CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-318

MEDICAL REVIEW(S)

NDA 21-318
Forteo (tereparatide) Injection
Lilly Research Laboratories

This section is not applicable at this time.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: November 25, 2002

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-318
Forteo (teriparatide) injection
Treatment of osteoporosis in men and post-menopausal women

SUBJECT: NDA review issues and recommended action

Background

This application was originally submitted on November 29, 2000. An advisory committee meeting was held on July 27, 2001, with extensive discussion of balance of risk and benefit and of the relevance of the rat carcinogenicity findings to human clinical risk. On October 2, 2001, an "approvable" letter was sent to the firm citing deficiencies in labeling and a requirement for the development of a Boxed Warning and Medication Guide specifically related to the finding of osteosarcomas in rats treated with teriparatide in carcinogenicity studies. In addition, the letter directed that use of the drug be restricted to those patients at high risk for fracture (e.g., history of osteoporotic fracture, multiple risk factors for fracture, failure or intolerance of previous antiosteoporosis therapy in such patients). In addition, the firm was instructed to submit a risk management plan to include an overall approach to marketing that would successfully limit use to the target population. A plan for post-marketing surveillance for osteosarcomas developing in patients treated with Forteo was also required by the letter. Two manufacturing facilities, one in Indianapolis and the other in Fegersheim, France had not yet received satisfactory inspections, required for approval. Finally, the division implied in the letter that the results of a repeat carcinogenicity study to assess the impact of age of initiation of therapy, dose, and duration of treatment on osteosarcomas in rats treated with teriparatide should be submitted and reviewed prior to final labeling and approval.

A subsequent "approvable" letter was issued on May 16, 2002, citing deficiencies noted during establishment inspection at Indianapolis requiring remediation and again awaiting the results of the repeat carcinogenicity study.

On September 19, 2002, the firm submitted a complete response to the May 16, 2002 letter. At this time, the Office of Compliance has declared overall cGMP status to be acceptable (9-25-02), labeling has been negotiated, phase 4 commitments are in place, and the results of the repeat carcinogenicity study have been reviewed and included in labeling.

*—21-318

Brief summary of final action

Forteo is indicated for the treatment of osteoporosis in postmenopausal women who are at high risk for fracture to reduce their risk of vertebral and non-vertebral fractures and to increase vertebral and femoral neck BMD. It is also indicated to increase BMD in men with primary or hypogonadal osteoporosis who are at high risk for fracture, though the effects of the drug on fracture risk in men has not been assessed. Use of the drug for more than two years is not recommended.

The labeling includes a Boxed Warning describing the osteosarcoma finding in rats and warning against use in patients with Paget's disease of bone or unexplained elevations in alkaline phosphatase, open epiphyses, or prior radiation therapy involving the skeleton. Caution is recommended in patients with active or current urolithiasis, and the possibility of transient orthostatic hypotension associated with the dosing of drug is described. The risk of mild hypercalcemia is described based on the clinical trial results. A Medication Guide has been written and will be included with each prescription fill. The label recommends that the initial dose of Forteo be administered "under circumstances in which the patients can sit or lie down if symptoms of orthostatic hypotension occur."

The CDER executive carcinogenicity assessment committee reviewed the results of the repeat carcinogenicity study and concluded that maturity of the skeleton at the time of initiation of treatment did appear to influence the tendency for tumor induction, though overall the findings do not permit exclusion of a risk of osteosarcoma in the setting of the approved clinical treatment regimen. The pharm-tox reviewer recommends that the NDA be approved if the clinical review team deems that the theoretical risk of osteosarcoma can be adequately managed in labeling and according to the agreed upon commitments for post-marketing risk management by the firm.

The medical team has recommended approval.

The action letter reminds the firm of their postmarketing study commitment agreed to in their letter of May 6, 2002. The study is a post-approval surveillance program to be initiated within 90 days of the first marketed use of Forteo and will monitor approximately 40% of the annual incident cases of osteosarcoma in the U.S. in men and women $\geq$ 40 years of age for demographic characteristics and history of use of Forteo. If warranted by the occurrence of cases in Forteo-treated patients, a case-control study will be initiated in order, potentially, to establish more definitively, a causal relationship between Forteo use and osteosarcoma. Progress reports are to be made at predetermined intervals to FDA, and the surveillance is to continue for 10 years.

Several other agreements are cited in the action letter. The first is an agreement to a phased introduction into the marketplace of Forteo with restricted initial marketing by a limited sales force, no direct-to-consumer advertising, and restrictions on physician receipt of samples. In addition, Lilly has agreed to a physician education program to emphasize the limited target population for [redacted]

Finally, the firm has agreed to provide prescription data by geographic regions of the USA in the quarterly periodic safety update reports for the first 3 years of marketing, and annually thereafter

and to extended follow up of patients treated in the Phase 3 studies for 5 years beyond the end of the original clinical trial, with a final report in Q3 of 2004.

Recommendation
This application may be approved.

21-318
Drug: Forteo (teriparatide) injection
Proposal: treatment of PMO and osteoporosis in men
11/25/02

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/s/

David Orloff
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MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

CLINICAL TEAM LEADER MEMO

DATE: November 20, 2002

DRUG: Teriparatide (PTH 1-34)

PRIMARY MEDICAL REVIEWERS: Bruce Schneider (efficacy) and Bruce Stadel (safety)

INDICATION: Treatment of [redacted]

COMPANY: Lilly

This is the third of my Team Leader memo's for the Teriparatide NDA. In my memo of 17 September 2002, I recommended that the Division do one of two things: issue an approvable letter pending outcome and review of the second rat study, or issue an approval letter with restrictions on the distribution of the drug. The Division followed the first option.

The second rat study has been submitted and reviewed by the pharmacology team. The findings of that study have been incorporated into the appropriate sections of the labeling. In addition, serum calcium data from a study of teriparatide in women previously treated with alendronate or raloxifene have also been incorporated into the labeling.

At this point, I recommend approval of Teriparatide NDA for the treatment of postmenopausal osteoporosis in women at high risk for fracture and to increase bone mineral density in men with osteoporosis, also at high risk for fracture.

Eric Colman, MD
HFD-510

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/s/

Eric Colman
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MEDICAL OFFICER

David Orloff
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MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

3. Risk Management Plan: Lilly will implement elements of the risk management program, submitted to the Agency in Q4, 2001, that include comprehensive measures regarding the appropriate use of Forteo in the target patient population. This program will be implemented when Forteo is approved.

   This program includes phased product uptake, limited initial marketing, no direct-to-consumer advertising, robust stakeholder education (physicians, patients, and pharmacists), and program evaluation as previously outlined. Also included are a black box warning in the labeling and use of a Medication Guide – which must be distributed by the pharmacist to patients with each refill.

4. Study B3D-MC-GHBJ (Extended Follow-up of Patients in LY333334 Trials):

5. [This is an observational study of over 1600 women and men who have participated in long- term teriparatide studies initiated by Lilly.]

   Lilly has extended observational Study GHBJ for a total of 5 years beyond the original clinical trials (up to 24 months of exposure in the original clinical trials). Lilly will submit an interim report from this study in July 2002, and a final abbreviated report in Q3, 2004.

6. Study B3D-MC-GHBQ (Sequential Use of Teriparatide and Raloxifene HCl in the Treatment of Postmenopausal Women with Osteoporosis): Lilly is collecting additional ECG data, as requested by the Agency, in ongoing Study GHBQ. Lilly will submit the analysis of ECG data in a final report in Q1, 2003.

Doctors Bruce Schneider and Bruce Stadel, clinical efficacy and safety reviewers, respectively, have recommended delaying a decision about approval of teriparatide until the ongoing rat study is completed and reviewed by the Division. I believe there is nothing to gain from waiting for this study to finish. If it turns out the rats treated with teriparatide from an adult age onward have a similar incidence of osteosarcomas as rats treated from weanling, I would still favor approval of teriparatide with the current restrictions in place.

Pediatric Studies: Since teriparatide is indicated for adults only and should not be used in patients with growing bones (because of the potential increase in risk for osteosarcoma), Lilly should not be required to perform pediatric studies of teriparatide. I recommend that we waive the requirements under the Pediatric Rule.

Nomenclature: In a recent memo from the Division of Medication Errors and Technical Support (DMETS), a second recommendation against use of the trade name, Forteo, was made. For the same reasons cited in a January 25, 2001 consult – sound-alike and look-alike confusion with Fortaz, Fiortal (sic)(I believe they mean Fiorinal), and Tao – DMETS does not support the use of the name Forteo. Given the large number of drugs on the market, it is probably rare to have a new drug name that does not sound or look like another drug. Therefore, unless a patient would be at risk of significant harm if he or she received one of the sound-alike or look-alike drugs rather than Forteo, or vice versa, I believe that approval of the trade name, Forteo, is justified. Forteo is delivered by subcutaneous injection – Fortaz is an injectable antibiotic given IV or intramuscularly TID or BID, Fiortal is an oral headache medication that contains butalbital, ASA, and caffeine, and Tao is an oral antibiotic administered QID. Because none of the sound-alike, look-alike compounds are administered subcutaneously, I do not believe the name Forteo poses undue risk to potential patients.

In sum, I believe the measures outlined above, in addition to the black box warning in the labeling, will greatly enhance the safe use of teriparatide and will provide a beneficial treatment option not currently available. I recommend approval of teriparatide to treat postmenopausal women with osteoporosis and men with idiopathic or hypogonadal osteoporosis – at high risk for fracture.

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Eric Colman, MD

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/s/

Eric Colman
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MEDICAL OFFICER

APPEARS THIS WAY
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: October 1, 2001

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-318
Forteo (teriparatide) injection
Eli Lilly & Company

SUBJECT: NDA review issues and recommended action

Background

Teriparatide is a peptide that is identical in sequence to the N-terminal 34 amino acids of human parathyroid hormone (hPTH 1-34). The current application is for a recombinant product proposed for the treatment of osteoporosis in men and post-menopausal women. Another teriparatide product, of synthetic origin, was previously approved and marketed as a diagnostic agent in hypocalcemic states. When administered daily as a subcutaneous dose as in the studies conducted by Lilly of their product, teriparatide acts as a bone anabolic agent to increase BMD with findings in animals of apparent favorable alterations in bone microarchitecture and increases in bone strength by formal biomechanical testing. The clinical trial program for this drug was abruptly terminated in late 1998 due to concerns arising from the finding of a marked, dose-related increased incidence of osteosarcomas in the 2-year rat carcinogenicity study. The clinical trial data generated up to that point were submitted for review as well as data from continued follow up off treatment of approximately 75% of the men and women enrolled in the original studies. No bone tumors have been documented to date in the patients treated. The osteosarcoma issue continues to be the major safety concern, biologically plausible even if purely hypothetical at this juncture. No further clinical studies are ongoing at this time. A study to further address the impact of age of the animals on bone carcinogenicity is underway in rats and a small monkey carcinogenicity study is likewise being undertaken. Data from these studies are anticipated by the end of 2002 (rats) and in several years (monkeys).

Clinical

Efficacy

Two doses of drug (20 mcg daily, 40 mcg daily) were studied in four phase 3 double-blind, randomized, parallel group, controlled trials, 3 in women with postmenopausal osteoporosis and the other in men with osteoporosis (~50% hypogonadal, ~50% idiopathic). The median duration of therapy in the approximately 1300 women studied was 19 months (min 5 months, max 29 months). For the nearly 300 men studied, the median duration of therapy was approximately 11 months.

In the pivotal trial in women with low BMD and/or a prevalent vertebral fracture, the primary efficacy endpoint of a reduction in the incidence of new vertebral fractures (morphometric, without necessary clinical presentation) was met. The outcome was a robust 9-10% absolute reduction in fracture incidence relative to placebo, which amounted to an approximate 60-70% relative reduction in risk compared to placebo. Dr. Mele has conducted analyses of the efficacy outcomes including in the denominator the ~20% of patients who were not valid for efficacy because no baseline and/or follow up spinal x-rays were available. In addition, she conducted an analysis excluding patients enrolled in the last month of the study. The original finding stood up to these tests of robustness.

The effects of treatment by dose on BMD at various skeletal sites were examined as secondary efficacy measures. Notably, there was a marked, dose-dependent increase in BMD at the lumbar spine relative to placebo and dose-dependent effects of lower magnitude at the femoral neck and total hip. At the midshaft and ultradistal radius, there was no positive effect of teriparatide at either dose relative to placebo.

The effects on markers of bone turnover were dose-dependent and consistent with the anabolic effect of the drug.

Analysis of the proportion of women with non-vertebral fractures on-study across treatment groups showed a fractional reduction relative to placebo (on an overall low rate) similar to that for morphometric vertebral fractures, thus a much smaller absolute reduction, overall supportive of the efficacy of the drug at the doses administered.

Despite the greater effect of the 40 mcg dose on BMD at critical sites, the finding of no additional fracture benefit relative to 20 mcg led the sponsor to propose 20 mcg SQ daily as the dose for marketing.

The study in men was not powered to detect a reduction in risk for fracture, but rather to detect an increase in BMD of the lumbar spine. As agreed in principle in past discussions with the Division, in the context of apparent favorable effects on bone in preclinical models, demonstrated efficacy in the reduction of fractures in women, in the absence of significant safety concerns that might counterbalance any benefit, a robust effect on BMD in men was to be considered a valid surrogate for reduction in fracture incidence in that population.

The study met its primary efficacy objective, and showed a dose-related effect to increase lumbar spine BMD by 5-10% relative to placebo. At other sites, the drug was variably mildly effective, with the 40 mcg dose generally showing greater apparent efficacy than placebo or 20 mcg. Again, the effects at the radius where minimal to none.

As for the women, the effects on markers of bone turnover in men were dose-dependent, with no apparent effect of placebo.

Of note, there were was one small study (146 patients) comparing teriparatide 40 mcg daily to alendronate 10 mg daily in postmenopausal women with osteoporosis for up to about 18 months. The results of the trial showed a marked superior effect on BMD at the lumbar spine of

teriparatide, and lesser, though still superior efficacy of teriparatide at the femoral neck, total hip, and Ward's triangle. Consistent with the placebo-controlled data, the effects of PTH at the radius were minimal and indeed inferior to alendronate at the distal radius. Dr. Schneider places little weight on the results of this trial, insofar as it employed only the 40 mcg dose of PTH.

Finally, while not explicitly studied, Dr. Schneider briefly addresses the potential unique utility of a bone anabolic agent such as teriparatide in clinical states associated with osteoporosis and low-bone-turnover states. These include many cases of male osteoporosis as well as glucocorticoid-associated osteoporosis.

Safety

Three principal, and somewhat interrelated, issues arise out of the review of the safety database for this NDA: effects on calcium metabolism and questions of cardiovascular and renal safety.

Dr. Stadel notes that transient hypotension (postural or otherwise) and tachycardia were observed in preclinical studies and in small phase 1 investigations. In humans treated with doses > 40 mcg daily, these signs were accompanied by an increased incidence of headache, nausea, and dizziness, as well as by transient asymptomatic hypercalcemia and hypercalciuria. Decreases in RR and QT interval were also observed. While vital signs and clinical follow up were obtained in the phase 3 trials, no EKGs were routinely performed to assess the pro-arrhythmic potential of the drug, either as a primary effect or secondary to its effects on electrolytes. Despite this, an exhaustive review of the adverse event information reveals no signal suggestive of a risk in this regard. There was a dose-related increase in the incidence of dizziness and nausea, in particular, relative to placebo, but no increase in the incidence of frank syncope, falls, or other injury. Notwithstanding these reassuring data, because of the transient effect to cause mild, postural hypotension (usually without symptoms) as well as a small increase in heart rate in the 6 hours after dosing, and because of the relatively small clinical exposure to the drug that fails to address safety in the broad spectrum of osteoporotic men and women with regard to age, underlying CV disease, and general physical well-being, Dr. Stadel recommends and I concur with a recommendation in labeling that the first dose of drug be administered in a setting in which the patient is able to sit or lie down for a reasonable (e.g., 30 minutes) period after administration. No clinical observation is warranted.

With regard to the transient hypercalcemia in patients treated with the drug, it appears to be dose-dependent, but generally very mild. Analyses in Dr. Stadel's review of the incidence of increases in serum calcium over normal by categories of magnitude reveals that the vast majority of elevations are minimal. The incidence appears dose-related and the 40 mcg dose was associated in both the male and female studies with a shift in the distribution with regard to peak serum calcium above normal towards somewhat higher values. Nevertheless, even among those treated with 40 mcg, there were very few patients who had calcium levels 4-6 hours post-dosing of > 3.0 mmol/L (ULN = 2.64), and this was only among the women. Overall, the effect of drug to increase the calcium levels was more marked in women than in men, with approximately 11% of women experiencing at least 1 episode and 3% experiencing at least 2 episodes of hypercalcemia at the 20 mcg dose. The incidence rates in men were about one-half that in women for both of these parameters. Dr. Stadel notes that the trials did allow for adjustments in doses of vitamin D and calcium which were undertaken in less than 10% of patients. To the

extent that these adjustments contributed to the apparent safety and tolerability of the drug with regard to calcium in serum and urine, the labeling must advise monitoring of serum calcium and adjustments of supplemental vitamin D and calcium accordingly. There were no apparent effects of treatment on the incidence of renal adverse events, including nephrolithiasis.

The effects on the heart from the phase 1 studies include small decreases in QTc, not expected to confer any arrhythmic risk. A small, single-dose, phase 1 study of the interaction between study drug and digoxin revealed no effects, though the theoretical augmentation in risk of digoxin toxicity due to transient hypercalcemia in susceptible individuals is addressed in labeling.

Finally, though there were no cases either on study or in follow up off therapy of malignant bone lesions, one male did present with Paget's disease after treatment of 13 month's duration with 40 mcg daily of teriparatide. This patient, fortuitously, had had a baseline bone scan and skeletal X-ray series prior to enrollment with no signs of Paget's. Paget's disease is associated with an increased risk for osteosarcoma (arising in the Pagetic bone). This case, while certainly proving nothing, is considered in the context of the known anabolic effects of the drug and in light of the animal findings of osteorsarcomagenesis of both teriparatide (rats) and PTH-related peptide (mice, published).

Dr. Schneider has addressed the osteosarcoma issue in his review as well, with a discussion of the biologic plausibility of the theoretical risk in humans as well as a point-by-point response to the sponsor's reasons for a conclusion that the rat finding is unlikely to be relevant to humans. This discussion begins on page 25 of his review. With regard to plausibility, he points out that the cellular origins of the osteosarcoma cells are osteoblasts or their precursors, precisely the cellular target for PTH in rats as well as humans. In addition, tumor incidence in the rats was dose dependent, extremely robust (up to 50% at the high doses), and without a threshold dose identified. He argues that while the rats were exposed at higher doses, for larger fractions of their lifetimes, and starting at a young age, in contrast to the use studied and intended in humans, nevertheless, this does not provide complete assurance of the absence of risk in humans. He and Dr. Stadel emphasize the lack of power of the completed studies to detect even single, specific, drug-related adverse events occurring at rates less frequently than 1 in 500 patients. In addition, while the response of bone in rats was much more dramatic than in humans, the absence of a no-effect dose for rat carcinogenesis still leaves open the possibility that, in humans, lower doses, less dramatic in their histologic effects, might still be potentially osteosarcomagenetic. Finally, it is perhaps relevant that hyperparathyroidism, a common disease, does not appear to be associated with an increased risk of osteosarcoma. This is not completely reassuring, for as Dr. Schneider points out, intermittent pharmacologic doses of PTH induce markedly different effects on bone metabolism than does tonic exposure as in hyperparathyroidism.

Dr. Stadel has proposed, and the sponsor has agreed to, a phase 4 osteosarcoma surveillance study to capture and evaluate in an ongoing manner a large percentage of the reported osteosarcoma cases in the U.S. (approximately 40%) with an eye toward initiating a formal case-control study should cases be identified in patients exposed to teriparatide.

Finally, Dr. Colman summarizes in his memorandum the design of the ongoing rat carcinogenicity study intended to address the question of effect of age at exposure to PTH as

well as duration of treatment on the induction of osteosarcomas in that species. Specifically, animals are treated starting at 2 or 6 months of age, for either 6 or 20-24 months. The 6-month treated animals will be followed for the appearance of cancer for up to 18 months. This study will be completed in July 2002, though analyses will not be available for some time after that.

Labeling
Preliminary labeling comments have been forwarded to the sponsor. The sponsor has been asked to propose a select target population among the larger populations of post-menopausal women and men with osteoporosis. The Division has suggested defining a population at high risk for fracture based on history and/or extreme low BMD as well as a population otherwise ineligible for, intolerant of, or having failed currently available therapies. A MedGuide is planned for this product to inform patients of the osteosarcoma finding in rats in order to permit informed assent to therapy with the product. The sponsor has also been asked to propose how restriction of use of the drug by the target population will be accomplished and assured. The initial proposal in this regard is discussed below.

Biopharmaceutics
The biopharmaceutics section of the NDA is acceptable to OCPB, and they have offered comments on labeling.

Pharmacology/Toxicology
The principal finding of the toxicology review is that of the osteosarcomas in rats treated in the 2-year carcinogenicity study. The pharmacologist has recommended waiting for the results of the ongoing rat carcinogenicity study prior to approval.

Chemistry/ Microbiology
The chemistry, manufacturing, and controls package for this application is satisfactory, and the application is approvable from the standpoint of ONDC, pending satisfactory inspections of two facilities, one in Indianapolis and one in France. On August 27, 2001, HFD-324 issued a memorandum recommending that approval be withheld because of significant problems uncovered at the Indianapolis site related to production of the active pharmaceutical ingredient. Apparently, the sponsor asked FDA not to inspect the French site at that time, citing a need to address similar problems. Documentation of FDA's intent to inspect the French site and of Lilly's request for delay are being obtained for the record.

A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

Microbiology recommends approval on the basis of sterility assurance.

DSI/Data Integrity
Two clinical sites were audited. No Forms 483 were issued. These are no outstanding issues with regard to data integrity.

Financial disclosure

The financial disclosure information is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts. This information is reviewed on page 162 of Dr. Schneider's review.

OPDRA/nomenclature

OPDRA was consulted about the proposed name, Forteo. Based on concerns about possible confusion with Fortaz (Ceftazidime injection), Fiortal (aspirin, butalbital, caffeine tablets), and Tao (troleandomycin capsules), the OPDRA consultant recommended against the proprietary name "Forteo." The Division feels that, because of the absence of any significant safety concerns related to medication errors that might plausibly arise, the name can stand, though we have requested that the ——— The sponsor has complied with this request.

Advisory Committee

The Forteo NDA was discussed at a meeting of the Endocrine and Metabolic Advisory Committee on July 27, 2001. The issue of osteosarcoma risk was discussed extensively by the committee. The committee was virtually unanimously convinced of the demonstrated efficacy of the drug in postmenopausal osteoporosis and in men with osteoporosis. Because of the unresolved question of osteosarcoma risk in humans and conceding the limitations of the database by its size to exclude anything by an extreme high risk, the committee agreed that the safety profile of the drug had, by definition, not been fully defined. Despite this, they voted unanimously to approve for the treatment of postmenopausal osteoporosis (apparently impressed by the combined BMD and fracture data), but split on the question of approval for use in men, apparently recognizing the less impressive BMD data and perhaps tempered in any enthusiasm by the absence of fracture information, though FDA described in some detail the rationale for reliance on BMD alone in men once the fracture efficacy of the drug was established in women.

Overall, the committee by their discussion and their votes on the questions posed by FDA, was supportive of restricting the target population for Forteo to those at high risk or those having failed other therapies. They were in favor of a Black Box Warning regarding the rat osteosarcoma finding.

Finally, the committee was supportive of further preclinical investigations related to osteosarcoma issue, of a post-marketing surveillance program, potentially including a registry of users, and of a case-control investigational approach should osteosarcoma cases by identified in patients treated with PTH.

Lilly's proposal for focused use of Forteo

The sponsor has submitted (9-25-01) a proposal that outlines the elements of a marketing plan as well as attributes of the product that they believe will effectively limit its use. In summary:

1. The target population will be those men and women with osteoporosis at high risk for fracture based on history, risk factors, and physician assessment.
2. Lilly will restrict and focus marketing activities to a small (———) group of specialty physicians, mediated by a new, relatively small sales force extensively trained.
3. There will be no direct-to-consumer advertising for Forteo.

4. ———

5. Lilly plans to provide periodic updates on product usage to FDA as part of a post-marketing commitment.

Summary and Recommendations

Adequate evidence has been presented in the NDA to establish the efficacy of the drug in the treatment of postmenopausal osteoporosis in women to prevent fractures at the lumbar spine and to increase BMD in men with osteoporosis. The clinical safety data for this drug derives from a relatively small database (< 1500 patients) treated for up to 2 years, though with average exposure across the pivotal studies of around 18 months. With this limited exposure, little in the way of serious safety concerns has arisen. The signals documented have been discussed above and by Dr. Stadel. Importantly, the risk of clinically significant hypercalcemia or hypercalciuria seems remote, likely more remote if some degree of serum calcium monitoring is undertaken in treated patients and if calcium and vitamin D doses are adjusted accordingly. There are no clear signals of a cardiovascular risk, despite mild, transient hypotension and increased heart rate in association with drug dosing. Again, risk in this regard will be addressed by the requirement that the first dose be given in a setting in which the patient can remain seated or supine for a period after dosing.

The most serious safety concern is a purely theoretical one, though admittedly difficult to dismiss completely: that of potential for induction of osteosarcoma. This, as discussed, is based on the findings in the rat carcinogenicity study. While the absence of any cases in the clinical trials is certainly a positive outcome, it is by no means definitively reassuring in the case of an AE with such a low background rate, rather excluding only a massive increase in risk. That being said, for several reasons, the risk would appear low. These include the fact that rat bone and human bone are biologically distinct, that the response as assessed by bone histology to the high doses in rats (~3-20X the exposures in humans) was markedly exaggerated relative to that in humans at proposed therapeutic doses. In addition, the absence of a link between primary hyperparathyroidism and osteosarcoma, notwithstanding the differences between tonic PTH action and intermittent pharmacologic dosing, is rather reassuring.

As such, even with the residual uncertainty about risk, it seems reasonable to approve teriparatide for use in patients at high risk for clinically significant fracture, either because of extreme low BMD, a history of recurrent fracture on available therapy, or because of intolerance or non-response to currently available therapy. Indeed, even if a low level risk were identified, it seems reasonable to permit such patients and their physicians to weigh benefits versus risks as they address what in many instances is a disease fraught with serious morbidity, in the form of pain and physical debility.

At this juncture, because of the need for satisfactory establishment inspections, this drug is therefore approvable for a restricted population as must be agreed on by the sponsor and the Division, and pending final labeling and a satisfactory plan for addressing the problem of limiting, to the extent possible, the use of the drug to that restricted population. There is agreement on the need for a Medication Guide (MedGuide) as part of patient education and to insure informed patient assent to this treatment. The drug is also potentially approvable at a later date for a broader population of osteoporotic females and males as studied in the clinical trials,

pending the additional information provided by the results of the ongoing repeat rat carcinogenicity study discussed above. If the results of the study suggest a lower to apparent absent risk of osteosarcoma in animals treated later in life and for shorter periods (as opposed to treatment from age of weaning to adulthood—a large portion of lifespan), the drug may be significantly less encumbered by labeling regarding risk and restricted target population than would be the case without these data or short of such an outcome.

CLINICAL TEAM LEADER MEMO

DATE: September 17, 2002

DRUG: Teriparatide (PTH 1-34)

PRIMARY MEDICAL REVIEWERS: Bruce Schneider (efficacy) and Bruce Stadel (safety)

INDICATION: [redacted]

COMPANY: Lilly

BACKGROUND

Postmenopausal women with osteoporosis have three drugs from which to chose if they want to reduce their risk for vertebral fracture. These are alendronate, raloxifene, and risedronate. Nasal calcitonin is indicated to increase spinal bone mineral density (BMD) in postmenopausal women and estrogens are indicated for the prevention of postmenopausal osteoporosis. Neither drug has convincingly shown the ability to reduce the risk for vertebral fractures. Older men with primary osteoporosis or osteoporosis secondary to hypogonadism may take alendronate to increase their BMD. The effect of alendronate on fracture risk in men with osteoporosis is unknown, but presumed to be favorable based on data from osteoporotic women.

All approved drugs to treat osteoporosis work by inhibiting osteoclastic bone resorption, which in turn inhibits bone formation and ultimately bone turnover. Since all approved agents only address one side of the bone turnover problem, there is a belief that the use of daily subcutaneous injections of teriparatide, which stimulates bone formation, will provide welcome relief to some osteoporotic patients.

Lilly's PTH compound, teriparatide, is composed of the first 34 amino acids of human parathyroid hormone. It is manufactured by recombinant DNA technology and shares all the known actions of native PTH 1-84. In contrast to sustained elevations in PTH, which leads to increased bone resorption (particularly of cortical bone), daily injections of teriparatide have been shown in animals, and now in humans, to stimulate new bone formation and increase BMD. The drug's effect is most pronounced in areas rich in trabecular bone (lumbar spine) and least effective (or possibly detrimental) in areas rich in cortical bone (ultra distal radius).

PRECLINICAL DATA

The preclinical finding of greatest concern was osteosarcoma. In a 2-year subcutaneous carcinogenicity study in Fisher 344 rats was carried out with teriparatide doses of 5, 30, and 75 ug/kg/day (low dose, mid dose and high dose). The number of animals treated was 60/sex/group. The animals were treated from an age of 6-7 weeks for a duration of 24 months. A summary of the osteosarcoma findings is shown in the following table.

Summary of Osteosarcoma Data

	MALES				FEMALES			
	Control	LD	MD	HD	Control	LD	MD	HD
Human Exposure‡	-	3X	20X	58X	-	3X	20X	58X
N Treated	60	60	60	60	60	60	60	60
N OsSarc	0	3	21	31	0	4	12	22

‡ based on AUC.

Osteosarcomas were detected at various bone sites. Identification occurred either upon gross observation of a bone nodule, or upon microscopic evaluation of four routinely examined bone sites: femur (distal end), tibia (proximal end), sternum (one or two sternebrae), and vertebrae (one lumbar vertebra). Osteosarcomas were clinically apparent in many animals from 12-18 months of age.

Of note, osteosarcomas have also been observed in Sprague Dawley rats and CD-1 mice treated with an analogue of PTH-related peptide, which activates the same receptor as teriparatide. Fatal tumors presented as bone tissue masses by 12 months of treatment in rats, and by 8 months of treatment in mice.

Lilly is currently conducting a second rat carcinogenicity study in order to provide information about the risk for osteosarcoma when teriparatide is administered to older animals and for shorter durations. Animals are being treated from either 2 or 6 months of age, for either 6 or 20-24 months. The 6-month treatment groups are will be followed up for 14-18 months. The results of this study will answer two important questions: 1) Is the risk for osteosarcoma in rats eliminated or reduced when treatment with teriparatide starts in mature animals? and 2) Is the risk for osteosarcoma in rats eliminated or reduced when treatment with teriparatide is shortened from 24 to 6 months? The results of this study will be available by the end of 2002.

Lilly believes that "the findings in rats are unlikely to be predictive of an increased risk of osteosarcoma in humans receiving teriparatide treatment for osteoporosis." The reasons Lilly cite for their position include, but are not limited to the following:

1. The magnitude of bone effects in rats is much greater than in humans or monkeys at comparable levels of teriparatide exposure for 18 to 24 months of treatment.
2. Certain kinds of tumors can be drug-induced in rats, but have no clinical relevance (i.e., phenobarbital and thyroid neoplasia, proton pump inhibitors and neoplasia of gastric enterochromaffin-like cells).
3. Long-standing primary and secondary hyperparathyroidism in humans have not been linked to an increased risk for osteosarcoma.

Of these explanations, I believe that the third has the most relevance to a discussion on the potential human risk from teriparatide. While it is true that there have been no published papers linking primary or secondary hyperparathyroidism to an increased risk for osteosarcoma in humans, one must remember that the pharmacodynamic effects of PTH on bone differ when administered as an intermittent bolus vs. when mild to moderate elevations of PTH are more or less constant throughout a 24-hour period. Under the latter conditions, bone resorption often exceeds bone formation and there is a net loss of bone (particularly cortical bone) and under the former conditions, bone formation exceeds bone resorption and there is a net gain of bone. (particularly trabecular bone). The difference in pharmacodynamic effects on bone between continuous vs. bolus PTH should temper our enthusiasm to accept the apparent lack of an association between hyperparathyroidism and osteosarcoma in humans when considering the clinical relevance of the rat findings.

CLINICAL DATA

There were two pivotal clinical trials: Study GHAC – which included 1637 postmenopausal, osteoporotic women with a mean age of 69 years; and Study GHAJ – which included 437 men with low bone mineral density and a mean age of 59 years. Trial participants from both studies were randomized in equal fashion to treatment with a daily subcutaneous injection of placebo, teriparatide 20 ug (proposed dose for marketing), or teriparatide 40 ug. At the time of termination of the pivotal postmenopausal osteoporosis treatment study, the median duration of observation was 19 months. In the male osteoporosis study, 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 during which time patients did not receive treatment with teriparatide (GHBJ). Approximately 75% of eligible patients enrolled in GHBJ.

Results of the primary efficacy analyses from GHAC and GHAJ are shown in the tables below.

Efficacy

Incidence of New Vertebral Fractures

	WOMEN STUDY GHAC			
	Pl	20 ug	40 ug	p-value
N	544	541	552	
% with new vertebral fx	14%	5%	4%	0.001‡
ARR vs. Pl		9%	10%	
RRR vs. Pl		65%	69%	

‡ both doses vs. placebo ARR=absolute risk reduction RRR=relative risk reduction

Percent Change in Spinal Bone Mineral Density (BMD)

	MEN STUDY GHAJ			
	Pl	20 ug	40 ug	p-value
N	147	151	139	
% ▲ spinal BMD	0.7%	5.0%	7.0%	0.0001‡

‡ both doses vs. placebo; LOCF on therapy

Thus, the pivotal studies provide sufficient evidence of teriparatide's efficacy in women (reduction in vertebral fracture risk) and men (increase in spinal bone mineral density).

Safety

Osteosarcoma

The principal safety concern with teriparatide is the theoretical risk for osteosarcoma. The duration of treatment in the rats was much longer as a percentage of lifetime than the proposed treatment period for osteoporosis in older men and women. Nonetheless, the dose-dependent occurrence of osteosarcomas in rats is a biologically-plausible finding and of particular concern because tumors were found in the low dose group that received only three times the human exposure (based on AUC). The no-effect dose is unknown.

Depending on the outcome of the ongoing second rat study — the results of which I believe the division should review before approving teriparatide for wide-spread use — a formal surveillance program may be required to attempt to estimate the risk of osteosarcoma in humans exposed to this drug. The details of such a post-approval surveillance program would need to be worked out between members of DMEDP and OPDRA with Lilly prior to drug approval.

The outcome of the second rat study will also greatly influence the drug's label. If older rats treated for less than two years do not develop osteosarcomas, a warning about the findings from the first rat study might only require a statement under Precautions. If, however, older rats treated for short durations develop osteosarcomas, it might be wise to consider a full-court press on the labeling and perhaps even explore the use of a restricted drug distribution program.

Hypercalcemia

One of the expected pharmacodynamic effects of teriparatide is a transient increase in serum calcium. During the phase 3 trials (GHAC and GHAJ), there was a median placebo-subtracted increase in the 4-6 hour post-dose serum calcium levels of approximately 0.08-0.12 mmol/L . During the course of study GHAC, approximately 3.0% of teriparatide 20 ug-treated subjects had two or more consecutive episodes of hypercalcemia vs. 0.2% of placebo-treated subjects. A small but significant percentage of teriparatide 20 ug-treated participants required adjustment of their dose of supplemental calcium and/or study drug (7.2%

vs. 0.6% and 2.8% vs. 0.6%, respectively). In study GHAJ, the pattern was similar for drug vs. placebo-treated subjects, but the absolute values were lower.

Although there was not a significantly greater percentage of clinical events that could be linked to hypercalcemia in the teriparatide vs. placebo groups, two issues remain a concern within this context. One is that all subjects had their serum calcium levels monitored at baseline and months 1, 3, 6, 12, and 18 and, as discussed above, some patients required adjustments in the dosage of calcium supplementation and/or study drug. It is unclear what the natural course would have been for these subjects if no dosage adjustments were made. Furthermore, it should be kept in mind that the risk for teriparatide-associated hypercalcemia would increase if a patient's daily intake of calcium and/or vitamin D exceeded the average consumed in the phase 3 trials. Therefore, I believe that the labeling should say something to the effect that "consideration should be given to periodic monitoring of the 4-6 hour post-dose serum calcium level during the first 6 months of treatment." Since the time-to-first episode of hypercalcemia indicates the risk is greatly reduced after approximately 150 days, the recommendation could be limited to the first 6 months of therapy. In a similar vein, I believe the patient package insert should clearly define the symptoms of hypercalcemia (which are unfortunately nonspecific) so that patients would seek medical attention if such symptoms developed.

The second clinical issue related to hypercalcemia is the potential for digitalis toxicity. It is well known that hypercalcemia lowers the threshold for digitalis-induced arrhythmia. While no clinically apparent cardiac arrhythmias were reported in the approximately 55 patients who received digitalis and teriparatide during in the phase 3 trials, this is a small sample size and provides little comfort regarding a potentially significant drug-drug interaction. I believe that in addition to periodic measurement of serum calcium levels, patients on digitalis should have frequent assessment of their serum digitalis levels.

Recommendation on Approval

Teriparatide (20 ug/day) has been shown to be an effective therapy for postmenopausal and male osteoporosis. However, because the osteosarcoma findings from the first rat study are biologically plausible and some tumors occurred in the low-dose exposure group, I favor following one of two regulatory approaches. The first option would be to issue an approvable letter pending review of the results of the ongoing rat study and encourage the company to open a treatment IND so that patients who continue to fracture on current therapies could have access to teriparatide. The second option would be to issue an approval letter that allowed marketing of teriparatide within a restricted distribution program. Details of such a program would have to be worked out between the Division and the company prior to approval. The overall goals of such a program would be to ensure that only high-risk patients receive the drug and to limit off-label use of teriparatide. Depending on the results of the second rat study, a decision would eventually be made to either expand the patient population indicated for the drug or continue with restricted use and distribution.

Eric Colman, MD
Clinical Team Leader
HFD-510

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Colman
10/1/01 08:01:32 AM
MEDICAL OFFICER

David Orloff
10/9/01 07:57:54 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

CLINICAL TEAM LEADER MEMO 02

DATE: April 24, 2002

DRUG: Teriparatide (PTH 1-34)

PRIMARY MEDICAL REVIEWERS: Bruce Schneider (efficacy) and Bruce Stadel (safety)

INDICATION: [redacted]

COMPANY: Lilly

In a memo dated 17 September 2001, I recommended that the Division follow one of two options regarding [redacted] The second option would be to issue an approval letter that allowed marketing of teriparatide within a restricted distribution program. Details of such a program would have to be worked out between the Division and the company prior to approval. The overall goals of such a program would be to ensure that only high-risk patients receive the drug and to limit off-label use of teriparatide. Depending on the results of the second rat study, a decision would eventually be made to either expand the patient population indicated for the drug or continue with restricted use and distribution."

We have pursued the second option, and I believe that it is reasonable to approve teriparatide at this time, with an indication to treat patients at high-risk for fracture. Lilly has agreed in writing (letter dated May 6, 2002) to the following features of post-approval company-directed drug regulation, which should enhance risk management:

Clinical

1. Post-Approval Surveillance Program: Lilly has agreed to conduct a Post-Approval Surveillance Study (B3D-MC-GHBX). A final protocol was submitted to FDA [redacted] on March 8, 2002. Study GHBX utilizes a case series design. The primary objective of the study is to identify approximately 40% of incident cases of osteosarcoma in the US annually. A telephone survey will be conducted to ascertain a history of Forteo treatment, if any, among the identified cases.

   Lilly has initiated steps to implement this study at a number of sites within the United States. The data collection phase of Study GHBX will be initiated within 90 days after the first marketed use of Forteo. Data from this study will be reported on a yearly basis. The sponsor is committed to a long-term study of 10-years duration. Lilly will review with the Agency at a mutually agreed-upon time the potential impact on this study of any new scientific developments relevant to the etiology of osteosarcoma.

   In the fifth year of the study, a meeting should be conducted between the sponsor and FDA to review relevant advances in oncology that might impact the study. Given Lilly's commitment to this long-term, large-scope study,

2. Lilly will submit prescription data on Forteo use by geographic regions of the USA in quarterly PSUR (Periodic Safety Update Report) for the first 3 years. After the first 3 years, reports will be submitted annually.

MEDICAL 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 Category: Recombinant peptide. Bone formation agent.
Route of Administration: Subcutaneous

Indication: [redacted]
Dosage: 20 micrograms per day

Reviewer: Bruce S. Schneider, MD
Dates of Review: Submission date: 11/28/00
Review completed: 8/24/01

Medical Safety Review: Bruce V. Stadel, MD, MPH
Chemistry Review: Yvonne Yang, PhD
Pharmacology Review: Gemma Kuijpers, PhD
Biopharmaceutics Review: Jim Wei, PhD
Statistics Review: Joy Mele, PhD

REVIEW SUMMARY: See Executive Summary

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies _____ **Clinical Hold** _____ **Study May Proceed**
NDA, Efficacy/Label supplement: _XXX_**Approvable** _____ **Not Approvable**
_____ **Approve**

SIGNATURES:
Medical Reviewer: __Bruce S. Schneider, MD
_____
Date: August 24, 2001

Medical Team Leader: _____
Date: _____

Medical Officer's Review of NDA # 21-138
Bruce S. Schneider, MD
Division of Metabolic and Endocrine Drug Products
August 24, 2001

EXECUTIVE SUMMARY

I. Recommendations regarding approval and post-marketing surveillance:

- **For the indication, treatment of postmenopausal women with osteoporosis: APPROVABLE, pending**

1. establishment of a system for long-term monitoring of osteosarcoma occurrence in women treated with teriparatide,

2. submission and review of additional study of osteosarcoma occurrence in rodents (see Section on preclinical pharmacology/toxicology as well as final conclusions and recommendations), and

3. 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 [redacted] and osteoporosis associated with primary hypogonadism: APPROVABLE, pending**

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

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. Based on currently available data, risk management steps should also include:

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

Limiting LY333334 therapy to patients in whom anti-resorptives have produced unsatisfactory efficacy or safety outcomes.

Limiting duration of use of LY333334 to two years.

If the drug is approved, and this will depend upon resolution of the safety concerns, I also recommend further research that will develop optimal 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 concerns are substantially allayed. The same considerations apply to other uses for recombinant PTH in children, including treatment of hypoparathyroidism.

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; bone anabolic agent; peptide hormone fragment, rDNA origin.

Indication: [redacted]

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 indications 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 (anti-resorptive agents). Drugs in this category 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). It is currently believed that we have derived the maximum benefit from the strategy of inhibiting bone resorption and 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 development program for LY333334 was based on abundant preclinical and clinical data demonstrating that intermittent injections of various preparations of PTH resulted in increases in skeletal mass. In this regard, the skeletal responses to intermittent PTH differ from those found in hyperparathyroidism. There is evidence that the anabolic effects of intermittently administered PTH are mediated through an increase in the functional osteoblastic cell pool. In the sponsor's preclinical studies, daily subcutaneous injections of LY333334 (at normocalcemic doses) increased trabecular and cortical bone at axial as well as appendicular sites in several rodent models. The bone was found to be of normal quality and architecture. Bone strength was also shown to increase in response to LY333334.

In these preclinical studies, the major serious adverse effect of LY333334 treatment was the appearance of osteosarcomas (clinically apparent by 18 months) in rodents treated from six weeks of age. 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 numbers of patients have been small and the observation periods have not been long enough to detect clinical tumor occurrence.

The clinical development program for LY333334 included 21 trials that enrolled more than 2800 women and men. The sponsor's phase 1-2 studies established pharmacodynamic dose-efficacy relationships, as well as a safety profile. These studies established 15 to 40 µg/day as the optimal dose range for Phase 3 testing. A total of 2030 postmenopausal women and 437 men were enrolled 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 the rodent osteosarcomas.

B. Efficacy results of phase 3 clinical trials

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. 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 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.

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 a few 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, 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.

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. Thus GHAC, together with the extensive phase 2 studies, established 20 µg as the optimal daily dose 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.

LY333334 in women. However, the trial did not identify the ideal duration of treatment with LY333334, for reasons beyond the sponsor's control.

To summarize the efficacy results of GHAC:

- **The study convincingly demonstrated a substantial treatment-related reduction 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. It should be noted, however, that the sponsor has made no provisions for dose adjustments.**

- **Histomorphometric analysis of trans-iliac biopsies derived from a subset of 34 patients disclosed no histological abnormalities following 12 or approximately 19 months of treatment with LY333334.**

- **There were no effects noted in any of the Health-Related Quality of Life indicators, as a result of treatment with LY333334.**

- **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 (including**

electrocardiographic) responses to LY333334. In addition, there remains a need to establish a long-term monitoring mechanism for detection of osteosarcomas if the drug is approved.[2]

- **Unresolved issues related to efficacy: In all likelihood, the premature termination of the trial resulted in an underestimation of the efficacy of this drug. Because of the abiding safety concerns, there remain questions regarding indication for LY333334, in terms of level of severity of osteoporosis, ideal treatment duration, and whether the drug should be used as first- or second-line therapy. We have no data on the effects of concomitant anti-resorptive therapy. Many postmenopausal women are currently on some form of anti-resorptive regimen. Should the concurrent medication be continued during LY333334 treatment? Should an anti-resorptive agent be added after treatment with LY333334? These will certainly appear as problems in clinical decision-making. Several years will be required to conduct the clinical trials that can provide the data needed to address these issues in labeling.**

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 % change in lumbar spine BMD following two years of treatment with LY333334 (20 µg/day or 40 µg/day) or PBO. Other efficacy outcome variables were essentially the same as in GHAC. The trial was not intended to detect treatment group differences in fracture rates.

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 µg/day of LY333334. Overall, 49 % of the patients had primary hypogonadism and 51% were classified as idiopathic. As in GHAC, all patients were supplemented with calcium, 1000 mg, plus vitamin D, 400-1200 IU/day, throughout the trial.

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[2] In this regard, the label should indicate that the drug is contraindicated in Paget's disease (which carries an increased risk for osteosarcoma, and which could conceivably worsen 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.

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.

Summary of efficacy results of GHAJ:

- **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 numerical increases in BMD 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).**

- **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_{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. As noted above, the sponsor has made no provisions for dose adjustments. 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 overall efficacy of LY333334 20 μg/day is slightly better than alendronate (the only currently approved agent for the treatment of male osteoporosis) 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 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 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.**

- **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. These studies were B3D-MC-GHAF, *Effects of LY333334 in postmenopausal women on estrogen and progestin therapy* and Study B3D-MC-GHAH, *LY333334 compared with alendronate in postmenopausal women with osteoporosis.*

Study GHAF demonstrated that LY333334, 40 µg/day for 15 months significantly increased BMD over that of the group treated with HRT only. The increases in BMD, compared with HRT alone, were found at the spine, total hip, and femoral neck. The utility of these data is limited by the inclusion of only a 40 µg dose of LY333334.

Study GHAH demonstrated that, in osteoporotic postmenopausal women, the increases in BMD at the lumbar spine, total hip, and femoral neck were significantly greater in the LY333334 40 µg group than in the alendronate 10 mg group after about 18 months of treatment. Again, the clinical utility of these data is limited by the absence of a 20 µg group.

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.

C. Safety

The integrated review of safety was completed by Bruce V. Stadel, MD, MPH

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 [redacted] 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.

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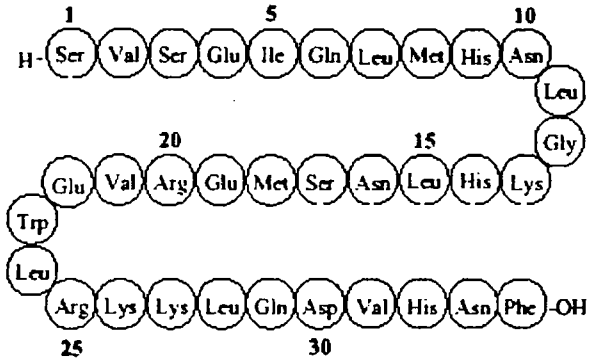
CLINICAL REVIEW

I. INTRODUCTION AND BACKGROUND

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

Chemical Structure:



rhPTH (1-34), m.w. 4117.8

Sponsor: Eli Lilly and Company, Indianapolis, IN

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

Indication: The proposed-labeled indications are treatment of postmenopausal osteoporosis and treatment of (adult) male osteoporosis.

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.

B. BRIEF OVERVIEW OF CLINICAL SECTION OF NDA

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 approved treatments for osteoporosis are anti-resorptive agents. Most of these have demonstrated efficacy in reducing the risk of fractures, but the risk reductions have been limited. It is widely believed that the development of new anabolic agents will fill a significant unmet medical need by increasing anti-fracture efficacy.

The scientific basis for the development program for LY333334 was derived from abundant preclinical and clinical data, originating as early as 1929, demonstrating that intermittent injections of various preparations of PTH resulted in increases in skeletal mass. In preclinical models, the increases in bone mass were accompanied by augmented bone strength (described in detail in section II below).

It should be noted at the outset that the idea of using PTH as a stimulator of bone formation runs counter to certain concepts about the skeletal consequences of primary and secondary hyperparathyroidism. Many earlier descriptions of these conditions have emphasized loss of bone mineral, with consequent fractures and renal stones. However, over the past three decades, the widespread use of multi-channel screening chemistries has permitted the detection of early and mild primary hyperparathyroidism. These cases are usually characterized by minimal elevations of serum calcium and PTH levels. Long term follow-up studies have shown that, in many patients, there is either no apparent loss of bone, or the loss is minimal and does not appear to progress. Osteopenia occurs in about 25% of patients with primary hyperparathyroidism, and about 25% of all patients with this disease will experience significant decreases in bone mineral density over a 10-year follow-up period without surgery. The overall risk of fracture in patients with mild primary hyperparathyroidism has not been established conclusively. In one recent population-based study (Khosla et al *J.Bone Miner Res*, 1999), the risk of fracture was increased in patients with (mostly mild) primary hyperparathyroidism, relative to standardized incidence ratios.

Thus, although it is well established that PTH increases the rate of bone turnover, the net effects of the hormone can be either catabolic or anabolic, depending on skeletal site and the levels and pattern of serum PTH concentrations. Persistently high concentrations of PTH are generally catabolic to bone, whereas mild elevations of the hormone may be neutral or slightly anabolic at some sites. More detailed observations using bone densitometry and iliac crest histomorphometry have indicated preservation of, or increases in, cancellous bone, with a decrease in cortical bone in primary hyperparathyroidism.

While mild, chronic elevations of endogenous PTH may increase bone mass slightly at some skeletal sites, intermittent administration of the peptide may have

profound anabolic actions. Thus the pharmacodynamic properties of PTH are critically 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.

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, intermittent injections of LY333334 (daily s.c. injections 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. Similar results were observed in ovariectomized monkeys and rabbits. The sponsor also has provided evidence that these positive effects may result from increased osteoblast differentiation, leading to an enhancement of the functional osteoblastic cell pool.

In the preclinical studies, LY333334 demonstrated very little acute toxicity and was not genotoxic. The primary effects found in studies lasting up to 1 year were due to the known biological actions of PTH. Renal histopathologic lesions found in monkeys were reversible and were not associated with major changes in renal function. The major serious effect of PTH 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 and there was no threshold dose. Focal hyperplastic lesions and benign 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. 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 anabolism that accompanies intermittent administration of exogenous peptide is not found in hyperparathyoid bone. This issue is discussed in further detail below. LY333334 treatment did not increase the incidence of other neoplasms in the preclinical studies.

In summary, preclinical studies confirmed that non-hypercalcemic doses of LY333334 resulted in substantial stimulation of bone formation. Histomorphometric and mechanical stress analyses of the bones from treated animals demonstrated that the bone was of normal quality. No unexpected safety issues arose during the preclinical development program, with the exception of the bone tumors. Further review of the preclinical pharmacology/toxicology program appears in Section II below.

The clinical development program for LY333334 included 21 clinical trials that enrolled more than 2800 women and men. The first trials began in 1995. The sponsor's early (Phase 1-2) studies tested the effects of single doses from 5 to

100 μg and multiple doses of 6 to 60 μg/day administered for up to 6 weeks. These studies demonstrated a strong dose-dependent effect of LY333334 on PICP, BSAP, and urinary NTX/Cr. 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[3].

In the Phase 1-2 studies of LY333334, doses > 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 ≥ 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. Further description of the Phase 1-2 pk-pd studies appears in Sections II and III below.

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 1 year. The planned duration of the Phase 3 trials was up to 3 years. However, the maximum exposure time on drug was 2

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[3] It should be noted that the qualitative nature of these changes in biomarkers, an increase in both formation and resorption, differs from that seen with anti-resorptive agents. With the latter, there is an initial decrease in bone resorption markers, due to a direct effect of the drugs on osteoclast function. This is followed by a decrease in indicators of formation, because the two processes are physiologically coupled. In postmenopausal osteoporosis, the result of treatment with anti-resorptive drugs results in a suppression of formation and resorption markers into the premenopausal range. This suppression of bone turnover has been confirmed histomorphometrically in several studies of the effects of anti-resorptive agents, such as bisphosphonates.

years because all clinical trials were terminated in December 1998 following the discovery of osteosarcomas in the ongoing rat carcinogenicity study. At the time of termination of the pivotal postmenopausal osteoporosis treatment study (GHAC), the median duration of observation was 19 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.

The four long-term Phase 3 trials included the two pivotal studies and two 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, also referred to as GHAC) was intended to be a three-year, double-blind, randomized, placebo-controlled, parallel design, multi-center (multinational) study of 1637 postmenopausal 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. Secondary endpoints included proportion of patients with new nonvertebral fractures, BMD of spine and hip, biomarkers of bone turnover, and height. The study also included evaluation of population pk and pd. Five health-related quality of life instruments were also evaluated as efficacy outcomes. 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.

Major outcomes of GHAC: This trial was interrupted prematurely (see above) and all data relate to 18-23 months of treatment. Treatment with LY333334, 20 µg/day or 40 µg/day for 18-23 months, resulted in a statistically significant reduction in the proportion of patients with new vertebral fractures, compared with placebo (14.3%, 5.0%, and 4.4% in PBO, 20µg/day, and 40 µg/day treatment groups, respectively). In addition, there were significant reductions in multiple vertebral fractures, as well in severity of such fractures, in the 2 groups treated with LY333334, compared to PBO (the last two outcomes were observed while counting and classifying fractures, but were not in themselves pre-specified objectives). There was also a statistically significant reduction in the proportion of patients with non-vertebral fractures (9.7%, 6.3%, and 5.8%, in PBO, 20 µg/day, and 40 µg/day groups, respectively). This last outcome was a pre-specified efficacy endpoint.

Treatment with LY333334 resulted in significant and very substantial increases in BMD at the lumbar spine (10% and 14% increases from baseline in the 20 µg and 40 µg groups respectively, compared to essentially no change in PBO). Of

note, increases in lumbar spine BMD were seen in both active treatment groups as early as 3 months (both about 4%). There was a greater increase in the 40 µg/day group than in the 20 µg/day group, beginning at about 6 months. This dose-dependency of pharmacodynamics is consistent with the results of the phase 2 studies. There were also statistically significant increases in BMD in active treatment groups at all other measured skeletal sites, except the radius. At the femoral neck, there was a 1% BMD decrease in PBO, compared with 3% and 5% increases in the 20 µg and 40 µg treatment groups, respectively. At the mid-shaft (distal 1/3) radius there were no changes in BMD vs PBO in the 20 µg group; however, there was a small decrease in the 40 µg group. This change was statistically significant, compared with PBO, and is consistent with published data (Neer et al, 1993) from a smaller trial using similar doses of PTH (1-34). The lack of efficacy at the distal radius is most likely due to the high content of cortical bone at this site.

These reductions in vertebral fracture rates exceed those found in efficacy trials with bisphosphonates or raloxifene. In addition, beneficial effects are manifest by 19 months, compared to 3 years for other (anti-resorptive) agents. The increases in spine BMD are substantially greater and occur earlier than with any known anti-resorptive agent.

Because the 20 µg and 40 µg treatment groups demonstrated essentially equal fracture prevention efficacy, GHAC established 20 µg as the indicated dose of LY333334 in the treatment of postmenopausal osteoporosis.

Safety: In this study of the use of LY333334 in postmenopausal women, there were no serious safety/tolerability concerns that were identified by the sponsor or individual investigators. Of importance, there were no significant changes in blood pressure or pulse seen in the study. Adverse effects that appeared to be related to treatment with LY333334 were judged to be relatively mild. These included leg cramps (in the 20 µg group), headache (in the 40 µg group), and nausea (in the 40 µg group). Only nausea, found more frequently in the 40 µg group, was significant enough to result in more frequent discontinuation from the study.

There were no reported serious laboratory safety concerns. Of special relevance, there were small, but statistically significant, increases in the 4- to 6-hour post-dose serum calcium levels, with a median increase of 0.17 mmol/l. In addition, and also consistent with the biological action of PTH, there were small increases in the 24-hour urinary calcium excretion rates, with median increases of 0.76 mmol/day. The 24-hour post-dose serum calcium level did not increase. There was no increase in reported instances of urolithiasis. However, there were significant increases in serum uric acid (13%-25%) and decreases in serum magnesium levels (6.7%-11.1%). A significant number of patients (2.8%-8.0%) developed antibodies to LY333334.

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

This pivotal Phase 3 study supporting a male osteoporosis treatment indication was intended to be a two-year, randomized, double-blind, placebo-controlled, parallel, multi-center (multinational) trial of the efficacy and safety of LY333334 in adult men with osteoporosis. The primary efficacy outcomes were changes in lumbar spine BMD following 2-years of treatment with LY333334 (20 µg/day or 40 µg/day) or PBO. Other outcome variables included BMD at other skeletal sites and changes in bone turnover biomarkers. Note that this trial lacked both the design and statistical power to detect treatment group differences in fracture rates. Four hundred thirty-seven men (age 30-85 years) with lumbar spine BMD T-scores < -2.0 were randomized (in a 1:1:1 schedule) to receive PBO or either dose of LY333334. Because of premature study termination (see above), patients received treatment (with active drug or PBO) for about 300 days.

Major outcomes of GHAJ: Treatment of men with primary osteoporosis for 11 months with LY333334 resulted in statistically significant increases in lumber spine BMD of 6% (the 20 µg/day group) and 9% (the 40 µg/day group). Statistically significant differences from placebo were seen in both groups as early as 3 months after beginning treatment. In the 20 µg group, there were no statistically significant increases in BMD, relative to PBO, at other skeletal sites, with the exception of the femoral neck (PBO-subtracted difference of 1.24 %). In the 40 µg group, statistical significance was achieved at several extra-vertebral sites, relative to PBO. The distal 1/3 radius and the ultra-distal radius showed no significant changes in BMD, compared with PBO, in either treatment group.

There were statistically significant changes in bone biomarkers, consistent with the anabolic action associated with intermittent administration of PTH. Increases in BSAP and PICP were seen after 1 month of treatment. There were also somewhat delayed but substantial and statistically significant increases in urinary NTX and free deoxypyridinoline, both markers of bone resorption. These changes are consistent with the coupling of the formation and resorptive processes, as well as the net increase in bone remodeling associated with PTH treatment.

Safety: The sponsor did not identify any serious clinical or laboratory-related safety concerns. In the 40 µg/day group, nausea seemed to be related to LY333334 administration and led to more frequent discontinuation. There were no reported significant changes in HR or BP. Laboratory testing disclosed small increases in the 4- to 6-hour post-dose serum calcium concentration and in the 24-hour urine calcium excretion rate. There were also increases serum levels of uric acid, as well as decreases in magnesium. None of these changes were judged to be clinically significant and all were reversible upon stopping treatment.

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.

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 the ultra-distal radius, the between-group differences did not differ. At the proximal 1/3 radius (forearm), the BMD in the LY333334 group was significantly less than in the alendronate group. The mean whole body BMD increased significantly in both treatment groups, but the between-group differences were not statistically significant.

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. Data from the one-year time point will be submitted with the 120-day safety report after the NDA is submitted and under review. The remainder of the data will be submitted subsequently.

Results: Following cessation of study drug, 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.

Safety and efficacy data are also presented by study. Thus far the reduction in non-vertebral fractures observed during the first two years of treatment was maintained at the 6-month follow-up time point. The data are displayed as a Kaplan-Meier curve in which the treatment-related differences continue to diverge after cessation of study drug. Maintenance of differences in BMD has also been observed at the 6-month time point in this study. Further analysis of this study is presented in Section VI below.

Summary: The clinical development of LY333334 for the treatment of osteoporosis included an extensive Phase 1-2 clinical pharmacology program that established optimal dosing schedules for LY333334, based on efficacy and safety/tolerability. These studies provided a thorough understanding of the pharmacokinetics and pharmacodynamics of r-hPTH (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 both postmenopausal women (BMD and fracture data) and adult males (BMD data only). Despite the early termination of the Phase 3 trials (at around 19 months), the efficacy of LY333334, in preventing vertebral fractures in women and increasing spinal BMD in women and men, exceeded that which has been demonstrated following treatment for 3-4 years with any known anti-resorptive drug. LY333334 20 µg increased BMD at other skeletal sites in women, but the increases were no greater than have been

observed in studies of other agents (there are no head-to-head comparisons of LY333334 20 µg with other approved drugs). Except for the femoral neck, efficacy in increasing BMD at non-vertebral sites was demonstrated with only the 40 µg dose in men.

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 the treatment of postmenopausal osteoporosis. In the opinion of this reviewer, the optimum dose schedule for male osteoporosis has not been established (see review of GHAJ below).

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. 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 AE's were not encountered with the 20 µg/day dose. Since 20 µg/day was an effective as 40 µg/day in reducing fractures, the dose for both osteoporosis indications 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.

C. Status of drug therapy for the treatment of osteoporosis:

Osteoporosis is characterized by loss of bone mineral density, with disruption of bone architecture, increased fragility, and a corresponding increase in the risk of fracture. All drugs that are approved for the prevention and/or treatment of postmenopausal osteoporosis and male osteoporosis are anti-resorptive agents. These act by inhibiting osteoclastic bone resorption. Anti-resorptive agents secondarily suppress osteoblastic bone formation, because the two processes are physiologically coupled. There are no approved drugs that are anabolic to bone.

For postmenopausal osteoporosis, approved drugs include oral bisphosphonates (alendronate, risedronate), estrogens (oral, transdermal), selective estrogen receptor modulators (raloxifene), and nasal calcitonin. Alendronate is the only approved drug for the treatment of osteoporosis in men, based on a two-year placebo-controlled trial that demonstrated statistically significant increases in BMD. Due to limitations in trial size and duration, drug-induced fracture reduction rates have not been demonstrated in men. Consequently, alendronate has been approved for the "treatment of osteoporosis in men to increase bone mass." In postmenopausal women, fracture reduction has been demonstrated for the two bisphosphonates and raloxifene in prospective placebo-controlled clinical trials. Observational studies suggest that estrogens may help prevent fractures, but there are no prospective trials that demonstrate this effect for estrogens. There are no convincing data that support efficacy for

Anti-resorptive therapy slows the loss of bone mineral, which is a significant part of the pathophysiology of osteoporosis. Anti-resorptive treatment suppresses bone remodeling, resulting in a low turnover state, in which bone formation slightly exceeds resorption. This generally results in a net increase in bone mineral content. However, anti-resorptive therapy does not restore the lost bone architecture, particularly the trabecular volume, number, and connectivity that are important to maintenance of bone strength. Thus, anti-resorptive therapy retards bone loss and increases bone mass, but does not restore or build "new" bone.

Combinations of different classes of anti-resorptives (e.g., a bisphosphonate plus estrogen) may lead to further increases in bone mineral density (BMD), but the increments have been small (e.g., the alendronate plus HRT trial), and anti-fracture benefits have not been demonstrated. It is currently believed that we have achieved the maximum benefit from the strategy of inhibiting bone resorption. Because inhibition of resorption leads secondarily to a significant decrease in bone formation, further decline in bone resorption rates may lead to a nearly complete dampening of the remodeling process in bone.

It should also be noted that loss of bone mineral is only one factor that diminishes bone fragility, particularly in elderly individuals. Aging itself, perhaps owing to loss of other elements in bone, also plays a major role in increasing fracture risk.

Because of these considerations, anti-resorptive agents are only modestly effective in reducing the incidence of osteoporotic fractures. For example, in large prospective, placebo-controlled trials in postmenopausal women, alendronate treatment reduced the risk of morphometric vertebral fractures by about 44%-48%, depending on dose. In similar trials, risedronate has been shown to reduce vertebral fracture risk by 41% and raloxifene, by 30 %. These agents are less effective in reducing the risk of non-vertebral, as opposed to

vertebral, fractures (about 12%-39% by 3 years, depending on the drug and the study population). The drugs have had minimal effects on height loss, even when statistically significant (generally, placebo-subtracted differences were of the order of 1.4 mm over 3-4 years). In considering the ultimate therapeutic potential of anti-resorptive agents as monotherapy for postmenopausal osteoporosis, it is interesting to note that this level of efficacy is seen in a population that experienced substantial increases in (especially spinal) BMD in response to the treatment. For example, alendronate has consistently increased lumbar spine BMD by about 7-8% over placebo in several trials. Furthermore, responder analyses have generally demonstrated that well over 90% of treated patients demonstrate significant BMD increases.

Based on these considerations, most authorities believe that there is a need to develop anabolic agents that will help restore normal bone architecture by increasing osteoblastic bone formation. Such drugs might be especially helpful in low turnover states (e.g., many cases of male osteoporosis) and perhaps in glucocorticoid osteoporosis as well. In addition, all currently approved agents have some associated side effects, most prominently GI irritation (bisphosphonates), hot flushes (raloxifene), and vaginal bleeding (estrogens). A bone formation agent that is safe and well-tolerated and that has increased efficacy in preventing fractures, reducing height loss, and ameliorating back pain, will help fill an unmet medical need.

D. Important milestones in product development:

These are detailed in the submission. The sponsor provides a complete description of meetings with the Division. The single important milestone was the premature discontinuation of all clinical studies in December 1998, following the findings of osteosarcomas in rats treated with LY333334. Details are provided in sections below.

E. Other relevant information:

Foreign marketing status: Neither teriparatide, nor any other PTH analog, has been marketed for the treatment of osteoporosis anywhere in the world. A synthetic PTH 1-34 analog, ——— is available for diagnostic purposes (differential diagnosis of pseudohypoparathyroidism). To the best of my knowledge, no PTH product has been denied marketing approval anywhere.

II.CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, TOXICOLOGY, MICROBIOLOGY, AND BIOPHARMACEUTICS REVIEWS:

Chemistry, statistics, biopharmaceutics and pharmacology/toxicology reviews have been concluded.

PTH (1-34) is expression cloned in plasmid pHMM193. A map of the plasmid, together with detailed descriptions of production and purification of the final peptide, are provided in the NDA and reviewed by chemistry. No clinically relevant concerns have been raised in this review.

No unexpected clinically relevant findings emerged from the pharmacology/toxicology review, with the notable exception of the bone tumors in rats. Of particular importance to the review of a new molecular entity, the preclinical program demonstrated rapid anabolic action of LY333334 in bone. Histological studies found no evidence of abnormal bone in LY333334-treated animals. Biomechanical testing demonstrated increases in bone strength following treatment with the drug.

Details of the occurrence of osteosarcomas in rats are provided in the pharm/tox review.

Comments: This is by far the most important safety-related finding and is the subject of intensive review, as discussed below. I believe that it is important to discuss this issue from a biological and medical perspective in the clinical review of LY333334. Our ability to evaluate the potential risk to humans, and to formulate strategies for monitoring an exposed population, will weigh heavily in decisions regarding approvability of LY333334.

Several aspects of the occurrence of osteosarcomas are especially noteworthy. First among these is that the mechanism of tumor formation most likely involves hormonal stimulation of known target cells (osteoblasts or osteoblast progenitor cells). Thus the development of osteosarcomas is biologically plausible. In addition, the tumors developed in a dose-dependent fashion and there was no threshold dose. Furthermore, the responses were robust: approximately 50% of male rats developed tumors following treatment with high doses of LY333334. To the best of my knowledge, this is the most striking example of hormonal promotion of tumor in a genetically and environmentally "normal" animal species.

According to the sponsor and their external experts, it is unlikely that the rodent findings are relevant to humans. This conclusion is based on consideration of seven mitigating factors, which are listed below, together with my evaluation of the cogency of each:

1. Rats received high exposure to drug for long periods of time.

The sponsor has maintained that these excessive total exposures cannot be extrapolated to the human situation. My interpretation is that the

differences are only quantitative; since there is no threshold dose, there is no complete assurance of safety at any effective human dose.

In the long-term carcinogenicity studies, rats were treated for about 50-75% of their lifetime before tumors were detected. Exposures ranged from about 3-50 times that which would result from the proposed human dose, based on AUC. Assuming humans would receive the drug for only 3% of lifetime, this yields an overall exposure in rats of about 25-1000 times the proposed human exposure, using percent of life span as the time dimension. In the high dose group, 50% of the animals developed osteosarcomas. Calculation of the rate of increase of osteosarcoma in rats depends on the spontaneous rate of the tumor in that species. The background rate of osteosarcomas in rats varies from 0% (Lilly's placebo control groups) to 0.1-0.2%, depending on the data sources (see pharm/tox review). If the background rate is 0.1%, then 1000X exposure led to a 500-fold increase in tumor formation. Assuming that there is linearity of dose effect (there is no evidence for or against linearity), then the proposed human dose would produce a relative risk of 1.5. Since the incidence of osteosarcoma in humans over 50 years of age is about four per million, this would predict an increase of two patients per million treated per year, which would not be detectable.

Now suppose the background rate in the sponsor's rat strain (Fisher) is 0.01%. The high dose of LY333334 would then yield a 5000-fold increase in tumor occurrence over background, as a result of a 1000-fold increase in exposure to the drug. Extrapolation to the human dose would predict a relative risk of about 6. This would result in 20 excess cases per million patients exposed per year. Similar analysis of the occurrence of tumors in the lower dose groups yield risk estimates that are slightly larger, but within reasonable agreement with the above estimates. For example, about 5% of rats developed osteosarcomas following treatment with 3X the human dose [AUC] for about 15 times longer. This yields a 50-fold tumor excess as a result of a 50-fold exposure to the drug, based on a background estimate of 0.1%. Extrapolation to humans would predict a relative risk of about 2. If the background rate of tumor in rats were 0.01%, then the relative risk in humans would be about 11, predicting 40 excess cases per million per year.

The above calculations are, of course, highly speculative. They are provided to illustrate one logical outcome of the sponsor's contention that the rat osteosarcomas occurred because of quantitative differences between the rat and human exposures. If there is no known threshold dose, there remains a theoretical risk. Depending on the true background rate of tumor in Fisher rats, the projected risk to humans could be small and undetectable or large (perhaps 11-fold) and most likely detectable and unacceptable (see discussion of proposed phase 4 monitoring programs).

2.Treatment of rats began at 6-7 weeks of age. Humans would be exposed only as adults.

This is true. However, we have no data that demonstrate that rodents exposed to the drug at an older age do not develop osteosarcomas. Indeed, these experiments are currently being conducted by the sponsor; they are scheduled to be completed by the end of 2002. If the young cohort of animals develops tumors in these experiments (positive controls), and the animals whose exposure began later in life do not, then this would lend some credence to the idea that younger rats are vulnerable to tumor formation. The data would provide some assurance, but would not settle the issue completely. Clearly, if tumors develop in the cohort given the drug at an older age, this would increase concern substantially. These are certainly important experiments. In the absence of better experimental protocols or more cogent data, it is my opinion, that the results of these experiments should be available prior to marketing the drug.

3. Negative monkey study.

The sponsor has observed no bone tumors in 80 monkeys treated with moderately elevated doses of LY333334 for 12-18 months. In my opinion, these observations are meaningless because the background tumor rate in monkeys is not taken into account. I am unaware of any data on the spontaneous rate of osteosarcomas in Cynomolgus monkeys (or other non-human primates). Suppose, however, that the background rate in monkeys is ten times that in humans. Suppose again that the total exposure in the monkeys was about 5X on the basis of AUC and about 3-5X on the basis of per cent of lifespan, yielding an overall exposure of about 20 times that proposed in humans. Based on rat data (the rat appears to be especially susceptible to PTH-induced osteosarcomas) and assuming linearity of response, a 20-fold exposure would produce about a 20-fold increase in tumors. Even if the increase in tumors were 100-fold, the overall rate of osteosarcoma in monkeys would be four per thousand per year. Thus, even under the most generous assumptions of promotional activity, it would be unrealistic to expect to detect a single tumor in 80 monkeys following exposure to LY333334 for 12-18 months.

4. Rat bone differs from human.

This is certainly true. The architecture, growth, modeling, and remodeling patterns differ between the two species. In addition, the sponsor maintains that the anabolic responses to LY333334 in rats were excessive or exaggerated. In this regard, it would be interesting to explore the relationship between BMD responses and tumor formation in rats, both

quantitatively and temporally. In my opinion, it is likely that tumor induction occurred many months before the tumors were detected. Thus tumor formation may have occurred well before the pronounced anabolic BMD responses were manifest.

These considerations notwithstanding, the important question is whether the two species differ in the ability of the osteoblast precursor pools to replicate and expand clonally in response to intermittent hormonal stimulation with PTH.

5. There is no increase in other malignancies in LY333334-treated rats.

PTH is not a carcinogen. The concern here is with the promotional effect of a hormone in its known target tissue.

6. *Humans with hyperparathyroidism do not develop osteosarcoma.*

Primary hyperparathyroidism is not uncommon. In the past three decades, multi-channel chemistry screening, combined with improved assays for PTH, have permitted the identification of many thousands of individuals with mild, generally asymptomatic, primary hyperparathyroidism. Current clinical practice guidelines offer allow many of these patients (generally, those with very mild disease, with no sequelae, who are elderly or poor surgical candidates) to live out their lives without parathyroidectomy.

Osteosarcoma is not known to occur with increased frequency in patients with hyperparathyroidism. In addition, the sponsor has searched large databases and found no evidence of osteosarcoma occurring in this patient group. Because there is such a large number of individuals who have chronic, mild elevations of PTH for years, if not decades, this should provide the strongest argument against an association of osteosarcoma with PTH treatment. However, patients with chronic, sustained PTH elevations do not manifest the profound bone anabolism that accompanies intermittent PTH administration. In addition, there may be different cellular responses to intermittent, vs sustained, PTH elevations, as there are with pharmacodynamics. These cellular responses may involve proliferation and/or inhibition of apoptosis. Thus my concerns cannot be fully set aside on the basis of the clinical experience with hyperparathyroidism.

7.Observations on clinical trial subjects post-treatment with PTH.

The sponsor has not noted osteosarcomas in patients who have been treated with intermittent PTH during clinical trials and offers this as reassurance that osteosarcoma is unlikely to accompany treatment with LY333334.

Again, this interpretation fails to take the background rate of tumor into account. Approximately 1500 individuals have received ≥ 3 months of treatment with various doses of LY333334. As noted above, the background rate of osteosarcoma in this population is about four per million per year. Extrapolating from the rat data, treatment with clinical doses of teriparatide for this period of time would not be expected to cause more than a doubling of the basal rate of tumor formation. Even if this exposure to LY333334 increased the tumor occurrence rate by a factor of ten, this would predict about one osteosarcoma per 25000 patients per year. The likely latency between tumor formation and clinical detection further decreases the probability of tumor detection in the treated patient population.

Thus the lack of clinically detected osteosarcomas in the sponsor's post-treatment population does not provide reassurance.

In summary, the single important toxicological finding was the development of osteosarcoma in rats treated with LY333334. There are no available data that allay my concerns about this finding.

I have provided my own summary of the biopharmaceutics program (**Section III**, below). A separate biopharmaceutics review accompanies this report.

III. Human pharmacokinetics and pharmacodynamics:

The following is a brief overview of the clinical pharmacology studies, with emphasis on findings that are relevant to the medical review of LY333334.

Clinical pharmacology studies that were conducted in all phases of development employed both traditional (i.e., intensive sampling of individuals) and population approaches. Pharmacokinetic studies of LY333334 have been carried out in healthy men and women across a broad age range, in patients with mild to severe renal insufficiency, and in osteopenic (Phase 2 study GHAA) and osteoporotic patients (Phase 3 studies GHAC and GHAJ).

Data derived from healthy individuals:

Traditional pharmacokinetic data were obtained from approximately 200 healthy men and women. Each of these subjects received at least one subcutaneous dose of LY333334, ranging from 5 - 100 µg. In addition to the 6 studies that focused on s.c. delivery, there were 5 studies that investigated non-injection delivery routes (inhaled, buccal, nasal). These are not reviewed here, but each used a subcutaneous reference dose of LY333334, and data derived from the s.c. doses are included in the sponsor's integrated pk-pd and safety summaries.

Data derived from individuals representing the proposed targeted marketing population:

Pharmacokinetic data were obtained from 36 postmenopausal women with low bone mass (one Phase 2 study, LY333334 dose range 6-60 µg) and from 611 men and postmenopausal women with osteoporosis (these were subsets of the Phase 3 trial populations; doses were 20 and 40 µg in these pivotal trials). The age of the women in the osteoporosis studies ranged from 49-85 years. In the male osteoporosis study, the age range was 31-84 years.

The sponsor presents a detailed breakdown of the demographics of the populations used to generate the pk data. Nearly all of the subjects were over 50 years old. Forty-four % were men.

PK studies, including studies in special populations:

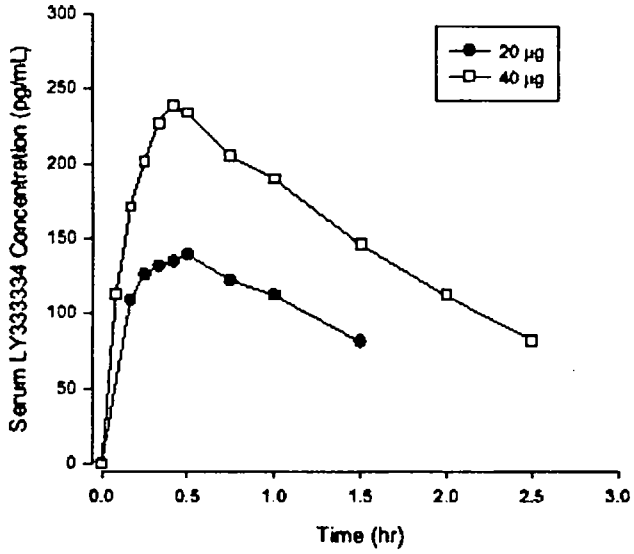
The absolute bioavailability of LY333334 was estimated to be 95%. This was determined in both older women and men by comparing serum concentration-vs-time profiles following i.v. infusions and s.c. injections of the drug.

LY333334 was rapidly absorbed following s.c. injection into the abdominal wall or thigh. Peak serum concentrations were attained approximately 30 minutes after injection and declined to non-quantifiable levels by 3 hours. Systemic clearance was approximately 94 L/hr, greater than normal liver plasma flow. This suggested both hepatic and extra-hepatic clearance.

The disappearance half-life following s.c. injection was approximately 1 hour. The half-life of the drug following i.v. infusion was about 5 minutes. This conforms to a model in which the rate of elimination is about 15 times faster than the rate of absorption, so that the overall rate of disposition of the molecule is determined by the slower absorption rate. There was no evidence for drug accumulation following multiple daily doses.

Comments: The data relating to hepatic clearance are typical of many peptides and proteins, which are generally cleared from plasma as a result of proteolytic cleavage at multiple anatomic sites. Such clearance usually follows first order kinetics. Both the lack of accumulation of peptide following repeated daily administration, and the pharmacokinetics following s.c. and i.v. injection, are not surprising, based on published experience with other peptides.

To illustrate the mean serum concentrations following a single s.c. dose of LY333334, I have included the sponsor's figure below:



Note that for the (sole indicated) 20 µg dose, the peak concentration of LY333334 [PTH (1-34)] is about 4-5 times the physiological maximum of endogenous PTH (1-84), on a molar basis. However, these supra-physiological levels of the drug are maintained for no more than 2 hours.

The sponsor also presents composite mean concentrations for the 3 pk parameters C_{max}, AUC_{0-t}, and T_{max}. C_{max} and AUC_{0-t} differed significantly between men and women, whereas T_{max} did not differ according to gender. The mean values for C_{max} were 131 pg/ml for women vs 113 pg/ml for men; for AUC_{0-t}, 184 pg·hr/ml for women and 155 pg·hr/ml for men. The sponsor also presents the data as three frequency histograms (by gender and overall) that can be approximated by log-normal distributions. Analysis of these data shows that, in general the systemic exposure to LY333334 was lower in men than in women. Although the sponsor maintains that these gender-related differences in systemic exposure to LY333334 were not clinically or pharmcodynamically meaningful, it is my opinion that the lower systemic exposure in men is therapeutically important, as suggested by results of the male osteoporosis trial, GHAJ.

Overall, the between-subject coefficient of variation for pk parameters ranged from 30-50%.

Linear dose proportionality was demonstrated over the range 5-100 µg for C_{max} and 15-100 µg for $AUC_{0-\infty}$. The dose proportionality was independent of site of injection (thigh vs abdomen) or gender for C_{max}. However, the increase in $AUC_{0-\infty}$ in response to increasing dose was slightly greater for females and for injections into the thigh in females.

Distribution, metabolism, and excretion of LY333334:

The sponsor has performed no serum or plasma protein binding studies with LY333334; and there is no published literature regarding protein binding of this peptide or of the endogenous PTH (1-84).

Comments: A few peptide hormones bind to plasma proteins; most circulate unbound. Given the rapid plasma elimination half-life of LY333334 following i.v. injection (5 minutes), binding of the peptide to plasma proteins would seem unlikely.

The sponsor performed no metabolism or excretion studies of LY333334. However, there is extensive published literature (cited and reviewed in detail by the sponsor) on the metabolism of PTH and PTH fragments. It is known that both synthetic and endogenous PTH are cleared by the liver, kidneys, and perhaps other tissues. Hepatic Kupffer cells are the major site for the cleavage of both PTH (1-34) and PTH (1-84) into smaller fragments. Published data demonstrate that hepatocytes do not play a role in the metabolism of PTH. Consequently, limitations of hepatic blood flow, rather than hepatic insufficiency, would in theory reduce the clearance of PTH (1-34).

There are extensive studies of the role of the kidney in the metabolism and clearance of PTH and PTH fragments. It is well established that mid- and carboxy-terminal fragments of PTH (1-84) are elevated in the plasma of patients with renal failure. To investigate the effects of altered renal function on the clearance of LY333334, the sponsor conducted extensive pharmacokinetic studies in patients with mild, moderate, and severe renal insufficiency. These are reviewed in the next section.

Pharmacokinetics in Special Populations:

The sponsor analyzed the effects of age, gender, race, smoking status, renal status, hepatic impairment, heart failure, and alcohol consumption, on the pharmacokinetics of LY333334.

Population analyses were employed to assess the effects of age, smoking status, and alcohol use on LY333334 pk. In the pk analyses of subjects in GHAC (postmenopausal osteoporotic women, age 49-85 years) and GHAJ (osteoporotic men, age 31-84 years), there was no discernible effect of age on pk parameters.

Smoking status and alcohol consumption were determined from self-reported data. In the GHAC and GHAJ pk study populations, 20% were smokers and 56% used alcohol. Neither behavior affected the disposition of LY333334.