

CONTENTS: Enclosed are an executive summary for the Advisory Committee and a draft of my review of the efficacy of LY333334 for the treatment of postmenopausal osteoporosis and osteoporosis in men. The latter document contains a description of the background for development of LY333334, followed by review of the clinical pharmacology program and review of each of the pivotal phase 3 trials.

EXECUTIVE SUMMARY FOR ADVISORY COMMITTEE

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I. Recommendations

A. Recommendation

I have not provided formal recommendations at this point.

Treatment of postmenopausal osteoporosis: LY333334, subcutaneous injection of 20 µg/day, appears to offer advantages over current therapy for treatment of postmenopausal osteoporosis. Although some safety issues remain, none would preclude or delay approval for this indication, except for the unresolved concern over the occurrence of osteosarcomas in rodents treated with LY333334. The final risk/benefit judgment depends on the level of concern and, in part, on the proposals for post-marketing surveillance, since the drug has clearly demonstrated efficacy in preventing fractures and increasing bone mass.

Treatment of osteoporosis in men: For the treatment of osteoporosis in men (idiopathic osteoporosis and osteoporosis associated with primary hypogonadism), the clinical benefits of LY333334 20 µg/day are less apparent. Consequently, the decision regarding approval would be made on less certain grounds. Since the drug has clearly demonstrated efficacy in increasing bone mineral density at the lumbar spine, approval could be based on this outcome alone, if there were no safety concerns. However, the outstanding safety issues for men are essentially the same as for women. Balanced against these are the efficacy outcomes, which suggest that the proposed 20 µg dose offers somewhat less overall benefit than can be achieved with current therapy (the spine BMD increases exceeded those that have been reported with alendronate, while alendronate appeared to be superior at other skeletal sites). In addition, no currently approved therapy has demonstrated anti-fracture efficacy in male osteoporosis.

There are several options for this indication: One course of action would be to grant LY333334 an approvable status for the male osteoporosis indication, pending determination of a dose that yields efficacy at peripheral sites or provides advantages over current therapy. There are

cogent data from the trials that suggest that the 20 µg dose was sub-optimal and that the 40 µg dose provided the required efficacy. However, clinical and laboratory events (none immediately serious) related to safety/tolerability began to appear at 40 µg. Accordingly, an additional placebo-controlled or active-controlled (alendronate) study of the effects of LY333334 in doses of 25 or 30 µg/day in men with osteoporosis should yield a more favorable benefit profile (at non-vertebral sites) with no increase in adverse events.

Another course of action might be to grant approvable status for this indication, pending design of a method for dose titration in men (in the range 20-40 µg/day), based on safety/tolerability and BMD responses of individual patients. This would eliminate the need for another placebo-controlled trial.

B. Recommended Phase 4 studies and/or risk management steps

See Integrated Safety Review for suggested safety monitoring protocols for osteosarcoma and for further evaluation of cardiovascular responses to LY333334.

Risk management steps should also include:

Limiting LY333334 therapy to patients who are at significant risk for osteoporotic fracture.

Indicating LY333334 as second line therapy to be used in combination with an anti-resorptive agent or in patients in whom anti-resorptives have produced unsatisfactory efficacy or safety outcomes.

Limiting duration of use of LY333334 to two years.

I also recommend further research that will develop the best treatment regimens. What are the benefits of combining an anti-resorptive agent (bisphosphonate, estrogen, SERM) with LY333334? When should each agent be given? What is the optimum duration of treatment with LY333334? Trials of LY333334 in patients with glucocorticoid-induced osteoporosis should also be encouraged. A pediatric development program that targets osteoporosis or osteogenesis imperfecta should be considered only after the osteosarcoma concern is either settled or substantially allayed.

II. Summary of Clinical Findings

A. Brief overview of clinical program

DRUG GENERIC AND PROPOSED TRADE NAME: Forteo™ [teriparatide injection (rDNA origin), recombinant human parathyroid hormone (1-34), LY333334].

Sponsor: Eli Lilly and Company, Indianapolis, IN

Pharmacological Category: Recombinant peptide; peptide hormone fragment, rDNA origin.

Indication: Treatment of postmenopausal osteoporosis and treatment of (adult) male osteoporosis (idiopathic or associated with primary hypogonadism).

Dosage Form and Route of Administration: Solution (250 µg teriparatide/ml) for subcutaneous injection. Forteo is supplied in a 3 ml cartridge within a pre-filled delivery device that delivers 20 µg teriparatide per dose. The proposed dose for both indication is 20 µg/day, delivered subcutaneously to abdomen or thigh.

Summary: The sponsor has developed teriparatide [recombinant human PTH (1-34), LY333334] as a bone-specific anabolic agent for the treatment of postmenopausal osteoporosis and male osteoporosis. All of the currently approved treatments for osteoporosis depend on drugs that inhibit bone resorption by osteoclasts. Drugs in this category of “anti-resorptive” agents include bisphosphonates (e.g., alendronate, risedronate), estrogens, SERMs, and calcitonin. Many of the drugs in this class have shown efficacy in reducing fracture risk, in addition to increasing bone mineral density (BMD). However, the fracture risk reductions are limited (e.g., generally in the range of 40% for vertebral fractures). Combinations of different classes of anti-resorptives (e.g., a bisphosphonate plus estrogen) can lead to further increases in bone mineral density (BMD), but the increments have been small and clinical benefits have not been demonstrated (owing to size and duration of studies). It is currently believed that we have derived the maximum benefit from the strategy of inhibiting bone resorption. This may well derive from the fact that inhibition of resorption leads secondarily to a significant decrease in bone formation, and that further decline in bone resorption rates may lead to a nearly complete dampening of the remodeling process in bone. For this reason, it is believed that the development of drugs that stimulate new bone formation (“anabolic” agents) will further increase our ability to prevent osteoporotic fractures. Such anabolic agents will fill a significant unmet medical need.

The scientific basis for the development program for LY333334 was derived from abundant preclinical and clinical data, originating as early as 1929, demonstrating that injections of various preparations of PTH resulted in increases in skeletal mass. In experimental animal models, the increases in bone mass were accompanied by augmented bone strength. Thus, intermittently

administered PTH results in a greater net anabolic action than is generally seen with primary or secondary hyperparathyroidism, in which consistently elevated levels of the hormone can cause loss of (mainly cortical) bone, with preservation or even small increases in the cancellous compartment.

Thus the pharmacodynamic properties of PTH are partially dependent upon pharmacokinetics. This feature of PTH action on bone has been confirmed in numerous *in vitro* and *in vivo* models, including cell culture, organ culture, and a variety of intact and ovariectomized animal species. There is evidence that the positive effects of intermittently administered PTH result from increased osteoblast differentiation, leading to an enhancement of the functional osteoblastic cell pool.

Expanding on the earlier published observations, the sponsor has conducted a large preclinical pharmacology/toxicology program in support of the clinical studies. In several rodent models, daily subcutaneous injections of recombinant human PTH 1-34 (LY333334) at normocalcemic doses increased trabecular and cortical bone at axial as well as appendicular sites. The bone was found to be of normal quality and architecture. Bone strength was also shown to increase in response to LY333334 in rodent models. In monkeys, the drug caused an increase in cancellous bone. However, in cortical bone, the effects were not as clear. There was evidence for increase in cortical bone remodeling and porosity, with an increase in endocortical bone formation. There was preservation of bone strength at the humerus, but it is not known whether this is true of other cortical sites in monkeys. Details of the effects of LY333334 on bone in preclinical models are provided in the Pharmacology/Toxicology Briefing Document.

In the preclinical studies, non-hypercalcemic doses of LY333334 demonstrated very little acute toxicity, with no evidence of genotoxicity. The major serious effect of LY333334 treatment was the appearance of osteosarcomas (clinically apparent by 18 months) in rodents treated from weaning. The appearance of this malignant neoplasm occurred in a dose-responsive manner. Focal hyperplastic lesions and benign bone neoplasms were also observed. These included focal osteoblast hyperplasia, osteoma, and osteoblastoma. The growth of osteosarcomas in PTH-treated animals is biologically plausible, based on the mechanism of action of the drug, and is the subject of intensive review and recommendations. The discovery of the rodent osteosarcomas led to the abrupt termination of all clinical trials. Although there is no evidence to date that osteosarcomas (or any other bone lesion) occur in humans treated with PTH, the observation periods have been relatively short (that is, to detect clinical tumor occurrence), and the issue remains a serious concern. It should be noted that there is no known increase in the incidence of osteosarcoma in patients with primary or secondary hyperparathyroidism. However, the pronounced net bone anabolism that accompanies intermittent administration of exogenous peptide is not found in hyperparathyroidism. LY333334 treatment did not increase the incidence of other neoplasms in the preclinical studies.

The clinical development program for LY333334 included 21 trials that enrolled more than 2800 women and men. The sponsor's early (Phase 1-2) studies established pharmacodynamic dose-efficacy relationships, as well as a safety profile. The sponsor tested the effects of single and multiple doses (multiple dose range from 6 to 60 µg for periods up to 6 weeks). These studies demonstrated a strong dose-dependent effect of LY333334 on the levels of biomarkers of bone formation (procollagen I carboxy peptide [PICP] and bone specific alkaline phosphatase [BSAP], as well as on urinary N-telopeptide (NTX), a marker of bone resorption. For PICP and BSAP (markers of bone formation), responses were seen as early as 3 weeks after initiation of treatment, with a strong dose-response relationship in the range 15- 40 µg/day. In these studies, 6 µg/day produced no effect on the levels of bone biomarkers. At doses > 40 µg/day, there was a variable increase in response.

In these phase 1-2 studies, LY333334 doses \geq 40 µg/day were associated with increased incidence of headache, nausea, dizziness, and orthostatic hypotension. There was also an increase in mild, transient, asymptomatic hypercalcemia, as well as asymptomatic hypercalciuria, at doses \geq 40 µg/day. Taken together, the overall efficacy and safety data from the Phase 1 and 2 studies suggested that 40 µg/day was the highest tolerable dose for long-term studies and established a range of 15 to 40 µg/day as the optimal dose range for Phase 3 testing.

As part of the clinical pharmacology program, as well as the major phase 3 trials, the sponsor conducted both traditional (intensive, individual) and population-based pharmacokinetic and pharmacodynamic studies. These studies identified no population subgroup that would require dose adjustments. These studies are described in sections D and E, below. A complete description of the Phase 1-2 pk-pd and overall population pk-pd studies appears in the efficacy review.

Based on results of the preclinical pharmacology/toxicology studies, the clinical Phase 1-2 studies, and the known medical complications of hyperparathyroidism, the sponsor designed the large pivotal Phase 3 trials, as well as additional clinical pharmacology studies, to include the evaluation of specific potential adverse events. These included hypercalcemia, hypercalciuria, urolithiasis, diminished renal function, hypertension, and acute hypotension following administration of the peptide. The sponsor also measured antibodies to LY333334. The additional clinical pharmacology studies focused on evaluation of acute hemodynamic effects that might be associated with treatment. Of importance, in the Phase 3 studies, patients remained under observation at the study sites for at least 3 hours after the first dose of LY333334, in order to detect and evaluate possible hypotension. In addition, the sponsor monitored serum and urine calcium, renal function, and vital signs. Of note, the trials excluded patients with nephrolithiasis occurring within 2 years of enrollment.

The sponsor enrolled a total of 2030 postmenopausal women and 437 men in the four long-term Phase 3 clinical trials. Of these, 1970 subjects received LY 333334 (738 received 20 µg and 1107, 40 µg). In these trials, 1137 patients received LY333334 for more than one year. The planned duration of the Phase 3 trials was up to three years. However, the maximum exposure time on drug was two years because all clinical trials were terminated in December 1998, following the discovery of osteosarcomas in the ongoing rat carcinogenicity study.

There were two pivotal clinical trials. The indications studied in these trials were postmenopausal osteoporosis (GHAC) and osteoporosis in men (GHAJ). At the time of termination of the pivotal postmenopausal osteoporosis treatment study (GHAC), the median duration of observation was 19 months. In the male osteoporosis study (GHAJ) the median exposure time was 11 months. All patients who had been enrolled in any long-term study were offered the option to participate in an observational follow-up study (Study B3D-MC-GHBJ). Approximately 75% of eligible patients enrolled in that study.

B.Efficacy

The four long-term Phase 3 trials included the two placebo-controlled pivotal studies and two active-controlled supportive studies.

Study B3D-MC-GHAC, treatment of postmenopausal osteoporosis:

The pivotal efficacy study supporting the indication for the treatment of postmenopausal osteoporosis (Study B3D-MC-GHAC) was intended to be a three-year, double-blind, randomized, placebo-controlled, parallel design, multi-center (multinational) study of 1637 postmenopausal osteoporotic women who were randomized to placebo or LY333334 20 µg/day or 40 µg/day (1:1:1 randomization schedule). The entry criteria included presence of one or more atraumatic vertebral fractures.

The primary efficacy outcome variable was reduction in incidence of new vertebral fractures, which were defined by morphometric analysis of digitized spine radiographs. The radiographs were taken at baseline and study end. Most of these fractures are not clinically apparent; however, this is a standard clinical efficacy outcome for osteoporosis treatment trials.

Secondary endpoints included proportion of patients with new non-vertebral fractures combined;¹ changes in BMD of spine and hip; changes in levels of bone turnover biomarkers; changes in height; and changes in health-related quality of

¹ All non-vertebral fractures were pooled for the analysis. The trial lacked statistical power to detect differences in fracture rates at individual non-vertebral sites. Non-vertebral fractures are usually clinically symptomatic and confirmed by appropriate x-ray studies.

life indices. The study also included evaluation of population pharmacokinetics and pharmacodynamics. Safety evaluation included all clinical adverse events, routine hematology and chemistry, urinalysis, post-dose serum calcium, 24-hour urine calcium, creatinine clearance, bone biopsy (selected study sites), and detection of LY333334 antibodies.

The trial enrolled 1637 women, aged 30-85 years, who had been postmenopausal for at least 5 years prior to randomization. Each patient had at least one moderate or two mild atraumatic vertebral fractures at baseline. For patients with fewer than two moderate fractures, the spine or hip BMD T-score had to be -1 or lower. Women were excluded if they had illnesses affecting bone or mineral metabolism (including Paget's Disease, hyper- or hypoparathyroidism, elevated endogenous PTH 1-84, and other diseases affecting bone), recent history of urolithiasis, impaired liver or renal function, or if they had taken drugs affecting bone or mineral metabolism within two years of enrollment. All patients received adequate calcium + vitamin D supplementation (1000mg elemental calcium + 400-1200 IU of vitamin D).

The baseline characteristics of the trial population were similar to those of patients in other studies of postmenopausal osteoporosis and essentially the same across all three arms of the study. The mean lumbar spine BMD T-score at baseline was -2.6 in the three treatment groups. The presence of prevalent baseline vertebral fractures undoubtedly ensured a reasonably high incident vertebral fracture rate during the trial. The overall retention rate was about 80% (until the trial was prematurely terminated by the sponsor), which is very much in keeping with results of most osteoporosis trials and certainly consistent with reliable analyses of endpoints. The median exposure to the drug was 19 months. About 70% of patients in all three groups completed more than 17 months of treatment, and 82% completed more than 15 months.

Despite the premature termination of the study, the sponsor was able to meet the primary efficacy goal, as well as nearly all the secondary outcomes. For the primary efficacy endpoint (reduction in the risk of new morphometric vertebral fractures), and some of the secondary endpoints, the effects of 19 months of treatment with this new anabolic agent equaled or exceeded those that have resulted from 36-48 months of exposure to any known anti-resorptive drug. Of the 1636 women who entered the trial, 1326 (81%) had adequate baseline and follow-up spine radiographs. By study end, 105 patients had one or more new vertebral fractures, 64 (14.3%) in the placebo group, 22 (5.0%) in the LY333334 20 μg group, and 19 (4.4%) in the 40 μg group ($p < 0.001$ for either LY333334 group vs placebo). This yields relative risk reductions of 65% for the 20 μg treatment group and 69% for the 40 μg group. The absolute risk reductions in these two LY333334 dose groups were 9.3% and 9.9%, respectively. In similar studies, the relative risks of suffering a new vertebral fracture were reduced by 47% with alendronate, 41% with risedronate, and 30% with raloxifene. At the time of this writing, nasal salmon calcitonin has not demonstrated consistent

fracture reduction efficacy, and there are no data from randomized prospective trials of the fracture-prevention efficacy of estrogen. It is worth noting that the treatment periods for all the comparison drugs were substantially longer than 19 months².

Because the majority of morphometric vertebral fractures are clinically silent, it is difficult to evaluate the overall direct clinical impact of these data taken alone. The presence of vertebral fractures is highly predictive of the occurrence of subsequent vertebral fractures, some of which will be clinically symptomatic. Unfortunately, the sponsor did not include an analysis of clinical vertebral fractures (fractures that usually present as back pain and are confirmed radiologically) in this application. The incidence of these has been low (about 1-5%, depending on the population) in past clinical trials, and it has been difficult to power trials to examine this endpoint specifically.

Although the pharmacodynamic responses (i.e., changes in levels of biochemical markers and increases in BMD) to 40 µg/day exceeded those of the 20 µg dose, the two doses were equal in anti-fracture efficacy. This finding was of particular importance, in view of the increased safety/tolerability concerns that are associated with the higher dose of the drug. Thus GHAC, together with the extensive phase 2 studies, established 20 µg as the optimal daily dose of LY333334 in women. However, the trial did not identify the ideal duration of treatment with LY333334, for reasons beyond the sponsor's control. This is unfortunate: judging from the trajectory of the BMD accumulation curves, one might anticipate substantial increases in bone mass with further treatment. It is quite likely that these increases in BMD would translate into enhanced clinical benefits, given the anti-fracture efficacy of the drug during the initial 19 months and the necessary time interval between pharmacodynamic actions and clinical effects on bone strength.

Secondary endpoints of GHAC:

² Although not pre-specified as a trial objective, a further analysis showed that there was a substantial reduction in the proportion of patients with multiple new vertebral fractures [22 (4.9%) in placebo, 5 (1.1%) in the 20 µg group, and 3 (0.7%) in the 40 µg group]. In addition, this analysis demonstrated that the proportions of patients with "new moderate + severe" and "new severe" vertebral fractures were reduced in both LY333334 dose groups, compared to placebo. New moderate + severe fractures occurred in 42 (9.4%) placebo patients, in 4 (0.9%) patients in the 20 µg group, and in 9 (2.1%) patients in the 40 µg group. Of the 64 placebo patients who experienced at least one new vertebral fracture, 42 had at least one new moderate or severe fracture. In contrast, only four patients in the 20 µg group had moderate or severe fractures. This means that 18 of the 22 patients who fractured while taking 20 µg had mild fractures. These hypothesis-generating data suggest that the beneficial effects of LY333334 extend beyond reduction in fracture number.

A key secondary endpoint was the proportion of patients with new non-vertebral fractures. Each LY333334 treatment group demonstrated a statistically significantly lower proportion of patients with new non-vertebral fractures, compared to placebo. At least one non-vertebral fracture occurred in 6.3% of patients in the 20 µg and in 5.8% in the 40 µg group, compared with 9.7% in the placebo group. Relative risk reduction for the 20 µg and 40 µg LY333334 treatment groups, compared to placebo, was 35% and 40%, respectively ($p < 0.05$). The absolute risk reduction for a non-vertebral fracture was 3.6% in the 20 µg group and 3.9% in the 40 µg group.

Non-vertebral non-traumatic fractures were reduced by 53% in the 20 µg LY333334 group, and by 54% in the 40 µg group. The two active LY333334 treatment groups did not differ significantly in fracture risk reduction.

These results can be compared to those derived from studies of similar populations, in which the risk of non-vertebral fractures was reduced by 20 % with alendronate, 39% with risedronate, and 10% with raloxifene. The duration of these studies was three years.

This study lacked sufficient statistical power to detect treatment-related differences at specific non-vertebral sites, and the numbers of fractures at these sites were low. At each non-vertebral site, there were numerically fewer fractures in the treatment groups than in placebo. At the hip there were four fractures in placebo, two in the 20 µg group, and three in the 40 µg group. At the wrist, the corresponding numbers of fractures were 13, 7, and 10. Thus, despite the overall substantial and statistically significant efficacy in preventing non-vertebral fractures as a group, LY333334, 20 µg/day, prevented two hip and six radius fractures in 541 patients treated for about 19 months. Clearly, a longer, and perhaps larger, trial would have been needed to demonstrate efficacy at individual extra-vertebral sites.

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

Although not specified as a secondary endpoint, the cumulative incidence of one or more new non-vertebral fracture was similar in the three treatment groups until about 12 months, when the protective effects of LY333334 became apparent (see Kaplan-Meier curves in review of GHAC). This is consistent with the necessary delay between pharmacodynamic action and fracture prevention.

Bone mineral density: LY333334 treatment increased BMD at all skeletal sites except the ultradistal and distal radius. The increases were consistently greater in the 40 µg treatment group, compared to the 20 µg group. There were small

increases in total body BMC in both LY333334 groups, whereas the placebo group lost total body BMC by study end. Consistent with the anabolic mechanism of the peptide, the speed and magnitude of increases in lumbar spine BMD exceeded those of any known anti-resorptive agent. Substantial and statistically significant increases of nearly 4% over baseline were seen as early as 3 months after beginning treatment. At 12 months, the placebo-subtracted increases were 7.42% in the 20 µg group and 11.02% in the 40 µg group. By study end, the placebo-subtracted increases in spinal BMD were 8.57% in the 20 µg group and 12.6% in the 40 µg group.

These results can be compared to the results of alendronate trials, which generally report spine BMD increases of about 5%, 6-7%, and 7% at 12, 18, and 24 months, respectively. However, following 20 µg/day LY333334 treatment for a median of 19 months, the increases in BMD at other skeletal sites were generally no greater than have been seen following 12-24 months of treatment with bisphosphonates. Because GHAC was terminated prematurely, the increases in BMD following longer treatment periods are not known.

A responder analysis showed that nearly all patients treated with either dose of LY333334 gained spinal BMD. Most patients gained 5% over baseline. Further analyses identified no patient subgroups in which the drug did not produce substantial and statistically significant increases in spinal BMD, relative to baseline and to placebo.

The changes in biochemical markers of bone formation and resorption were consistent with the anabolic action of LY333334. The pharmacodynamic responses to LY333334 40 µg were greater than observed in the 20 µg group; this dose-dependence was consistently observed during the clinical pharmacology studies. Also consistent with the known physiology of PTH, the increased bone formation (BSAP and PICP) was coupled to increased resorption, as shown by increases in urinary NTX and deoxypyridinoline. The increases in the two resorption markers followed the elevations in formation markers. Finally, the elevations in all four markers declined following discontinuation of the drug.

Height loss was a pre-specified secondary endpoint. All three treatment groups lost height during the trial (3.61 mm in placebo, 2.81 mm in the 20 µg group, and 3.16 mm in the 40 µg group; all within-group changes from baseline $p < 0.001$). The between-group differences were not statistically significant.

Extensive population-based pharmacokinetic-pharmacodynamic studies failed to identify baseline patient characteristics that would necessitate LY333334 dose adjustments. This statement is qualified by the limits of renal and hepatic impairment that were present in the trial population. In addition no pk-pd analysis identified specific baseline characteristics, or outer limits of baseline values (e.g., BMD), that precluded efficacy of LY333334.

As secondary endpoints, the sponsor also employed five independent QOL indicators. The results of this analysis failed to disclose any meaningful improvements as a result of LY333334 treatment, even in the two osteoporosis-related indices. No labeling claims are made for QOL improvements.

GHAC: CONCLUSIONS:

- **GHAC convincingly demonstrated a substantial treatment-related improvement in the proportion of patients with morphometric vertebral and pooled non-vertebral fractures, as well as impressive increases in spinal BMD and considerable increases in BMD at nearly all other skeletal sites. After 19 months of treatment, the reduction in risk of vertebral fractures, and the increases in spinal BMD, were greater than reported following longer treatment with any currently approved agent. There was no effect of LY333334 treatment on height loss in the study group as a whole.**
- **Although the pharmacodynamic effects of 40 µg/day LY333334 exceeded those of the 20 µg/day dose, the fracture efficacies (both vertebral and non-vertebral) of the two doses were indistinguishable. Given the added safety/tolerability concerns of the higher dose, GHAC successfully established 20 µg/day as the indicated dose for treatment of postmenopausal osteoporosis.**
- **Extensive population-based pharmacokinetic-pharmacodynamic modeling disclosed no population group or baseline characteristic that would preclude substantial and statistically significant efficacy of LY333334 in increasing lumbar spinal BMD. In addition, these analyses have indicated that dose adjustments are not required on the basis of any baseline demographic or other characteristic, within the limits of the trial population.**
- **A complete review of the safety of LY333334 in GHAC is included in the Integrated Safety Review. There was no increase in mortality or morbidity in groups treated with LY333334. There were very few treatment-related symptoms or adverse events in the 20 µg group, with an increase in nausea and headache in the 40 µg group (occasionally leading to discontinuation). As discussed in the safety review, there is a need for additional evaluation of cardiovascular responses to LY333334. In addition, in view of the occurrence of osteosarcomas in rodents treated with LY333334, there remains a need to establish a long-term monitoring mechanism post-approval³.**

³ In this regard, the drug should be labeled to indicate that the drug is contraindicated in Paget's disease (which carries an increased risk for osteosarcoma, and which could conceivably worsen

- **Unresolved issues related to efficacy: Questions regarding indication for LY333334 as first- or second-line therapy, level of severity of osteoporosis as indication for treatment, and duration of therapy have been presented above. Factors involved in overall risk/benefit estimates for this indication have also been presented.**

Study B3D-MC-GHAJ, treatment of osteoporosis in men:

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 would 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 data that demonstrate fracture reduction efficacy (vertebral or non-vertebral) for any agent in the treatment of osteoporotic men. In men, the risk of fracture is inversely related to BMD. However, the risk estimates for a given BMD T-score in men are not as well determined as in women. It is possible that men tend to fracture at a higher BMD value, compared to women. This may be due to the fact that men have larger bones than women; consequently, in 2-D images of bone, the areal density may appear to be increased. Whatever the cause of the uncertainty, the clinical impact of changes in BMD will be more difficult to judge in men, compared to women, in the absence of fracture data.

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 ≤ -2.0 . Exclusion criteria were the same as in GHAC.

when bone remodeling is stimulated). Patients with unexplained elevations of alkaline phosphatase (generally obtained as part of the workup of osteoporosis) should not be treated with LY333334.

Four hundred thirty-seven men (mean age 58.6 years; range 31-84 years) with lumbar spine or hip BMD T-scores ≤ -2.0 SD were randomized (in a 1:1:1 schedule) to receive PBO or either 20 μg or 40 $\mu\text{g}/\text{day}$ of LY333334. Ninety-nine percent of the patients were Caucasian. Overall, 49 % of the patients had primary hypogonadism 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.

Data from the 437 patients contributed to the primary efficacy analysis, and nearly all of the secondary analyses, using the intent-to-treat approach with last observation carried forward. Data from a subset of 251 patients who were taking LY333334, 20 or 40 $\mu\text{g}/\text{day}$, were used for the population pharmacokinetic studies. Because of the premature termination of the study, analyses of outcomes were provided for Visit 6 (the "12 month visit") and for Visit 7 (the endpoint visit). Both analyses used LOCF. The Division has decided to use the Visit 7 outcomes for the analysis, because this time point provides final data for everyone in the trial.

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) with LY333334 for an average of 11 months 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 $\mu\text{g}/\text{day}$ group, and 8.21% at Month 12 and 8.51% at endpoint in the 40 $\mu\text{g}/\text{day}$ group ($p < 0.001$ for all comparisons vs placebo and for all within-group comparisons vs baseline). 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 (as opposed to about 15% of the 20 μg group with 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 in the 20 µg group. 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 (Visit 7) 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. Thus, for the 20 µg group, the only BMD increases that were statistically significant, compared to placebo, were lumbar spine (5.35%, $p < 0.001$) and femoral neck (1.24%, $p < 0.029$).

Of great importance, 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 ($p = 0.06$), ultradistal, and distal radius.

At the lumbar spine, the BMD responses to LY333334 20 µg at 11 months were similar to those that were found in response to alendronate, in a similar osteoporotic male population, at 24 months (in the alendronate study, there were placebo-subtracted differences of about 4.5% at 12 months and 5.3% at 24 months). The spine BMD increases in response to LY333334 appeared somewhat earlier than with alendronate. However, at most non-vertebral skeletal sites (e.g., the trochanter, the femoral neck, the total hip, and total body), the effects of LY333334 20 µg/day for 11 months appear to be inferior to those that followed treatment with alendronate 10 mg/day for 24 months. With the 40 µg LY333334 dose, the BMD increases at non-vertebral sites were more comparable to the effects of alendronate at 24 months. At the lumbar spine, the placebo-subtracted BMD increase (8.51%) was far greater than 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 µg 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 µg group. For BSAP, at all visits, the 20 µg group had greater median percent change than in placebo, and the 40 µg group had higher levels than the 20 µg 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 µg and 40 µg 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 µg group were again greater than in the 20 µg 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 α -hydroxylase.

Changes in height constituted another secondary endpoint. 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 µg, and 40 µg 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.

The sponsor conducted an extensive population pharmacokinetic analysis as part of GHAJ. The analysis disclosed some variability in AUC or C_{max} , 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 because 99% of the patients were Caucasian.

GHAJ: CONCLUSIONS

- **In men with idiopathic osteoporosis or osteoporosis associated with primary hypogonadism, treatment with LY333334 20µg/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 5.35% in the 20 µg group and 8.51% in the 40 µg group. A responder analysis showed that 54.6% of LY333334-treated patients in the 20 µg group had spinal BMD increases of 5% or more, compared to 9.8% in the placebo group.**
- **In this same population, treatment with LY333334 20 µg/day for 11 months resulted in placebo-subtracted increases in BMD of 1.24% at the femoral neck (p<0.029). Although there were positive trends at several other skeletal sites, none achieved statistical significance, using endpoint data.**
- **LY333334 20 µg/day was effective in increasing lumbar spine BMD 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 P1CP, 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_{max}, 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. The overall efficacy of LY333334 20 µg/day is 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 of the drug has 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 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 (which osteoporotic patients should be treated,

whether LY333334 should be second-line therapy, and 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 possible that increasing the dose of LY333334 to 40 µg will dramatically increase 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 included 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 was 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 currently conducting a long-term follow-up study of patients who participated in the phase 3 trials.

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. 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.

C. Safety

An integrated review of safety accompanies this review.

D. Dosing

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.

E. 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 idiopathic 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.