division that financial disclosure would be limited to these two pivotal Phase 3 trials (July 12, 2000 pre-NDA meeting).

Study B3D-MC-GHAC (postmenopausal osteoporosis):

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/s/

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Bruce Schneider  
9/6/01 06:28:18 PM  
MEDICAL OFFICER

Eric Colman  
9/10/01 05:42:26 PM  
MEDICAL OFFICER

**APPEARS THIS WAY  
ON ORIGINAL**

## MEMORANDUM

DATE: 1 October 2001

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

TO: The File

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

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

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

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

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

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

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

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

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ON ORIGINAL**

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/s/

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Bruce Stadel  
10/1/01 12:03:36 PM  
MEDICAL OFFICER

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ON ORIGINAL**

## MEDICAL SAFETY REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: **21-318**

Application Type: **NDA**

Sponsor: **Eli Lilly & Company**

Proprietary Name: **Forteo**

USAN Name: **Teriparatide**

Pharmaceutical

Route of

Category: **Bone formation agent**

Administration: **Subcutaneous**

Indication: \_\_\_\_\_

Dosage: **20 micrograms per day**

Medical Safety

Dates of Review: **1 January -7 September 2001**

Reviewer: **Bruce V. Stadel, MD, MPH**

Medical Efficacy Reviewer: **Bruce Schneider, MD**

Chemistry Reviewer: **Yvonne Yang, PhD**

Pharmacology Reviewer: **Gemma Kuijpers, PhD**

Biopharmaceutics Reviewer: **Jim Wei, PhD**

Statistics Reviewer: **Joy Mele, PhD**

**REVIEW SUMMARY:** Preclinical studies at generally higher doses than proposed for marketing raised 3 potential safety issues: hypotension and tachycardia, renal histopathology and malfunction, and osteosarcoma. Dose-related hypotension and tachycardia were also seen in phase 1 clinical studies. These issues and overall safety were evaluated in data from 11 phase 2/3 clinical studies. In the 9 randomized clinical trials, the longest treatment was 2 years. A total of 1452 patients were treated for  $\geq 3$  months. This number provides 95% confidence for detecting an event that occurs once in 484 or fewer patients. In the randomized trials, the rates of mortality and morbidity were similar between the teriparatide and placebo groups, and the 20 mcg/day dose of teriparatide was associated with few adverse symptoms or changes in laboratory safety variables. The reported rates of syncope, other cardiovascular adverse events, and urinary tract adverse events were similar between treatment groups. Serum and urine calcium levels were monitored, and calcium supplements and teriparatide doses were reduced in patients with episodes of hypercalcemia, hypercalciuria, or related symptoms. Under these conditions, the increases in serum and urine calcium caused by teriparatide were not associated with clinical adverse events. No osteosarcomas or other bone cancers were reported. ECGs were not obtained, but a phase 4 commitment has been made to obtain ECGs in an upcoming randomized trial. The main safety issue is that teriparatide caused osteosarcoma in a 2-year rat study when treatment began at weanling age. Another rat study is in progress to clarify the effect on the frequency of osteosarcoma when treatment is begun at an older age. A phase 4 commitment for osteosarcoma surveillance has been made. In women and men  $\geq 50$  years of age, the annual incidence of osteosarcoma is about 4 per million. If teriparatide is marketed for osteoporosis, any adverse effect on the risk of osteosarcoma would probably require several years to detect.

**OUTSTANDING ISSUES:** None

**RECOMMENDED REGULATORY ACTION:**  **N drive location:**

New clinical studies _____	Clinical Hold _____	Study May Proceed _____
NDA, Efficacy/Label supplement: <input checked="" type="checkbox"/>	Approvable _____	Not Approvable _____
Approve _____		

**SIGNATURES:** Medical Safety Reviewer: \_\_\_\_\_

Date: \_\_\_\_\_

Medical Team Leader: \_\_\_\_\_

Date: \_\_\_\_\_

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

**Bruce V. Stadel, MD, MPH**

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<b>Attachment to Hardcopy: Cardiorenal Division Consult</b>	

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

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

The criterion for statistical significance was a 2-sided alpha = 0.05, and the criterion for a statistical trend was a 2-sided alpha = 0.10. The p-values shown below represent overall comparisons between treatment groups except where otherwise stated.

The findings from the phase 2/3 studies are summarized below. Findings from the preclinical and phase 1 studies are discussed in Appendix I. Details of the findings from the main study in women (GHAC) and the study in men (GHAJ) are presented in Appendix II.

**APPEARS THIS WAY  
ON ORIGINAL**

## 1. Summary and Recommendations

### 1.1 Summary

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

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

The phase 2/3 clinical studies of LY333334 appear to have been carefully done, and to provide the basis for thorough evaluation of safety. The 9 randomized clinical trials began in 1996-97 and ended in December 1998. Since then, most of the patients have been in a post-treatment follow-up study.

In the phase 2/3 randomized trials, the longest treatment with LY333334 was 2 years. The total number of patients treated for  $\geq 3$  months was 1452 (82% women, 18% men). This provides 95% confidence for observing an event that occurs once in 484 or fewer treated patients. If an event occurs less frequently, it will not be reliably detected. The annual incidence of osteosarcoma in women and men 50 years of age or older is about 4 cases per million.

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

rate, at 1 hour after dosing, was 5 beats per minute. One hour after injection, the range of standing pulse rates in the placebo group was 47-100 beats per minute and the range in the 40 mcg group was 68-104 beats per minute. These changes in pulse rates were not associated with any statistically significant differences or trends between the 40 mcg group and the placebo group in sitting or standing diastolic or systolic blood pressure. Post-dose pulse rates were not measured for the 20 mcg dose, and post-dose electrocardiograms were not done for either dose. Serum and urine calcium levels were monitored, and calcium supplements and LY333334 doses were reduced in patients with episodes of hypercalcemia, hypercalciuria, or related symptoms. Under these conditions, the increases in serum and urine calcium caused by LY333334 were not associated with clinical adverse events. In both LY333334 groups compared to the placebo group, there were statistically significant increases in 4-6 hour post-dose serum calcium, and in the frequency of transient postdose hypercalcemia. In the 20 mcg group compared to the placebo group, in women, the median increase in 4-6 hour post-dose serum calcium was 0.08-0.12 mmol/L during a 2-year study. The frequency of patients with  $\geq 1$  episode of postdose hypercalcemia increased from 1.5% in the placebo group to 11.1% in the 20 mcg group. In the 20 mcg group, there were no statistically significant increases or trends in 24-hour postdose serum calcium compared to baseline, but at 6 months the median was increased by 0.05 mmol/L compared to the placebo group. In the 20 mcg group compared to the placebo group, the median increase in 24 hour urine calcium excretion was 0.30-0.76 mmol over the course of the study, and there was no clear increase in the frequency of hypercalciuria. There was no evidence of renal malfunction in the LY333334 groups compared to the placebo group.

During the post-treatment follow-up study, the rates of mortality, morbidity, syncope, other cardiovascular adverse events, and urinary tract adverse events were similar between the patients from the LY333334 groups and the patients from the placebo or active control groups. In the women from largest and longest clinical trial, there were trends of increase in the frequency of patients with abnormally high serum creatinine, from 1.7% in the placebo group to 3.9% in the LY333334 groups. These patients are being evaluated further. There were no statistically significant differences or trends between the LY333334 groups and the placebo group for measured creatinine clearance. Statistically significant increases or trends in serum creatinine were not observed in the other phase 2/3 clinical trials.

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

## 1.2 Recommendations

Approvable pending completion of the rat carcinogenicity study that is currently in progress. This study will provide important information about the potential risk of osteosarcoma when LY333334 is given to adult humans. Data should be available by mid-2002.

If LY333334 is approved at this time:

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

The product label should state in a Black Box that: (1) LY333334 has been found to cause osteosarcoma in rats; and (2) LY333334 is contraindicated in patients with Paget' disease of bone and patients with unexplained elevations of alkaline phosphatase. Paget's disease of bone is a risk factor for osteosarcoma and unexplained elevations of alkaline phosphatase may be indicative of Paget's disease. These issues should also be discussed in the body of the label, under Contraindications, Warnings, and Precautions.

The product label should state that the efficacy and safety of treatment with LY333334 for longer than 2 years have not been investigated, and that treatment for longer that 2 years is not recommended. This should be stated under Warnings or Precautions and Dosage and Administration.

The product label should state that serum and urine calcium levels were monitored during the clinical trials. The median serum and urine calcium levels, and the frequency of hypercalcemia and hypercalciuria, should be presented for the patients treated with LY333334 and placebo. The label should state that the potential for serious hypercalcemia, or for

hypercalciuria, was minimized because calcium supplements and LY333334 doses were reduced in patients with episodes of hypercalcemia, hypercalciuria, or related symptoms. There is a potential risk of toxicity in patients receiving digitalis glycosides. These issues should be discussed under Warnings or Precautions.

Procedures should be developed for ensuring and recording the informed consent of patients treated with LY333334.

A phase 4 study should be conducted for surveillance of newly-diagnosed cases of osteosarcoma or other primary bone cancer in women and men in the osteoporosis age-range (e.g.,  $\geq 50$  years of age). This study should evaluate as many cases as feasible, on an ongoing basis, and determine how frequently the cases have histories of exposure to LY333334. If exposed cases begin to be identified, a case-control study should be initiated, to compare the prevalence of LY333334 exposure in the osteosarcoma cases to the prevalence in controls without osteosarcoma. A phase commitment has been made for this and an acceptable study plan has been submitted.

## **2. Issues from Preclinical and Phase 1 Clinical Studies**

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

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

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

**Appendix I** provides further details about the findings in the preclinical and phase I clinical studies, including the doses and durations of LY333334 treatment which produced the disorders described above.

### 3. Findings in Phase 2/3 Studies

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

#### 3.1 Description of Studies

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

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

The 9 randomized phase 2/3 clinical trials enrolled a total of 2627 patients, including 2190 postmenopausal women and 437 men. Of the 2190 women, 1637 (74.7%) were in study GHAC, 393 (17.9%) were in studies GHAF and GHAH, and 160 (7.3%) were in studies GHAA, GHAO, GHAM, GHAU, and GHAV. The 437 men were in study GHAJ. The main osteoporosis criterion for the enrollment of women in study GHAC was the presence on x-rays of  $\geq 1$  vertebral fractures. In the other studies of women and the study of men, the main osteoporosis criterion was low bone mineral density (BMD). The 6 patients in study GHAL had previously been in study GHAC. Study GHBJ enrolled 1930 (77.6%) of the 2486 patients who had been in studies GHAC, GHAJ, GHAF, GHAH, GHAL, GHAU, and GHAV. The numbers of patients by study are shown in Table 1 on page 30.

For LY333334 treatment of women, study GHAC compared 20 mcg and 40 mcg to placebo, study GHAF compared 40 mcg to placebo in women taking HRT, study GHAH compared 40 mcg to oral alendronate, study GHAM compared 40 mcg to placebo in women taking raloxifene or HRT,

and the other trials compared various doses to placebo. In study GHAL, all women were treated with 40 mcg. For LY333334 treatment of men, study GHAJ compared 20 mcg and 40 mcg to placebo.

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

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

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

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

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

### 3.2 Demographics and Disposition of Patients

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

In study GHAC, 9347 women were screened, of whom 1637 (17.5%) were enrolled and randomized to placebo (n=544), 20 mcg (n=541), or 40 mcg (n=552). Of the 7710 excluded patients, 68.8% did not meet x-ray criteria

at the initial reading, 18.3% did not meet protocol entry criteria, 5.8% withdrew due to patient's decision, 5.1% were excluded for unknown reasons, and the other 2.0% were excluded for 10 different reasons. Of the 1411 women who did not meet protocol entry criteria, 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.

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

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

### **3.3 Duration of Treatment**

The actual duration of treatment with study drug was 12-23 months for 1398 (85.4%) of the women in study GHAC, 12-17 months for 307 (78.1%) of the women in studies GHAF and GHAH, and 6-14 months for 381 (87.2%) of the men in study GHAJ. The duration of treatment in the other studies was from 6 weeks to 4 months. The total number of women and men treated with LY333334 for  $\geq 3$  months was 1452 (82.2% women, 17.8% men). This number provides 95% confidence for observing an event which occurs once in 484 or fewer treated patients.

### 3.4 Adverse Events

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

#### 3.4.1 Serious Adverse Events

Serious adverse events (SAEs) are defined as AEs which are fatal or life-threatening, result in hospitalization, prolongation of hospitalization, severe or permanent disability, cancer, congenital abnormality, or drug overdose, or are significant for any other reason. There were 406 patients with SAEs in the Phase 2/3 studies: 315 (77.6%) in study GHAC, 24 (5.9%) in study GHAF, 18 (4.4%) in study GHAH, 45 (11.1%) in study GHAJ, and 4 (1.0%) in the other studies.

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

##### 3.4.1.1 Deaths

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

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

In studies GHAC and GHAJ, the mean ages and (age ranges) in years of the patients who died were: 74 (66-78) in the placebo group, 74 (65-85) in the 20 mcg group, and 75 (66-84) in the 40 mcg group. The mean durations of treatment and (duration ranges) in days were: 309 (88-442) in the placebo group, 329 (46-538), in the 20 mcg group,

and 335 (58-538) in the 40 mcg group. The reported causes of death were: in the placebo group, myocardial infarction, cardiovascular disorder, respiratory disorder, and shock; in the 20 mcg group, myocardial infarction, heart arrest, pneumonia, pancreatitis, death not otherwise specified (nos), carcinoma of larynx, carcinoma of lung, and suicide; and in the 40 mcg group, iron deficiency anemia, cerebrovascular accident, pneumonia (n=2), bladder neoplasm, and lung cancer.

The death in study GHAH was a 75 year old woman with hypertension and thyroiditis who was treated with 40 mcg for 313 days and died of cardiac arrest. The death in study GHAL was a 75 year old woman with angina pectoris, hypertension, heart failure, and ventricular arrhythmia who entered study GHAL from the placebo group of study GHAC, was treated with 40 mcg for 79 days and died in her sleep.

### **3.4.1.2 Cancer**

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

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

In study GHAF, the numbers of patients with cancer SAEs were: 3(2.4%) in the HRT group and 1 (0.8%) in the 40 mcg+HRT group. In study GHAH, there were: 2 (2.7%) in the alendronate group and 3 (4.1%) in the 40 mcg group.

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

Further analyses of cancer are presented in Section 4.2.2.

### 3.4.1.3 Any Serious Adverse Event

In study GHAC, there were 197 different SAEs (i.e., SAE terms). The only specific SAE with a statistically significant difference between treatment groups was breast cancer, which was less frequent in the LY333334 groups than the placebo group (see Section 3.4.1.2). There were statistical trends toward increases in the frequency of hernia ( $p=0.095$ ) and pain ( $p=0.091$ ) in the LY333334 groups compared to the placebo group, but these findings were each based on a total of 9 patients, and did not show a consistent dose-response. In study GHAF, there were 27 different SAEs, in study GHAF there were 28, and in study GHAF there were 63. There were no statistically significant differences or trends between treatment groups for any specific SAE in these studies.

### 3.4.2 Discontinuations due to Adverse Events

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

In study GHAF, the numbers of discontinuations due to AEs were: 11 (8.8%) in the HRT group and 18 (14.8%) in the 40mcg+HRT group ( $p=0.146$ ). In study GHAF, there were: 7 (9.6%) in the alendronate group and 14 (19.2%) in the 40 mcg group ( $p=0.099$ ). In each of these studies, there were none due to nausea in the control (HRT or alendronate) group, compared to 3 in the 40 mcg group. In study GHAF, the numbers of discontinuations due to AEs were: 7 (4.8%) in the placebo group, 14 (9.3%) in the 20 mcg group, and 18 (12.9%) in the 40 mcg group ( $p=0.052$ ). Nausea was the only specific AE with a statistically significant difference or trend between treatment groups: none in the placebo group or the 20 mcg group, and 5 (3.6%) in the 40 mcg group ( $p=0.004$ ).

### 3.4.3 Adverse Events of Any Severity

In study GHAC, the numbers of patients with  $\geq 1$  AE of any severity were: 473 (86.9%) in the placebo group, 447 (82.6%) in the 20 mcg group, and 476 (86.2%) in the 40 mcg group ( $p=0.098$ ). In study GHAF, there were

107 (85.6%) in the HRT group and 107 (87.7%) in the 40 mcg+HRT group ( $p=0.627$ ). In study GHAH, there were 61 (83.6%) in the alendronate group and 66 (90.4%) in the 40 mcg group ( $p=0.219$ ). In study GHAI, there were 112 (76.2%) in the placebo group, 121 (80.1%) in the 20 mcg group, and 112 (80.6%) in the 40 mcg group ( $p=0.600$ ). The statistical trend at the 20 mcg dose in study GHAC was not seen in study GHAI, and may be due to chance. AEs were classified as mild, moderate, or severe on the basis of patient reporting. This is discussed for selected AEs

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

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

In study GHAC, the screening process identified 16 AEs, of which 7 were statistically different between 20 mcg and placebo. Of these, back pain, diabetes mellitus, and breast cancer were less common in the 20 mcg group, and leg cramps, nail disorder, hypokalemia, and tooth caries were more common. The findings for back pain and leg cramps were based on 214 and 23 patients, respectively, and were supported by data from other trials. These AEs are discussed further in Section 3.4.4. The findings for the other disorders were each based on 10 or fewer patients in the placebo and 20 mcg groups combined. Further information about these is presented in Appendix II.

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

### 3.4.4 Further Analysis of Selected Adverse Events

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

**Back Pain:** In study GHAC, the numbers of patients with back pain were: 123 (22.6%) in the placebo group, 91 (16.8%) in the 20 mcg group, and 87 (15.8%) in the 40 mcg group ( $p=0.007$ ). For severe back pain, there were: 29 (5.3%) in the placebo group, 13 (2.4%) in the 20 mcg group, and 21 (3.8%) in the 40 mcg group ( $p=0.043$ ). These findings are similar for the 20 mcg and 40 mcg groups, and are consistent with the decreased incidence and severity of vertebral fractures in the LY333334 groups compared with the placebo group. In study GHAI, the numbers of patients with back pain were 19 (12.9%) in the placebo group, 14 (9.3%) in the 20 mcg group, and 11 (7.9%) in the 40 mcg group ( $p=0.342$ ). For severe back pain, the numbers were: 4 (2.7%) in the placebo group, none in the 20 mcg group, and 2 (1.4%) in the 40 mcg group ( $p=0.130$ ). The difference in findings between studies GHAC and GHAI may be related to the severity of osteoporosis and frequency of fractures, since 1 or more prevalent fractures was the main entry criterion for study GHAC, whereas low BMD was the main criterion for study GHAI.

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

**Nausea:** In study GHAC, the numbers of patients with nausea were: 41 (7.5%) in the placebo group, 51 (9.4%) in the 20 mcg group, and 98 (17.8%) in the 40 mcg group ( $p < 0.001$ ). For severe nausea, there were: none in the placebo group, 4 (0.7%) in the 20 mcg group, and 6 (1.1%) in the 40 mcg group ( $p = 0.062$ ). In study GHAJ, the numbers of patients with nausea were: 5 (3.4%) in the placebo group, 8 (5.3%) in the 20 mcg group, and 26 (18.7%) in the 40 mcg group ( $p < 0.001$ ). There was no severe nausea. There were not a statistically significant difference or trend between the placebo group and the 20 mcg group in the frequency of nausea, in either study.

**Headache:** In study GHAC, the numbers of patients with headache were: 45 (8.3%) in the placebo group, 44 (8.1%) in the 20 mcg group, and 72 (13.0%) in the 40 mcg group ( $p = 0.008$ ). For severe headache, there were: 4 (0.7%) in the placebo group, 3 (0.6%) in the 20 mcg group, and 7 (1.3%) in the 40 mcg group ( $p = 0.411$ ). In study GHAJ, the numbers of patients with headache were: 6 (4.1%) in the placebo group, 8 (5.3%) in the 20 mcg group, and 15 (10.8%) in the 40 mcg group ( $p = 0.053$ ). For severe headache, there were none in the placebo group or the 20 mcg group, and 2 (1.4%) in the 40 mcg group. There was not a statistically significant difference or trend between the placebo group and the 20 mcg group in the frequency of headache, in either study.

**Leg Cramps:** In study GHAC, the numbers of patients with leg cramps were: 6 (1.1%) in the placebo group, 17 (3.1%) in the 20 mcg group, and 13 (2.4%) in the 40 mcg group ( $p = 0.069$ ). For severe leg cramps, there were: 2 (0.4%) in the placebo group, 2 (0.4%) in the 20 mcg group, and none in the 40 mcg group. The overall frequency of leg cramps was similar for the 20 mcg and 40 mcg groups, and an increase in the frequency of leg cramps in women treated with 40 mcg was also found in studies GHAF and GHAH. In study GHAJ, the numbers of patients with leg cramps were: 3 (2.0%) in the placebo group, 1 (0.7%) in the 20 mcg group, and 1 (0.7%) in the 40 mcg group ( $p = 0.455$ ). Two patients in the placebo group and none in the 20 mcg or 40 mcg groups had severe leg cramps.

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

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

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

**Dizziness and Vertigo:** In study GHAC, the numbers of patients with dizziness were: 33 (6.1%) in the placebo group, 50 (9.2%) in the 20 mcg group, and 44 (8.0%) in the 40 mcg group dizziness ( $p=0.144$ ). For severe dizziness, there were: none in the placebo group, 6 (1.1%) in the 20 mcg group, and 2 (0.4%) in the 40 mcg group ( $p=0.028$ ). These findings suggest an increase in the frequency of severe dizziness in the 20 mcg and 40 mcg groups, but the numbers of patients were small. For vertigo, there were: 18 (3.3%) in the placebo group, 24 (4.4%) in the 20 mcg group, and 27 (4.9%) in the 40 mcg group ( $p=0.407$ ). There were 3 patients with severe vertigo, 1 in each treatment group. In patients receiving treatment with nitrates, the numbers of patients with dizziness or vertigo were: 8/52 (15.4%) in the placebo group, 20/70 (28.6%) in the 20 mcg group, and 7/54 (13.0%) in the 40 mcg group ( $p=0.063$ ). In patients not receiving nitrates, there was no statistically significant difference or trend between treatment groups in the frequency of dizziness or vertigo. In study GHAJ, the numbers of patients with dizziness were: 4 (2.7%) in the placebo group, 5 (3.3%) in the 20 mcg group, and 9 (6.5%) in the 40 mcg group ( $p=0.231$ ). There was no severe dizziness. For vertigo, there were: 1 (0.7%) in the placebo group, 2 (1.3%) in the 20 mcg group, and 4 (3.9%) in the 40 mcg group ( $p=0.316$ ). There was no severe vertigo.

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

**Patients Taking Digitalis Glycosides:** In study GHAC, 55 patients took digitalis glycosides: 20 in the placebo group, 20 in the 20 mcg group, and 15 in the 40 mcg group. In these patients, there were no statistically significant differences or trends between treatment groups for patients with  $\geq 1$  AE or any specific AE, except for decreases in the 20 mcg group in the frequency of pain and depression. These findings were not seen in the 40 mcg group and may have been due to chance.

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

### 3.5 Vital Signs

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

rates were not associated with any statistically significant differences or trends between the 40 mcg group and the placebo group in sitting or standing diastolic or systolic blood pressure.

### 3.6 Electrocardiograms

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

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

### 3.7 Laboratory Safety Variables

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

#### Study GHAC: LY333334 20 mcg Compared to Placebo

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

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

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

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

6 weeks, the 24 hour urine calcium excretion was decreased, in the 20 mcg group compared to the placebo group ( $p=0.124$ ). The median decrease was 0.20 mmol/L.

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

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

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

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

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

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

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

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

There was not a statistically significant difference or trend in the frequency of leukocyte counts above the upper limit of normal, in the 20 mcg group compared to the placebo group. There were 37 (6.9 %) patients in the 20 mcg group with leukocyte counts below the lower limit of normal, compared to 60 (11.2%) in the placebo group ( $p = 0.016$ ). There were no statistically significant differences or trends in the frequency of abnormal values for the segmented neutrophil, band, lymphocyte, monocyte, eosinophil, or basophil counts, in the 20 mcg group compared to the placebo group.

**Parathyroid Hormone (1-84):** Of the blood samples obtained for measuring PTH (1-84), 89.1% in the 20 mcg group and 71.7% in the placebo group were below the level of quantitation. The blood samples were collected 2.3 hours after dosing with study drug, on average, and it is likely that PTH (1-84) was suppressed during this postdose interval in the patients receiving LY333334.

**LY333334 Antibodies:** A positive test for anti-LY333334 antibodies was defined as at least a 2-fold increase in binding plus at least 40% inhibition. Fifteen (2.8%) patients had at least 1 positive antibody test in the 20 mcg group, compared to 1 (0.2%) in the placebo group ( $p < 0.001$ ). Preliminary data from follow-up testing about 6 months after study closeout indicates that the binding activity decreased and the inhibitory activity remain about the same.

No differences were found between the patients with and without positive antibody tests in serum calcium, BMD, or adverse events. Hypocalcemia should be a sensitive indicator for impairment of PTH (1-84) activity by antibodies, and loss of BMD response should be an indicator for clinically significant neutralization of LY333334 by antibodies. Serum calcium and

BMD response were similar in patients with or without positive antibody tests, which suggests that the serum binding activity did not have detectable adverse effects.

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

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

**Appendix II** provides further details about the findings in study GHAC in women and study GHAJ in men.

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

### **4.1 Post-treatment Follow-up Study GHBJ**

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

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

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

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

### **4.2 Safety Update**

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

The Lilly safety database was searched through 5 February 2001 for any reports of death, osteosarcoma, or coronary artery disease in patients who had been in the clinical studies. The information on deaths, updated through 4 June 2001, is discussed below. No reports of osteosarcoma or previously unknown coronary disease were found. The additional follow-up data are from study GHBJ, through 9 February 2001 for SAEs, and 7 December 2000 for other data.

### 4.2.1 Deaths

A total of 47 patients who were in the clinical studies are known to have died, including 20 who died during the studies and 27 who died after discontinuation. The occurrence of death during the studies is discussed above (see Section 3.4.1.1). The discussion here includes all deaths. Table 2 on pages 31-32 shows a list of the deaths by gender, age, and cause.

Of the 47 patients, 40 were in study GHAC, 5 were in study GHAJ, 1 was in study GHAH, and 1 was in study GHAL (Table 2). The death rates by treatment group are the number of deaths/number of patients in a group.

Combining data from studies GHAC and GHAJ accounts for 45 (96%) of the deaths and provides a valid comparison between placebo and the two LY333334 groups. The total death rates during or after discontinuation from these studies were: 13/691 (1.9%) in the placebo group, 17/692 (2.5%) in the 20 mcg group, and 15/691 (2.2%) in the 40 mcg group ( $p=0.764$ ).

However, the proportion of patients >70 years of age was higher in the LY333334 groups compared to the placebo group: 281 (40.7%) in the placebo group, 308 (44.5%) in the 20 mcg group, and 318 (46.0%) in the 40 mcg group. Taking account of this difference, the death rates during or after discontinuation from the studies were: in patients <70 years of age, 4/410 (1.0%) in the placebo group, 6/384 (1.6%) in the 20 mcg group, and 5/373 (1.3%) in the 40 mcg group ( $p=0.528$ ); in patients  $\geq 70$  years of age, 9/281 (3.2%) in the placebo group, 11/308 (3.6%) in the 20 mcg group, and 10/318 (3.1%) in the 40 mcg group ( $p=0.811$ ).

Figure 1 on page 33 shows survival curves by treatment group for the patients in studies GHAC and GHAJ from randomization through post-treatment follow-up in study GHBJ (These are not age-adjusted).

### 4.2.2 Cancer

No osteosarcomas have been reported for any patient treated with LY333334. However, an increase in osteosarcoma in the patients treated with LY333334 would have to be very large to be reliably detected in the available data, since the incidence of osteosarcoma in untreated women and men 50 years of age or older is about 4 cases/million persons/year<sup>1</sup>.

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

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

Paget's disease is associated with an increased risk of osteosarcoma. Initially, Paget observed the development of sarcomas in 5 of 23 patients with osteitis deformans.<sup>2</sup> Since then, reports in the literature since then have described osteosarcomas in 0.7-5.0% of patients with Paget's disease, with the lower frequencies being in studies which followed both asymptomatic and symptomatic patients.<sup>3-6</sup> Paget's disease may also be associated with osteoporosis, according to one study, which reported histories of osteoporosis in about 18% of women with Paget's disease compared to 9% of women of similar age who did not have the disease.<sup>7</sup> About 1% of people 55 years of age or older have Paget's disease to an extent that is detectable on x-rays, primarily in the pelvis, according to data from the First (1971-75) National Health and Nutrition Examination Survey. The findings were similar for women and men, and for black and white patients. The disease was more common in the northeastern states than in other states.<sup>8</sup>

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

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

The numbers of patients skin cancer or other neoplasia AEs during studies GHAC and GHAJ were: 48 (6.9%) in the placebo group, 39 (5.6%) in the 20 mcg group, and 51 (7.4%) in the 40 mcg group ( $p=0.399$ ). For the follow-up period in study GHBJ, the numbers of patients from studies

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

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

#### 4.2.3 Any Serious Adverse Event

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

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

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

#### 4.2.4 Discontinuations Due to Adverse Events

Five patients discontinued the follow-up study due to AEs: 2 from the GHAC placebo group discontinued due to gastrointestinal carcinoma; 2 from the GHAC 20 mcg group discontinued, 1 due to memory loss and 1 due to asthma; and 1 from the GHAF HRT group, due to breast carcinoma.

#### 4.2.5 Adverse Events of Any Severity

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

Only the follow-up period will be discussed here.

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

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

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

study GHBJ than was found during the treatment period in study GHAC, rather than a higher frequency in the LY333334 groups. Of the 23 cases of anemia, 20 were reported as mild and 3 as moderate.

In the patients from study GHAC, the numbers with cardiovascular disorder as an AE were: 7 (1.7%) in the placebo group, 15 (3.4%) in the 20 mcg group, and 20 (4.9%) in the 40 mcg group ( $p=0.040$ ). Of the 42 cases of cardiovascular disorder, 34 were rated as mild and 8 as moderate. The most common disorders were heart murmurs or valve abnormalities. Possible implications of these findings for more serious disease were investigated by grouping cardiovascular system AE terms related to common forms of cardiovascular disease: congestive heart failure, coronary artery disease, any arrhythmia, supraventricular arrhythmia, ventricular arrhythmia, and extracardiac thrombosis. This investigation showed no statistically significant differences or trends between treatment groups for any of these disorders except coronary artery disease: 17 (4.1%) in patients from the placebo group, 34 (7.8%) in patients from the 20 mcg group, and 20 (4.9%) in patients from the 40 mcg group ( $p=0.046$ ). This finding may be due to chance, since there is no difference between the placebo and 40 mcg groups. Also, the baseline frequency of patients with a history of myocardial infarction or angina pectoris was somewhat higher in the 20 mcg group compared to the placebo and 40 mcg groups, although no direct evidence was provided that the patients with these conditions at baseline were the patients with coronary artery disease AEs in the follow-up period. There is not a clear explanation for the increased frequency of heart murmurs or valve abnormalities in patients treated with LY333334.

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

#### **4.2.6 Laboratory Safety Variables**

The laboratory safety variables were evaluated in study GHBJ by comparing the treatment groups from each contributing study for the change from baseline in that study to the last value obtained in study GHBJ.

The findings from study GHAC patients for 20 mcg compared to placebo are presented here, because study GHAC was the largest clinical trial, and 20 mcg is the dose proposed for marketing. The 40 mcg dose and the other studies are considered when adding useful information.

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

Abnormally high serum creatinine (>101 mcmol/L) was found in 17 (3.9%) patients in the 20 mcg group compared to 7 (1.7%) in the placebo group ( $p=0.055$ ), and the findings for 40 mcg were similar. In the 17 patients in the 20 mcg group, the median creatinine was 110 mcmol/L and the range was 104-137; in the 7 patients in the placebo group, the median was 109 and the range was 104-115. The frequency of 4-6 hour postdose hypercalcemia during study GHAC was not related to the frequency of abnormally high serum creatinine during study GHBJ. In follow-up data from 5 of the 17 patients in the 20 mcg group, serum creatinine had increased in 2 patients, decreased in 2, and was unchanged in 1. Although there was a proportionally similar increase in the frequency of abnormally high serum creatinine in the patients from study GHAJ, in the LY333334 groups compared to the placebo group, this was based on very small numbers of patients, and may have been due to chance. ( $p>0.1$ ). There were no statistically significant differences or trends between treatment groups in the patients from any of the studies for measured creatinine clearance.

Serum total alkaline phosphatase was decreased by about 3% in the 20 mcg group compared to the placebo group ( $p=0.063$ ), and the findings for 40 mcg were stronger. There were statistical trends for serum potassium, total protein, and albumin, but these were <1% different between the 20 mcg group and the placebo group, and the findings for 40 mcg were not supportive. There were no other statistically significant differences or trends between the 20 mcg group and the placebo group.

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

## References

1. Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-1998). National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2001, based on the August 2000 submission.
2. Paget J. Remarks on osteitis deformans. *Illus Med News*. 1889;2:181-2.
3. Freydingler JE, Duhig JT, McDonald LW. Sarcoma complicating Paget's disease of the bone: a study of seven cases with report of one long survival after surgery. *Arch Pathol* 1963;75:496-500.
4. Wick MR, Siegal GP, Unni KK, Greditzer HG. Sarcomas of bone complicating osteitis deformans (Paget's disease): fifty years' experience. *Am J Surg Pathol* 1981;5:47-59.
5. Greditzer HG, McLeod RA, Unni K, Beabout JW. Bone sarcomas in Paget disease. *Radiology* 1983;146:327-33.
6. Hadjipavlou A, Lander P, Srolovitz H, Enker IP. Malignant transformation in Paget disease of bone. *Cancer* 1992;70:2802-8.
7. Siris ES. Epidemiologic aspects of Paget's disease: family history and relationship to other medical conditions. *Semin Arthritis Rheum*. 1994;23:222-5.
8. Altman RD, Bloch DA, Hochberg MC, Murphy WA. Prevalence of Paget's disease of bone in the United States. *J Bone Miner Res*. 2000;15: 461-5.

Table 1

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

Prior Study	Prior Study Treatment							Total Enrolled in B3D-MC-QHBJ	Prior Study Enrollment	Percent of Prior Study Enrollment in B3D-MC-QHBJ
	Placebo	PTH20	PTH40	HRT	HRT/ PTH40	AL EN	No TRT			
B3D-MC-QHAC	414	436	412					1262	1637	77.09%
B3D-MC-QHAJ	127	121	107					355	437	81.24%
B3D-MC-QHAF				97	94			191	247	77.33%
B3D-MC-QHAH			52			53		105	146	71.92%
B3D-MC-QHAL			3				4	3	6	50.00%
B3D-MC-QHAV		4	2				1	10	13	76.92%
Total	541	561	579	97	94	53	5	1930	2486*	77.63* <del>77.44</del> %

\* All B3D-MC-QHAL patients were previously enrolled in B3D-MC-QHAC.

Abbreviations: PTH20 = LY333334 20 µg/day; PTH40 = LY333334 40 µg/day; HRT = Hormone Replacement Therapy; AL EN = alendronate 10 mg/day; TRT = treatment.

Table 2

## Deaths During Participation in Clinical Studies of LY333334

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

<sup>a</sup> Patient initially treated in placebo group in Study B3D-MC-GHAC, then entered Study B3D-MC-GHAL.

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Table 2-concluded.

## Deaths Subsequent to Participation in Clinical Studies of LY333334

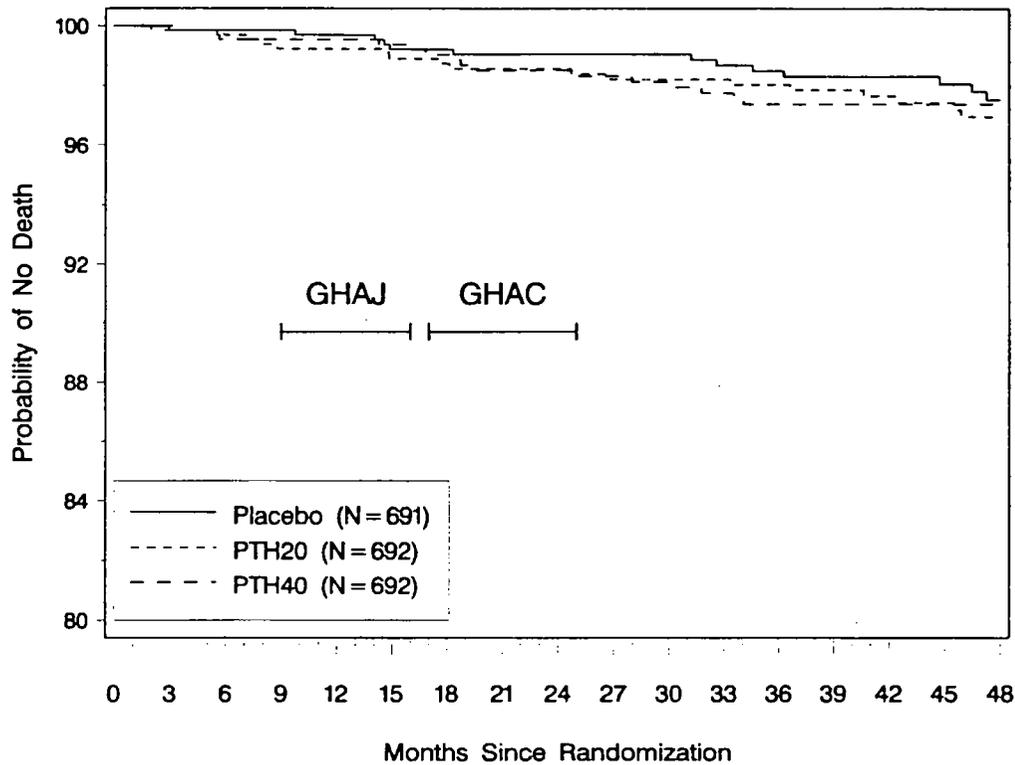
Patient Number	Previous Study	Sex	Age at Baseline (years)	Dose ( $\mu\text{g}/\text{d}$ )	Random-ization to Last Dose (days)	Random-ization to Death (days)	Cause of Death
GHAC-150-3869	GHAC	F	66	Placebo	181	427	Breast cancer
GHBJ-015-0251	GHAC	F	75	Placebo	596	1439	Emphysema
GHBJ-040-0614	GHAC	F	75	Placebo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

<sup>a</sup> Date of last hospital discharge; death occurred within 3 months (date of death unknown).

Figure 1

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

Kaplan–Meier Curves for the Time to Death  
Continuing Patients Censored at 4 June 2001  
All Randomized Patients  
All Patients From Previous LY333334 Protocols GHAC and GHAJ



LOG-RANK p-value = 0.780

WILCOXON p-value = 0.713

Horizontal lines indicate when randomized studies stopped and follow up period began.  
Program in RMPB3DSBJV2.SASPGM(AEGCJ1RB)  
Source: Eli Lilly ClinTrace Database 4 June 2001

## Appendix I

### Findings in Preclinical and Phase 1 Clinical Studies

#### 1. Preclinical Pharmacology and Toxicology Studies

##### 1.1 Hypotension and Tachycardia in Rats, Dogs, and Monkeys

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

##### 1.2 Renal Histopathology in Monkeys

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