

**Fortéo™**

**Teriparatide Injection  
NDA 21-318**

**Endocrinologic and Metabolic Drugs  
Advisory Committee Briefing Document**

**Volume 1**

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## List of Abbreviations

ADME	absorption, distribution, metabolism, and excretion
AUC	area under the concentration-time curve
BMC	bone mineral content
BMD	bone mineral density
BSA	body surface area
BSAP	bone-specific alkaline phosphatase
CEE	conjugated equine estrogens
$C_{max}$	peak concentration
COSTART	Coding Symbol and Thesaurus for Adverse Reaction Terms
DPD	urinary free deoxypyridinoline
DVT	deep venous thrombosis
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
FDA	Food and Drug Administration
HCTZ	hydrochlorthiazide
HPT	hyperparathyroidism
HRT	hormone replacement therapy
LLN	lower limit of normal
LOCF	last observation carried forward
LY333334	teriparatide injection
NCI	National Cancer Institute
NNT	number needed to treat
NOAEL	no-observed-adverse-effect levels
NOEL	no-observed-effect level
NTX	urinary N-telopeptide
OVX	ovariectomized
PICP	serum procollagen I carboxy-terminal propeptide
PTH	parathyroid hormone (1-84)
PTHrP	parathyroid hormone-related peptide
PTH20	teriparatide 20- $\mu$ g/day treatment group
PTH40	teriparatide 40- $\mu$ g/day treatment group
pQCT	peripheral quantitative computed tomography
QCT	quantitative computed tomography
QTc	electrocardiographic QT interval corrected for heart rate
RBC	red blood cell
rhPTH(1-34)	recombinant human parathyroid hormone (1-34)
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SERM	selective estrogen receptor modulator
TESS	treatment-emergent adverse events
$T_{max}$	time to reach peak serum concentration
$T_{1/2}$	elimination half-life
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cells

## List of Clinical Studies

GHAB	Phase 1: LY333334: Single-Dose Dose-Ranging Study, Pharmacokinetics and Pharmacodynamics Properties
GHAD	Phase 1: Effect of LY333334 on Calcium Homeostasis in Healthy Postmenopausal Women
GHAE	Phase 1: Safety of LY333334 in Hypertensive Women
GHAM	Phase 1: Assessment of Renal Effects of LY333334 Alone or in Combination with Raloxifene HCl or Continuous Combined Hormone Replacement Therapy
GHAW	Phase 1: Pharmacokinetics and Acute Pharmacodynamics of LY333334 When Administered Alone and with Furosemide in Stable Chronic Renal Insufficiency
GHBA	Phase 1: LY333334; Thiazide Diuretic Interaction Trial
GHBC	Phase 1: Safety, Pharmacokinetics, and Acute Pharmacodynamics of LY333334 in Patients with Stable Heart Failure
GHBI	Phase 1: Absolute Bioavailability of LY333334 Administered by Subcutaneous Injection
GHBO	Phase 1: Assessment of LY333334 on Cardiac Conduction and Repolarisation
GHRB	Phase 1: Randomized, Single-Blind, Crossover, Interaction Study of LY333334 and Digoxin Pharmacodynamics in Healthy Volunteers
<b>Alternative Delivery</b>	
GHAK	Phase 1: Relative Bioavailability Administered by Inhalation and Subcutaneous Injection with Scintigraphic Evaluation of Lung Deposition
GHAN	Phase 1: A Relative Bioavailability Study of the Buccal Route of Administration Compared with Subcutaneous Delivery in Healthy Subjects
GHAO	Phase 1: Effects of Pulmonary Inhalation of Teriparatide on Biochemical Markers of Bone Metabolism and Pulmonary Function Tests in Healthy Postmenopausal Women
GHAS	Phase 1: A Relative Bioavailability Study of Pulmonary Route of Administration Compared with Subcutaneous Route and Single and Multiple Dose Safety and Pharmacokinetics of LY333334 and Inhalation
GHAT	Phase 1: Evaluation of Nasal Absorption and Tolerability of Teriparatide Following Administration of a Novel Nasal Formulation in Healthy Volunteers
GHBF	Phase 1: Multiple Dose Safety Study of Inhaled LY333334 and Relative Bioavailability to the Subcutaneous Route
GHAA	Phase 2: Safety and Pharmacological Effects of LY333334 on Biochemical Markers of Bone Metabolism in Healthy, Postmenopausal Women
GHAC	Phase 3: Effects of LY333334 in the Treatment of Postmenopausal Women with Osteoporosis
GHAF	Phase 3: Effects of LY333334 in Postmenopausal Women on Estrogen and Progestin Therapy
GHAH	Phase 3: LY333334 Compared with Alendronate in Postmenopausal Women with osteoporosis
GHAJ	Phase 3: Effects of LY333334 in Treatment of Men with Osteoporosis
GHAL	Phase 3: Effects of LY333334 in Postmenopausal Women Who Experience Rapid Bone Loss or Multiple Osteoporotic Fractures in Study B3D-MC-GHAC
GHAU	Phase 3: Effects of LY333334 on Bone Mineral Density in Early Menopausal Women
GHAV	Phase 3: Effects of Antiresorptive Drug on Bone Formation in Osteoporotic Postmenopausal Women Treated with LY333334
GHBJ	Phase 3: Extended Follow-up of Patients in LY333334 Trials

## Executive Summary

This briefing document has been developed to support the FDA Advisory Committee Meeting scheduled for 27 July 2001 to evaluate teriparatide injection [recombinant human parathyroid hormone (1-34), rhPTH(1-34)]. Teriparatide is biosynthetic human PTH(1-34) that has been developed for the treatment of osteoporosis. It has the same primary amino acid sequence as the N-terminal portion of the naturally secreted human PTH (an 84-amino-acid peptide), as well as the synthetic teriparatide that has been used in most of the clinical and animal studies of human PTH(1-34) reported in the literature. There are no amino acid substitutions or chemical modifications, and teriparatide differs from synthetic human PTH(1-34) only in its method of production and purification. Furthermore, the biologic activity of teriparatide is identical to synthetic human PTH(1-34) in both in vitro and in vivo assays. Once daily subcutaneous injection of teriparatide stimulates osteoblasts to synthesize new bone on trabecular, endocortical, and periosteal surfaces, and it has been shown to be an effective anabolic, bone formation agent to treat osteoporosis in postmenopausal women and in men. This document summarizes the nonclinical and clinical efficacy and safety data for teriparatide.

### Nonclinical Program

The nonclinical program for teriparatide consisted of acute and chronic studies conducted in rodents, rabbits, and monkeys.

Teriparatide increased bone mass and resistance to fracture (bone strength), and improved skeletal architecture (for example, cortical thickness and trabecular connectivity, number, thickness, and volume) in rats, monkeys, and rabbits. These effects resulted from activation of osteoblasts, which increased apposition of new bone at trabecular, endocortical, and periosteal surfaces, with minimal effect on bone resorption. Increases in trabecular bone mass did not occur at the expense of cortical bone. In short- and long-term studies in species that have cortical remodeling (monkeys and rabbits), teriparatide increased cortical bone thickness and had beneficial effects on cortical bone strength in parallel with an increase in haversian remodeling. In ovariectomized monkeys administered doses of 1 or 5  $\mu\text{g}/\text{kg}/\text{day}$  for 18 months, teriparatide increased bone mineral density (BMD) and resistance to fracture of the proximal femur (hip) and vertebra. Treatment increased bone formation with normal mineralization and improved bone architecture. Increased trabecular connectivity was observed at all trabecular bone sites examined. No abnormal bone was observed.

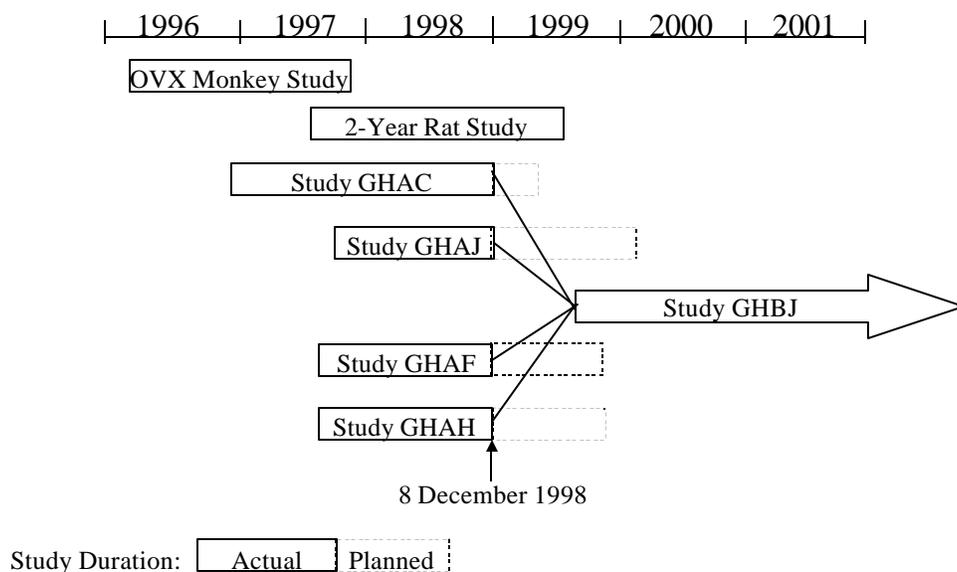
In male and female rats treated with teriparatide, BMD and strength of the vertebra, femoral neck, proximal tibia, and femoral diaphysis were increased dose dependently. Compared with monkeys, rabbits, and humans, rats showed an exaggerated skeletal response to teriparatide. Ovariectomized rats treated with teriparatide 40  $\mu\text{g}/\text{kg}/\text{day}$  for 1 year had a 72% increase in bone mass of the femoral midshaft with significant loss of marrow space and altered shape of femora. The greater response of the rat skeleton to teriparatide is consistent with known differences in bone physiology (compared with

monkeys, rabbits, and humans), such as the nearly continuous growth of the rat skeleton throughout life and the lack of haversian remodeling in cortical bone.

In nonclinical safety evaluations, teriparatide was tested in a wide variety of toxicology studies. These included in vivo and in vitro genotoxicity assays, single-dose toxicity studies, repeated-dose chronic studies in rats and monkeys, a special renal function study in monkeys, reproductive toxicology studies, and a 2-year carcinogenicity study in Fischer 344 rats (2-year rat study). Teriparatide was associated with extremely low acute toxicity and was not genotoxic. The primary effects of teriparatide in repeated-dose studies with rats and monkeys up to 1 year in duration were either directly or indirectly related to the known pharmacologic actions of PTH on bone metabolism and mineral ion regulation. Teriparatide produced no important developmental or reproductive toxicity in rats or mice. However, extensive embryotoxicity occurred in pregnant rabbits, due primarily to this species' exaggerated sensitivity to the effects of teriparatide on blood ionized calcium. Systemic exposure of rats and monkeys to teriparatide at the no-observed-adverse-effect levels (NOAELs) in the chronic studies were approximately five to six times greater than for humans given a dose of 20 µg/day. Overall, the findings of these nonclinical studies supported the clinical development of teriparatide for the treatment of osteoporosis in postmenopausal women and in men.

As illustrated in the following diagram, a 2-year rat study was initiated approximately 8 months after enrollment began in the pivotal Phase 3 study in postmenopausal women with osteoporosis, Study GHAC. In this study, neoplastic bone lesions (osteosarcoma) were observed in rats after near-lifetime treatment with teriparatide. At this time (8 December 1998), the sponsor halted all ongoing clinical studies with teriparatide in order to evaluate the rat findings. After extensive discussions with external experts and the FDA, these findings in rats were considered unlikely to be predictive of an increased risk of skeletal neoplasms in humans treated with teriparatide because of important differences between the rat carcinogenicity model and the intended clinical use of teriparatide in the treatment of osteoporosis.

## Chronological Sequence of Primate, 2-year Rat, and Phase 3 Studies



### Clinical Program

The clinical program for teriparatide consisted of 25 clinical studies (16 Phase 1, 1 Phase 2, and 8 Phase 3) that enrolled over 2800 men and postmenopausal women. The 4 Phase 3 studies of greater than 1-year duration enrolled 2030 postmenopausal women and 437 men.

In the clinical pharmacology program, the pharmacokinetics of teriparatide were characterized in healthy men and women across a broad range of age, in subjects with mild to severe renal insufficiency, in subjects with mild to moderate congestive heart failure, and in patients with low bone mass or osteoporosis. Both traditional (intensive blood sampling) and population (sparse blood sampling) pharmacokinetic studies contributed to the overall clinical pharmacology assessment of teriparatide.

Teriparatide was extensively absorbed from the subcutaneous tissue; the absolute bioavailability averaged 95%. Rapid absorption and elimination characterized the pharmacokinetic profile, and serum concentrations of teriparatide increased linearly over the tested dose range of 20 to 80  $\mu\text{g}$ . Serum concentrations of immunoreactive teriparatide peaked approximately 30 minutes after injection of a 20- $\mu\text{g}$  dose, then declined to nonquantifiable concentrations within 3 hours. Drug accumulation did not occur with daily dosing, and total systemic daily exposure in patients treated with teriparatide for up to 2 years was similar to the exposure in healthy subjects who received single doses of the drug. Although systemic exposure to teriparatide was approximately 20% to 30% lower in men than in women, there were no gender differences with respect to safety, tolerability, or BMD responses. Thus, the same dose may be administered to both men and women.

The Phase 3 clinical program evaluated the efficacy and safety of teriparatide in postmenopausal women and in men. The primary objective of Study GHAC, the pivotal, randomized, double-blind, placebo-controlled clinical study in postmenopausal women with osteoporosis, was to evaluate the effect of teriparatide treatment on the proportion of patients with new vertebral fractures. In this large, multinational study, postmenopausal women with osteoporosis and with a minimum of one moderate or two mild prevalent vertebral fractures were randomly assigned to daily self-administered injections of teriparatide 20 or 40 µg/day, or placebo. All women received supplemental calcium and vitamin D. Incident vertebral fractures were ascertained by central review of paired baseline and endpoint spinal radiographs using a semiquantitative method that scored fracture severity.

The primary objective of Study GHAJ, the pivotal, randomized, double-blind, placebo-controlled, clinical study in men with primary osteoporosis, was to evaluate the effect of treatment with teriparatide 20 or 40 µg/day, or placebo on vertebral BMD.

Along with other efficacy endpoints, such as effects on nonvertebral fracture and biochemical markers of bone formation and resorption (bone metabolism), the clinical program evaluated the overall safety of administering teriparatide once daily. This program established the efficacy and safety of teriparatide in a large population of postmenopausal women and of men with osteoporosis.

Additionally, two smaller studies were initiated to compare teriparatide 40 µg/day with an active control. Study GHAF was designed to compare changes in lumbar spine BMD after treatment with either teriparatide 40 µg plus hormone replacement therapy (HRT) or HRT monotherapy. Study GHAH was designed to compare changes in lumbar spine BMD after treatment with either teriparatide 40 µg/day or alendronate 10 mg/day.

The pivotal study in postmenopausal women (Study GHAC) was originally planned to be of 3 years' duration, with an earlier filing for regulatory approval if the primary vertebral fracture endpoint was achieved by 2 years of treatment. While the Phase 3 studies were in progress (with some patients in the study of postmenopausal women having reached the 2-year time point and some patients in the study of men having reached the 1-year time point) the sponsor informed regulatory agencies and investigators of the observation of osteosarcomas in a 2-year rat study. While it was believed this finding in rats was unlikely to predict a risk for participants in the clinical studies, investigators were instructed to suspend treatment with injectable study medication while this finding was evaluated further. Nine days later, a decision was made to bring the studies to an early conclusion because it became apparent that scientific and logistical issues could not be resolved quickly enough to facilitate the planned objectives of the trials.

An observational, follow-up study, Study GHBJ, was initiated which was open to all patients who had received injectable study material in any one of the Phase 3 studies. This study was designed to collect both safety and efficacy data following discontinuation of teriparatide treatment. As will be discussed in the safety section, no

increased risk of any malignancy has been observed in patients treated with teriparatide, and no occurrence of osteosarcoma has been observed either during treatment or during the follow-up period, an overall period of approximately 39 months.

### **Teriparatide is an Effective Treatment for Osteoporosis in Postmenopausal Women and in Men**

The effectiveness of teriparatide 20 and 40 µg/day was evaluated in Phase 3 studies by assessment of incident vertebral and nonvertebral fractures in postmenopausal women, and of BMD and biochemical markers of bone metabolism in both postmenopausal women and in men with osteoporosis. In the pivotal study of fracture reduction, Study GHAC, postmenopausal women with osteoporosis were treated for up to 2 years. Teriparatide significantly decreased the incidence of vertebral and nonvertebral fractures compared with placebo, and increased BMD in the total body, lumbar spine, and hip. Compared with the placebo group, the 20- and 40-µg groups experienced 65% and 69% reductions, respectively, in the proportion of patients with new vertebral fractures.

Further analyses showed reductions in the risk of two or more new vertebral fractures for the 20- and 40-µg groups (77% and 86%, respectively) compared with placebo. For the 20-µg group, the risk of moderate or severe vertebral fractures was reduced by 90%, and there was also a reduction (78%) in risk for the 40-µg group. Thus, the two doses of teriparatide did not differ significantly with respect to reduction in risk of vertebral fracture.

The incidence of nonvertebral fragility fractures was reduced significantly, and to the same extent, by 20- and 40-µg doses of teriparatide. The two doses of teriparatide caused statistically significant reductions in risk (53% and 54%) of nonvertebral fragility fractures. There was no evidence of an increase in fracture risk at any time during the study.

Teriparatide treatment caused rapid increases in spinal BMD. Statistically significant increases in vertebral BMD were observed after only 3 months of treatment, and at all subsequent visits. In postmenopausal women, treatment with teriparatide 20 or 40 µg/day for up to 2 years produced highly statistically significant, dose-related increases in lumbar spine and total hip BMD. Patients treated with teriparatide 20 and 40 µg/day had increases in lumbar spine BMD of 10% and 14%, respectively, and increases in hip (femoral neck) BMD of 3% and 5%, respectively, at study endpoint. Statistically significant increases in BMD were also observed for other hip subregions and for total body BMC compared with placebo.

Teriparatide treatment of men with osteoporosis for up to 14 months resulted in statistically significant, dose-related increases in lumbar spine BMD of approximately 6% in the 20-µg group, and 9% in the 40-µg group. For the femoral neck, significant BMD gains of approximately 2% and 3% were observed in the 20- and 40-µg groups, respectively. Similar changes were observed for the total hip and other subregions, although these did not consistently achieve statistical significance.

The significant increases in BMD for postmenopausal women and for men produced by teriparatide 20 µg/day were less than those from the 40-µg/day dose. For the clinical outcome, that is, the reduction in risk of vertebral and nonvertebral fractures, the two doses were neither statistically nor clinically different. Because dose selection should be based on outcomes (fractures) rather than surrogates (BMD), 20 µg is the more appropriate dose.

In the supportive Study GHAF, teriparatide 40 µg/day plus HRT increased BMD more than HRT alone, regardless of previous use of HRT in women with postmenopausal osteoporosis. In a second supportive study (Study GHAF), postmenopausal women with osteoporosis or osteopenia who received treatment with teriparatide 40 µg/day had significantly greater increases in lumbar spine and hip BMD compared with women who received alendronate 10 mg/day.

Administration of teriparatide 20 or 40 µg/day to men and postmenopausal women with osteoporosis rapidly stimulated bone formation as shown by early increases in the markers of bone formation, bone-specific alkaline phosphatase (BSAP), and propeptide of type I procollagen (PICP). Concentrations of both markers had increased in the 20-µg group by 1 month of treatment and the concentration of BSAP continued to rise more slowly from Months 6 through 12. Maximum increases of BSAP achieved were 45% above baseline in women. Peak concentrations of PICP were observed at 1 month of treatment, followed by a decline to near baseline values by 12 months.

Dose-proportional increases in BSAP and PICP occurred in the 40-µg group. The increases in formation markers were accompanied by secondary increases in the markers of bone resorption, urinary N-telopeptide (NTX), and deoxypyridinoline (DPD), consistent with the physiological coupling of bone formation and resorption in skeletal remodeling.

### **Treatment With Teriparatide Provides Durable Reductions in Fracture Risk**

The effects of teriparatide treatment withdrawal were evaluated in the observational follow-up study, Study GHBJ. The results of that study to date demonstrate that patients continued to benefit from prior treatment with teriparatide for 18 months beyond the last visit of the previous Phase 3 study. In the 18 months after treatment ended, there continued to be a reduction in the risk of new fractures in women previously assigned to treatment with teriparatide versus women previously assigned to placebo. Specifically, there were 40% and 45% reductions in the proportion of women with a minimum of one new vertebral fracture for women previously assigned to the 20- and 40-µg groups, respectively, compared with women previously assigned to placebo. During this follow-up study, there was also a reduction in the incidence of moderate or severe vertebral fractures in women previously treated with teriparatide compared with those previously assigned to placebo.

Radiographic assessment was not performed at the endpoint of Study GHAJ in men; however, comparison of baseline radiographs in Study GHAJ with radiographs in

follow-up study GHBJ permitted assessment of fracture incidence from Study GHAIJ baseline through the observational follow-up period (approximately 30 months). Twenty-two men had one or more new vertebral fractures during this period. In these men, there was a statistically nonsignificant reduction in risk (52% and 48%) in the 20- and 40- $\mu$ g groups compared with placebo. However, the magnitude of risk reduction in new vertebral fractures in the men treated with teriparatide for up to 14 months plus 18 months follow-up was similar to the reduction observed in postmenopausal women treated with teriparatide for up to 2 years plus 18 months follow-up. The study in men was powered to detect statistically significant change in BMD, not vertebral fracture. Therefore, it is likely that insufficient statistical power prevented the observed reductions in new vertebral fractures in men from reaching statistical significance.

### **Teriparatide is Safe and Well Tolerated for the Treatment of Osteoporosis**

On a molar basis, peak concentrations of teriparatide measured in long-term, clinical studies briefly (minutes) exceeded the upper limit of normal for endogenous PTH by 4- to 5-fold. However, the rapid disappearance of the peptide from serum, and subsequent slight suppression of endogenous PTH for a few hours, resulted in a 24-hour total PTH (teriparatide plus endogenous PTH) exposure that was less than the 24-hour exposure of a subject who maintains endogenous PTH concentrations at the upper limit of normal (65 pg/mL [7.0 pM]).

Treatment with teriparatide 20 and 40  $\mu$ g was well tolerated. There were no serious adverse effects or increase in mortality. The adverse effects that appeared to be related to teriparatide administration were leg cramps, headache, and nausea. Leg cramps were infrequent (2% to 3%) and mild. Headache was not more frequent in the 20- $\mu$ g group compared with placebo, but it was consistently associated with administration of higher doses in short-term and long-term studies. Nausea was also consistently associated with high doses of teriparatide in short-term and long-term studies. The incidence of nausea in the 20- $\mu$ g group was slightly, but not significantly, higher than in the placebo group. All of the adverse events in the Phase 3 studies were relatively mild, and only nausea caused more frequent discontinuation in the 40- $\mu$ g group compared with placebo. The discontinuation rate due to nausea in the 20- $\mu$ g group was not statistically different from placebo.

There was a significant reduction in the reporting of back pain as an adverse event in patients treated with teriparatide, suggesting a clinical benefit related to the reduction in occurrence of new vertebral fractures. Following withdrawal of treatment, there was no longer a difference among treatment groups in the incidence of nausea, headache, or leg cramps. However, the significant reductions in new and worsened back pain persisted following withdrawal of treatment and throughout the 18-month, follow-up period.

In the Phase 3 studies, there was no indication of orthostatic hypotension, but in clinical pharmacology studies, several subjects experienced dizziness upon standing following a 20- $\mu$ g dose, and one of them manifested orthostatic hypotension. In clinical

pharmacology studies, teriparatide at doses in excess of 20 µg was associated with modest and transient hemodynamic effects in the standing position manifested by a slight lowering of diastolic blood pressure and increase in heart rate. Orthostatic hypotension was not a clinically significant finding in the Phase 3 studies.

Laboratory evaluation of teriparatide demonstrated the known effects of PTH on serum and urine calcium, which were mild and not associated with any clinically significant adverse outcomes. The serum calcium concentration increased transiently in patients treated with teriparatide, but typically remained within the normal range. The increase began approximately 2 hours after dosing and reached a peak concentration between 4 to 6 hours after dosing. The serum calcium concentration began to decline approximately 6 hours after dosing and returned to baseline by 16 to 24 hours after each dose. Similarly, increases in urinary calcium excretion were small and were not associated with urolithiasis or other adverse clinical outcomes. The increase in urinary calcium excretion lasted only a few months, returning to near the placebo values within 12 months following initiation of treatment in postmenopausal women and within 6 months in men. Treatment with teriparatide produced small increases in serum uric acid that were asymptomatic and rarely resulted in hyperuricemia, the incidence of which was not different from placebo.

Evaluations of bone biopsies from women with osteoporosis treated with teriparatide for up to 2 years identified no safety concerns and indicated that teriparatide-treated women had increased trabecular bone volume, wall width, mean orthogonal intercept length, and mineral apposition rate.

#### **Treatment of Patients With Teriparatide Was Not Associated With Osteosarcoma or Cardiovascular-Related Events**

There was no increase in the incidence of malignancy in patients treated with teriparatide, compared with placebo, either at the end of active treatment or during the 18 months of follow-up in the observational study, nor was there any evidence for increased mortality due to malignancy. Specifically, neither osteosarcoma nor any primary bone tumors have been reported in any patient.

Once daily administration of teriparatide was not associated with any significant changes in blood pressure or pulse in the Phase 3 studies. Furthermore, teriparatide did not prolong QTc, even when administered in the clinical pharmacology studies at four times the therapeutic dose (80 µg). Examination of treatment-emergent adverse events in the Phase 3 studies did not reveal an association of teriparatide treatment with atherosclerotic cardiovascular disease or any of its manifestations.

**In Conclusion**

The benefits of teriparatide on the skeleton have been demonstrated by large-scale, clinical studies conducted in postmenopausal women and in men. In postmenopausal women, teriparatide significantly reduced the risk of vertebral fractures and nonvertebral fractures. Teriparatide effectively increased lumbar spine BMD, femoral neck BMD, and total body BMC in postmenopausal women and in men.

Risks associated with teriparatide were few. Leg cramps, nausea, and headaches were side effects associated with teriparatide therapy. While symptomatic orthostatic hypotension was observed in 1 patient receiving teriparatide 20 µg in the clinical pharmacology studies, this was not a significant finding in the Phase 3 studies.

The optimally effective dose of teriparatide for treatment of osteoporosis in postmenopausal women and in men is 20 µg once daily, because there is no clinical difference between the doses in terms of fracture efficacy and the 20-µg dose is better tolerated than the 40-µg dose. The proposed trade name for teriparatide injection 20 µg is Fortéo™.

The aggregate health benefits of teriparatide are therefore substantial and the risks minimal. The achievement of this strong vertebral and nonvertebral fracture efficacy within a relatively short treatment period represents a major advantage to the patient for this new approach to osteoporosis treatment.

# 1. Introduction

This briefing document has been developed to support the FDA Advisory Committee Meeting scheduled for 27 July 2001 to evaluate teriparatide injection [recombinant human parathyroid hormone (1-34), rhPTH(1-34)]. Teriparatide is biosynthetic human PTH(1-34) that has been developed for the treatment of osteoporosis. It has the same primary amino acid sequence as the N-terminal portion of the naturally secreted human PTH, as well as the synthetic teriparatide that has been used in most of the clinical and animal studies of human PTH(1-34) reported in the literature. There are no amino acid substitutions or chemical modifications, and teriparatide differs from synthetic human PTH(1-34) only in its method of production and purification. Furthermore, the biologic activity of teriparatide is identical to synthetic human PTH(1-34) in both in vitro and in vivo assays.

This section of the briefing document provides overviews of the following:

- osteoporosis and the significance of osteoporotic fractures in women and men
- the medical need for alternatives to existing osteoporosis treatments
- the biological and medical effects of PTH
- the regulatory history of the development of teriparatide
- the pen-injector device developed for subcutaneous self-administration of teriparatide.

## 1.1. Osteoporosis

Osteoporosis has been defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration with a consequent increase in bone fragility and susceptibility to fracture (Consensus Development Conference 1993). It is a major health issue in countries with an increasing proportion of elderly people and currently afflicts approximately 150 million people worldwide, including one third of all postmenopausal women. In the United States alone, osteoporosis accounts for 1.5 million fractures, more than 400,000 hospitalizations, 44 million patient-days of nursing home care, and nearly \$14 billion in health care spending each year (Ray et al. 1997).

Although the cost of treatment varies by fracture site, any osteoporosis-related fracture is painful and has a significant negative impact on the affected individual. An estimate of days of limited activity per year due to back pain in women with new vertebral fractures is similar to the estimated increase in annual days of limited activity for patients with diabetes, ischemic heart disease, arthritis, and rheumatism (*Nevitt et al. 1998* [references in italics are included in Volume 2]). Furthermore, there is increasing evidence that vertebral fractures are associated with an increased risk of subsequent mortality (Kado et

al. 1999; Ensrud et al. 2000; Melton 2000). The detection of prior vertebral fractures is both an important disease diagnostic criterion and a primary determinant of the expected rate of subsequent osteoporotic fractures (*Ross et al. 1991*). A prior vertebral fracture is a more powerful predictor of new vertebral fractures than BMD, and increases the risk of a subsequent fracture by at least 4-fold.

Osteoporosis is considered to be more prevalent in women than in men because the diminution of endogenous estrogens at menopause triggers a period of accelerated bone loss (Christiansen 1994). This is characterized by osteoclastic bone resorption activity that is greater than osteoblastic bone formation activity. This increased resorption results in greater structural damage than that resulting from reduced osteoblastic formation during the age-related slow phase of bone loss. Excessive osteoclastic activity may lead to perforation and loss of entire trabeculae in cancellous bone, so that the subsequent formation phase is eliminated (Riggs and Melton 1992). Overall, the typical untreated woman loses about 20% to 30% of her bone during the postmenopausal period and has a 40% to 50% lifetime risk of suffering an osteoporotic fracture.

Bone loss that occurs with aging is an important feature of osteoporosis in men and women. In some men, age-related bone loss alone may cause osteoporotic fractures. The universal decline in bone mass that happens with aging has the potential for eventually producing clinical osteoporosis in all individuals, and some idiopathic osteoporosis may represent this age-related process or its premature onset.

In men, vertebral osteoporosis and fractures have received increased attention since it was recognized that the prevalence of vertebral deformities is higher than once thought and, in some countries, exceeds the prevalence in women (O'Neill et al. 1996). Hypogonadism is an important cause of osteoporosis in men, but corticosteroid use, gastrectomy, alcoholism, and neurologic disease are other risk factors (Cummings et al. 1985). Osteoporosis in men is termed idiopathic if no known cause can be identified on clinical and laboratory grounds. Men with idiopathic osteoporosis may have low bone turnover; thus, an anabolic treatment could be a rational treatment for these men (Orwoll and Klein 1995; *Kurland et al. 2000*). Men with symptomatic osteoporosis present in middle age have a low BMD regardless of the etiology of their condition and sustain multiple vertebral fractures (*Evans and Davie 2000*). As in women, decreased bone density in men is associated with an increased risk of fracture (Fatayerji et al. 1999). Hip BMD is more strongly associated with risk of vertebral fracture in men than spine BMD (Legrand et al. 1999), but the lumbar spine T-score associated with 50% prevalence of vertebral fracture is similar in men and women (Selby et al. 2000).

### **1.1.1. Medical Need for a Bone Formation Agent**

Despite availability of approved antiresorptive therapies, there is significant unmet medical need for treatments that safely reduce the incidence of osteoporotic vertebral and nonvertebral fractures and the associated pain and deformity.

The currently marketed therapies for treatment of osteoporosis include bisphosphonates, calcitonin, and raloxifene hydrochloride (HCl), a selective estrogen receptor modulator (SERM). These antiresorptives have demonstrated antifracture efficacy in adequately controlled clinical studies. Women with postmenopausal osteoporosis who had vertebral deformities present at baseline were enrolled in the teriparatide fracture prevention study (Study GHAC). Studies of antiresorptive treatments in patients similar to those enrolled in the sponsor's fracture prevention study have demonstrated the following fracture efficacy: alendronate 10 mg/day alone, or preceded by 2 years of 5 mg/day or 20 mg/day, produced 48%, 47%, or 44% reductions in the risk of a new vertebral fracture (Lieberman et al. 1995; *Black et al. 1996*); risedronate 5 mg/day reduced fracture risk by 41% (*Harris et al. 1999*); and raloxifene HCl 60 mg/day reduced risk by 30% (*Ettinger et al. 1999*).

Comparable data are not available for estrogen therapy, because estimates of fracture risk reduction for this treatment are based on cohort observations and case-control surveys, or very small prospective trials (Lindsay et al. 1980; Lufkin et al. 1992).

There are populations of patients at risk for fracture for whom current treatments appear to provide little benefit, or who cannot tolerate the therapy. Antiresorptive agents, while effective, have limitations in their tolerability. For example, frequent gastroesophageal reflux occurs in more than 20% of all women over age 65 (Locke et al. 1997), and bisphosphonate therapy would be problematic for those so affected. Erratic bleeding may make HRT unacceptable. Both HRT and raloxifene are contraindicated in women with a history of deep venous thrombosis (DVT), and each increases the risk of DVT. A treatment without these contraindications and treatment-limiting side effects would be an important alternative to current therapies.

Current treatments for osteoporosis in men are more limited than the treatment options available for women. Some treatments (for example, estrogen) cannot be used in men. While bisphosphonates have recently been shown to be effective in men, anabolic or bone formation agents have been suggested as an ideal approach for men with idiopathic osteoporosis (*Kurland et al. 2000*). Because low bone turnover is common in men with osteoporosis, a bone formation agent may be especially valuable as an alternative to antiresorptive agents that reduce low bone turnover in men even further.

Antiresorptives are limited in their ability to prevent vertebral fractures and their associated clinical manifestations such as height loss and back pain. Additionally, they have limited efficacy in reducing the risk of nonvertebral fractures. Many patients (men and women alike) cannot take current treatments due to contraindications or, because antiresorptives may take up to 3 years to significantly reduce nonvertebral fracture risk, do not tolerate them long enough to gain the important clinical benefits.

Thus, a bone formation agent with the potential for substantial reductions in vertebral and nonvertebral fracture risk would further enhance the ability of physicians to effectively treat patients with osteoporosis.

## 1.2. PTH and Teriparatide

### 1.2.1. Physiologic Effects

The physiological role of PTH is to control calcium homeostasis by regulating calcium reabsorption by the kidney and osteoclastic resorption in the bone, and indirectly, by regulating calcium uptake from the intestines via 1,25-dihydroxyvitamin D. The PTH secreted by the human parathyroid glands is 84 amino acids in length (referred to as PTH throughout the remainder of the document), but both PTH and PTH(1-34), the N-terminal 34 amino acid portion of the molecule, have similar affinities for the PTH/PTHrP receptor. The sponsor has developed teriparatide, recombinant human PTH(1-34) [rhPTH(1-34)] as a therapeutic anabolic agent for osteoporosis treatment. The amino acid sequence of teriparatide is identical to human PTH(1-34).

### 1.2.2. Bone Formation Effects

Parathyroid hormone is the only known skeletal agent that can stimulate de novo normal bone formation to increase bone mass without impairing its quality, and improve bone architecture (*Dempster et al. 1993, 1995; Cosman and Lindsay 1998; Marcus 2000*). Previous studies of teriparatide treatment have demonstrated that its powerful anabolic effect on bone is reflected by large increases in lumbar spine BMD (*Cosman and Lindsay 1998*). These increases in BMD have ranged from 13% in a 3-year study in women with osteoporosis treated with concomitant estrogen (*Lindsay et al. 1997*) to 10.2% over 2 years in women with osteoporosis treated with a 3-month cyclical teriparatide regimen (*Hodsman et al. 1997*). Lumbar spine BMD increased by 11% after 12 months of daily teriparatide and HRT in women with corticosteroid-induced osteoporosis (*Lane et al. 1998*).

Although other possible anabolic agents such as fluoride, growth hormone, growth hormone-releasing factor, growth factors, prostaglandins, vitamin D analogs, androgens, and progestins have been examined, none has induced a reproducible, safe, and significant increase in bone mass in vivo (*Riggs and Melton 1992*). Fluoride is approved in some parts of the world for the treatment of osteoporosis, but its long-term safety, efficacy, and appropriate dosage remain to be established. In animals and in some human studies, fluoride actually increases the frequency of fractures and has detrimental effects on bone quality (*Riggs et al. 1990; Sogaard et al. 1994*). Unlike fluoride, PTH increases resistance to fracture and does not alter bone quality in experimental animal models (*Marcus 2000*).

Studies in humans, monkeys, and rats have shown that exogenous PTH(1-34), given once daily by subcutaneous injection, stimulates new bone formation to increase bone mass, bone architecture, and resistance to fracture (*Cosman and Lindsay 1998; Dempster et al. 1993; Jerome et al. 1999, 2001; Sato et al. 2000*). Bone quality is normal, and while transient increases in serum and urine calcium have been observed at high doses, no significant safety concerns have been reported in the literature. The results of these

nonclinical and clinical studies suggest that teriparatide is a promising bone anabolic agent for increasing bone mass and reducing fracture risk in individuals with osteoporosis.

### **1.2.3. Pathophysiological Effects**

Excessive and incompletely regulated secretion of PTH from the parathyroid glands produces the clinical condition recognized as primary hyperparathyroidism (HPT). A brief review of this chronic condition is included to provide a perspective on the results of the sponsor's studies.

The only manifestation of the mildest asymptomatic form of primary HPT may be an abnormal sustained increase in serum calcium (*Heath et al. 1980*). Other patients may have recurring urolithiasis or renal colic. Patients with severe HPT suffer marked hypercalcemia and exhibit symptoms classically associated with the disease, which include polydipsia, polyuria, abdominal pain, weakness, fatigue, weight loss, vomiting, neurologic abnormalities, debility, and bone pain. A low serum phosphorus, hypercalcemia, and an abnormally high plasma PTH concentration are the typical laboratory manifestations of HPT. Osteitis fibrosa cystica, the resorptive bone disease associated with severe HPT, can cause bone pain or pathologic fracture. Notably, patients who undergo surgical treatment (parathyroidectomy) typically have chronic symptomatic disease and/or severe hypercalcemia.

Reports of increased mortality from cardiovascular disease and malignancy in primary HPT have been based mostly on patients who have undergone parathyroidectomy. These represent patients with relatively severe HPT or other reasons to undergo surgical treatment, who might be expected to have worse survival or associated cancers. In population-based studies, hypertension (*Jorde et al. 2000*) and severe hypercalcemia (*Wermers et al. 1998*) have been implicated as risk factors associated with cardiovascular disease in patients with HPT, but overall survival is not adversely affected.

The clinical literature demonstrates that HPT is not associated with an increased risk of osteosarcoma. While there are differences in PTH exposure between chronic HPT and the intended clinical use of teriparatide, the degree of osteoblast stimulation (based on serum alkaline phosphatase concentrations) in HPT is often greater than that observed in patients treated with teriparatide in the Phase 3 trials. There is a single case report of the co-occurrence of hyperparathyroidism and osteosarcoma (*Smith et al. 1997*). A search of the national Swedish cancer registry from 1959 to 1998, comprising 114,000 patient-years of observation of women and men with parathyroid adenomas, revealed no cases where the two diagnoses (osteosarcoma and parathyroid adenoma) occurred in the same patient (*Johnell 2001*, personal communication). In this cancer registry, the incidence of osteosarcoma was 10 cases per million registrants. Additional data on patients with parathyroid hyperplasia comprised 40,000 patient-years of observation, and again, in this cohort there were no cases of osteosarcoma identified.

### 1.3. Regulatory History and Agreements

The clinical development plan for teriparatide was formulated following input from several external consultants and consultation with the FDA Division of Metabolic and Endocrine Drug Products. Key points of the FDA draft guidelines on “Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis” published in April 1994 (US FDA) were taken into consideration while designing the clinical studies.

Between 15 October 1996 and September 1998, the FDA provided advice in meetings and written communications on development issues that included: 1) the primary endpoint in a single well-controlled clinical study of sufficient size to support an indication for the treatment of osteoporosis in postmenopausal women, 2) the statistical approach to use in the 2-year interim analysis of the Phase 3 study, and 3) protocol design for a Phase 3 study in males.

On 7 December 1998, the sponsor submitted an investigational new drug (IND) safety report to the FDA reporting unexpected findings of osteosarcoma in a 2-year rat carcinogenicity study. The following day, the sponsor participated in a teleconference with the FDA to discuss these nonclinical findings and announce the sponsor’s decision to temporarily suspend treatment of patients in the ongoing clinical studies with teriparatide while the finding was evaluated further.

On 18 December 1998, the sponsor had a teleconference with the FDA to inform them of the decision to bring to early closure all the clinical studies with teriparatide because it became apparent that scientific and logistical issues could not be resolved within a time frame consistent with the planned objectives of the trials. The sponsor also presented findings of the data monitoring board on safety from the 1-year data from the Phase 3 study GHAC. The sponsor instructed the study investigators to have all patients complete the Early Discontinuation Visit, which included x-ray film evaluations. Patients were encouraged to continue the calcium and vitamin D supplements, even though injectable study drug was discontinued. The median duration of treatment with study drug for all patients randomly assigned to a treatment group was 19 months. At the time of study closeout, the median duration of observation in Study GHAC was 21 months, because of the time elapsed between discontinuation of study drug and the close-out visit.

On 14 April 1999, the sponsor submitted to the FDA the recommendations of an external oncology advisory board. This board, chaired by Dr. Bruce Chabner (Chief Hematology/Oncology, Massachusetts General Hospital), was convened by the sponsor in February 1999 to assist in the evaluation of the nonclinical osteosarcoma findings and to gain agreement on the appropriate follow-up of patients previously enrolled in long-term studies with teriparatide. The external consultants on the board included experts in the fields of oncology, epidemiology, toxicology, bone pathology, and

endocrinology. Their input was used in the development of a follow-up study, Study GHBJ.

On 5 May 1999, the sponsor submitted Protocol GHBJ to the FDA. This multinational, observational follow-up study was designed by the sponsor to continue to collect safety information in all patients previously enrolled in Phase 3 studies of teriparatide.

On 9 July 1999, the sponsor, the FDA, and external experts from the sponsor's oncology advisory board participated in a meeting held at the FDA's request. The purpose of the meeting was to provide an update on teriparatide development to the FDA, and to discuss the nonclinical findings.

On 21 September 1999, the sponsor and the FDA met to discuss preliminary safety and efficacy results of the pivotal Phase 3 study (GHAC) and a proposal for new drug application (NDA) contents. Agreement was obtained from the FDA that an NDA package consisting of clinical pharmacology studies, completed Phase 3 clinical studies including Study GHAC, and the first visit of Study GHBJ appeared adequate to support submission of teriparatide as a new agent for the treatment of postmenopausal osteoporosis in women. Subsequent discussions between the sponsor and the FDA concerned additional nonclinical studies in rats and primates, and the timelines for providing interim data from these studies to the FDA.

On 12 July 2000, the sponsor and the FDA held a pre-NDA meeting. Agreement was obtained from the FDA that the NDA package consisting of the clinical studies, clinical pharmacology studies, and nonclinical studies appeared adequate to support submission of teriparatide as a new agent for the treatment of postmenopausal osteoporosis in women. The agency also indicated that the data from Study GHAJ seemed adequate to seek an indication for the treatment of osteoporosis in men.

On 29 November 2000, the NDA was submitted. The primary conclusions concerning the safety and efficacy of teriparatide (FORTÉO) were based on the data from 1637 postmenopausal women with osteoporosis in Study GHAC utilizing vertebral fracture rates, nonvertebral fracture rates, and lumbar spine and femoral neck BMD as efficacy endpoints. Study GHAJ provided BMD data for 437 males with osteoporosis. Supportive information from two Phase 3 clinical studies (Studies GHAH and GHAF) and data from the first 6 months of observational follow-up study GHBJ, were also provided.

On 29 March 2001, the 4-month safety update was submitted. This update included an additional 12 months of withdrawal data from Study GHBJ, and included data on the incidence of vertebral fractures in men treated with teriparatide.

The proposed label indication is:

FORTÉO is indicated for the treatment of osteoporosis in postmenopausal women and in men.

#### 1.4. Injection Delivery System

The pen-injector is a delivery device that facilitates the subcutaneous delivery of teriparatide for its users. It is based on the design of the Humulin® pen-injector, which was utilized in the pivotal teriparatide Phase 3 study (Study GHAC). A 28-day supply of teriparatide is provided in a prefilled glass cartridge in a disposable pen device. The teriparatide pen-injector is designed to deliver a fixed, 20- $\mu$ g dose with each injection. Patients will be trained in their physician's office to self-administer the daily injection. A user manual is supplied for further reference. Teriparatide should be administered as a subcutaneous injection into the thigh or abdominal wall. The recommended dosage is 20  $\mu$ g once daily.

The pen-injector is shown in the picture below.



The pen-injector has been thoroughly tested in accordance with the International Standard for Pen-Injectors for Medical Use, and has passed tests for dose accuracy under a wide range of conditions of temperature and handling. Two user studies have been conducted with teriparatide pen-injectors containing saline-filled cartridges. Training for self administration, dose setting and injection, and appropriate pen-injector handling were easily mastered by the 156 participants in the user studies. The stability and sterility of teriparatide stored in cartridges under the recommended refrigerated conditions has been verified.

## 2. Nonclinical Pharmacology and Absorption, Distribution, Metabolism, and Excretion

The skeletal effects of teriparatide in studies with monkeys, rabbits, and rats are presented in this section, as well as a summary of the studies characterizing the absorption, distribution, metabolism, and excretion (ADME) of teriparatide in animals. The primary findings are summarized in the following bullets.

### Nonclinical Pharmacology and Proposed Mechanism of Action

- At the cellular level, teriparatide increases the number of osteoblasts active in synthesizing new bone matrix; however, the specific molecular mechanisms mediating the anabolic action of teriparatide on bone have not been fully elucidated.
- In both in vivo and in vitro model systems, recombinant teriparatide, synthetic teriparatide, or PTH induced essentially identical biological responses via the PTH/PTHrP receptor.
- The anabolic response of bone to teriparatide is dependent on a daily pulsatile exposure. The length of time each day that serum concentrations of teriparatide are above baseline levels of endogenous PTH is a primary factor in determining whether the bone response is anabolic or catabolic.
- In all species studied, teriparatide stimulated apposition of lamellar bone onto trabecular, endosteal, and periosteal surfaces, resulting in increased bone mass, trabecular number, connectivity, and resistance to fracture.
- Increased trabecular bone mass resulting from teriparatide treatment did not occur at the expense of cortical bone mass in any species studied.
- In monkeys, increased BMD and biomechanical strength achieved during teriparatide treatment were largely retained 6 months after treatment was discontinued.
- Rats treated with teriparatide showed exaggerated increases in both trabecular and cortical bone formation, strength, and architecture, compared with monkeys, rabbits, and humans. This skeletal response in rats was attributable to species differences in bone remodeling.
- Cortical bone quality was maintained throughout treatment in monkeys and rabbits. In both species, teriparatide induced an increase in bone turnover, resulting in increased porosity. However, biomechanical strength was not significantly affected in either species because the porosity was preferentially localized to the endocortical surface.
- No bone anomalies (such as neoplasia, woven bone, or fibrosis) attributable to teriparatide were observed in monkeys treated for up to 18 months at an exposure

level that was approximately eight times greater than that for women given 20 µg/day.

### **Absorption, Distribution, Metabolism, and Excretion**

- In monkeys and rats, teriparatide was rapidly absorbed and eliminated following subcutaneous injection, with time to reach peak serum concentration ( $T_{max}$ ) generally occurring 15 to 30 minutes after dose administration, and a half life ( $T_{1/2}$ ) of elimination of 15 to 30 minutes.
- In monkeys and rats, area under the curve (AUC) and peak concentration ( $C_{max}$ ) of teriparatide increased with increasing dose in an approximately dose-linear fashion following subcutaneous injection. Teriparatide did not accumulate following repeated dosing.
- Teriparatide did not induce liver-metabolizing enzymes in monkeys or rats.
- Previous publications showed that the liver, kidney, and bone are the primary sites of metabolism and clearance of PTH. The ultimate metabolic fate of teriparatide and PTH is considered to be catabolism into its constituent amino acids.

### **2.1. Proposed Mechanism of Action**

At the cellular level, PTH increases the number of osteoblasts active in synthesizing new bone matrix and alters gene expression in bones *in vivo*. However, the specific molecular mechanisms mediating the anabolic action of PTH on bone have not been fully elucidated. Some of the factors involved in the actions of PTH are as follows:

- PTH binds to the PTH/PTHrP receptor leading to rapid (within minutes) activation of at least two different intracellular signal transduction pathways: stimulation of adenylyl cyclase and phospholipase C activities.
- Within 1 hour after PTH administration, changes in gene expression occur (increases in *c-fos*, *c-jun*, *c-myc*, and interleukin-6 mRNA and a decrease in histone H4 mRNA) which are consistent with a down-regulation of cell proliferation (Lee et al. 1994; Liang et al. 1999; Onyia et al. 1995).
- Intermittent PTH treatment for 2 to 5 days up-regulates a number of extracellular matrix and matrix-modifying proteins (McClelland et al. 1998), consistent with an enhancement of osteoblast differentiation.
- Reported effects of PTH on apoptosis are varied, with inhibition occurring in mice (Jilka et al. 1999) and stimulation in rats (Hock 1999).
- *In vivo* animal studies have shown that several mediators postulated to be responsible for the skeletal effects of PTH (prostaglandins, calcitriol, endogenous PTH, growth hormone, insulin-like growth factor) most likely do not play a primary role in initiating the anabolic response of bone.

Teriparatide and PTH induced essentially identical biological responses in both in vivo and in vitro test systems. While there may be some quantitative differences between the two peptides, these differences have been difficult to quantify in vitro and in vivo due to potency and species specificity issues.

- Teriparatide and PTH have similar binding affinities for the PTH/PTHrP receptor (Pliam et al. 1982), although there is some evidence that PTH may also bind to a receptor, with an unknown biological function, that recognizes the carboxy-terminal portion of the protein (Divieti et al. 2001; Inomata et al. 1995).
- Studies in rats suggest that teriparatide and PTH have equivalent effects on bone (Ejersted et al. 1993; Mosekilde et al. 1991) and activate the same signaling pathways in osteoblasts (Lowik et al. 1985).
- Teriparatide and PTH have qualitatively similar effects on renal and cardiovascular physiology (Horiuchi et al. 1983; Saglikes et al. 1985).

## 2.2. Nonclinical Pharmacology

The pharmacological effects of teriparatide were evaluated in studies with monkeys, rabbits, rats, and mice. Daily doses (0.03 to 80 µg/kg/day) of teriparatide were administered subcutaneously for up to 12 months in rats. Adult, feral, ovariectomized cynomolgus monkeys were administered a once daily subcutaneous injection of teriparatide at a dose of 1 or 5 µg/kg for 18 months or for 12 months, followed by 6 months of withdrawal.

### 2.2.1. Pharmacodynamic Effects on Bone

Studies to investigate the skeletal efficacy of teriparatide (synthetic or recombinant) were conducted in rats, a species devoid of haversian remodeling, and in monkeys and rabbits which, like humans, have osteonal remodeling of the skeleton. Because recombinant and synthetic teriparatide consistently induce equivalent biological effects in in vivo and in vitro test systems, results obtained with synthetic teriparatide are directly comparable to those generated using recombinant teriparatide.

#### Monkeys

Adult, feral, ovariectomized cynomolgus monkeys (20 monkeys/group) were administered daily subcutaneous injections of 0, 1, or 5 µg/kg teriparatide for 18 months or for 12 months followed by 6 months of withdrawal. Systemic exposure (AUC) at 5 µg/kg was approximately eight times greater than that for women given 20 µg/day and was not associated with any adverse effects. Teriparatide was well tolerated with no sustained hypercalcemia. Teriparatide stimulated formation of new bone on trabecular and endosteal surfaces in the vertebrae, femoral neck, proximal tibia, and iliac crest, resulting in increased trabecular bone volume and cortical width. No bone anomalies (such as neoplasia, woven bone, or fibrosis) attributable to teriparatide were observed at

any time point. Bone strength was increased dose dependently by 41% and 23% in the spine and femoral neck, respectively. Increased bone mass and resistance to fracture achieved during the 12-month treatment period were largely retained 6 months after teriparatide treatment was discontinued. Teriparatide stimulated intracortical remodeling, as well as intratrabecular remodeling of thickened trabeculae, resulting in increased trabecular number, and stronger lumbar vertebrae and proximal femur.

Longitudinal analysis of the midshaft radius showed no significant effect of treatment on cortical bone mass; therefore, the increase in trabecular bone did not occur at the expense of cortical bone. Teriparatide treatment had no deleterious effect on the material properties of cortical bone in the femoral midshaft. The increase in transient remodeling space observed in the cortex, associated with a dose-dependent increase in activation frequency, was manifested as increased porosity. However, the observed porosity had no effect on bone strength because compensatory changes in geometry of the cortex resulted from increased endocortical apposition, which produced a thicker cortex, and preferential localization of the porosity to the endocortical region (*Burr et al. 2001*). Because this region of bone bears less mechanical stress during bending than the periosteal region, resistance to fracture was increased, despite the observed increase in porosity. Teriparatide administration clearly increased trabecular bone mass, improved skeletal architecture, and strengthened the axial and appendicular skeleton in this nonhuman primate model. In addition, the improved bone quality was maintained for at least 6 months after treatment was discontinued, which corresponds to about two bone remodeling periods. This is equivalent to 1 to 1.5 human years, as the bone remodeling period in humans is about 7 months.

### **Rabbits**

The effects of teriparatide on cortical bone properties were further evaluated in ovary-intact New Zealand rabbits, a species that is characterized by osteonal remodeling (*Hirano et al. 1999; 2000*). Treatment with 10 or 40 µg/kg/day teriparatide for 35, 70, or 140 days (0.5 to two bone remodeling periods) stimulated endocortical and periosteal apposition, resulting in increased cross-sectional area, bone mass, femoral strength, and increased osteonal remodeling resulting in cortical porosity. However, compensatory changes in cortical bone geometry similar to those seen in monkeys were observed, including preferential localization of porosities to the endocortical surface, increased cross-sectional area (periosteal apposition), and greater resistance to fracture for the femoral midshaft. At no time point was cortical bone strength decreased by teriparatide treatment.

In both remodeling species (monkeys and rabbits), cortical bone quality was increased or maintained during teriparatide treatment, and there was no reduction in cortical bone mass.

## Rats

Studies in rats utilized intact or ovariectomized females and intact males that ranged in age from 1 to 23 months at initiation of treatment and were up to 17 months postovariectomy. In male and ovariectomized female Fischer 344 rats (approximately 6 months old), subcutaneous administration of 8 or 40  $\mu\text{g}/\text{kg}/\text{day}$  teriparatide for 1 year increased bone mass by up to 154% in the proximal tibia and 72% in the femoral midshaft. Biomechanical analyses showed that strength was increased by up to 144% in the lumbar vertebrae, 76% in the proximal femur, and 124% in the femoral midshaft. These data indicate that the magnitude of the skeletal effects in rats was markedly greater than those observed in monkeys and rabbits. However, rats are much less sensitive to the effects of PTH on serum ionized calcium than are monkeys and rabbits, which allowed higher doses to be administered to rats. This is consistent with known differences in calcium metabolism among these species.

In aged, ovariectomized, Sprague Dawley rats, teriparatide stimulated apposition onto trabecular, endosteal, and periosteal surfaces with improved resistance to fracture in the vertebra, femoral neck, and femoral diaphysis. These effects were observed when teriparatide treatment began either immediately after ovariectomy or after the rats had become significantly osteopenic due to sustained estrogen deficiency. In the latter case, teriparatide treatment, with a minimally efficacious dose of 0.3 to 1  $\mu\text{g}/\text{kg}/\text{day}$ , restored lost bone mass in the proximal tibia, distal femur, and vertebrae to above sham-ovariectomy and baseline levels.

The skeletal effects of teriparatide depend on the duration of systemic exposure. Teriparatide increased bone mass and strength in rats when administered once daily at 80  $\mu\text{g}/\text{kg}$  as a subcutaneous dose. In contrast, decreased bone mass was observed in rats administered 80  $\mu\text{g}/\text{kg}$  teriparatide three times per day or 13.3  $\mu\text{g}/\text{kg}$  administered six times per day over 6 to 8 hours by subcutaneous injection, or 40 to 80  $\mu\text{g}/\text{kg}/\text{day}$  as a continuous subcutaneous infusion. These findings are consistent with a catabolic response following sustained systemic exposure to teriparatide. The pharmacokinetic profiles of immunoreactive teriparatide in these dosing regimens suggest that the skeletal response to teriparatide (whether anabolic or catabolic) is determined primarily by the length of time each day that serum concentrations of teriparatide remain above baseline levels of endogenous PTH.

## 2.3. Absorption, Distribution, Metabolism, and Excretion

### 2.3.1. *Bioanalytical Methods*

Teriparatide concentrations have been measured in serum samples from rats, monkeys, and humans using commercially available immunoradiometric assays. This assay format uses two affinity-purified, polyclonal antibodies, one immobilized onto a plastic bead that was used for solid-phase capture, and the other radiolabeled for detection of the bound complex. The immobilized antibody was purified against the carboxy-terminal half of rat PTH(1-34). In the assay used for rat samples, the radiolabeled antibody was generated against human PTH, and was affinity-purified against an amino-terminal fragment of PTH(1-34). The assay for monkey and human serum samples used a radiolabeled antibody that was generated against rat PTH(1-34) and affinity-purified against an amino-terminal fragment of rat PTH(1-34). Parathyroid hormone is immunoreactive in these assays. Further cross-reactivity evaluation was conducted with the assay used for monkey and human samples. These experiments showed that peptides containing amino acids 1-34, 2-34, 3-34, and 1-31 were detected comparably in the immunoassay, and that peptides 4-34 and 1-27 demonstrated cross-reactivity of 16% or less. Smaller peptides (8-34, 13-34, 1-20) were not immunoreactive. Overall, the amino acid domains needed for immunoreactivity in the assay correlated well to domains required for biological activity (Habener et al. 1984).

### 2.3.2. *Pharmacokinetics and Toxicokinetics*

In rats and monkeys, teriparatide was rapidly absorbed and eliminated following subcutaneous injection, with  $T_{max}$  generally occurring 15 to 30 minutes after dose administration, and a  $T_{1/2}$  of elimination of 15 to 30 minutes. As in humans, the duration of exposure in animals given subcutaneous teriparatide was brief, consistent with an anabolic response in bone. No accumulation was observed in monkeys or rats that received daily doses of teriparatide for up to 18 months. Mean exposure at the 5- $\mu\text{g}/\text{kg}$  dose in rats was approximately three and nine times greater based on AUC and  $C_{max}$ , respectively, than exposure in humans administered a 20- $\mu\text{g}$  dose (0.3  $\mu\text{g}/\text{kg}$ ) of teriparatide. Mean exposure based on AUC at the 5- $\mu\text{g}/\text{kg}$  dose in monkeys was approximately eight times greater than humans administered a 20- $\mu\text{g}$  dose of teriparatide.

When multiple dose levels were administered to monkeys or rats, both AUC and  $C_{max}$  increased with dose. There were no apparent gender differences in the serum pharmacokinetics of teriparatide in the rat or monkey following a single dose of 10  $\mu\text{g}/\text{kg}$  or less.

### 2.3.3. *Absorption*

In male and female rats administered 10  $\mu\text{g}/\text{kg}$  teriparatide by subcutaneous injection, absolute bioavailability was estimated as 61% and 55%, respectively. In cynomolgus

monkeys, bioavailability following a 10- $\mu$ g/kg subcutaneous dose was estimated as 39% for males and 34% for females. These studies demonstrated that teriparatide was well absorbed from the subcutaneous space, and that bioavailability was comparable between males and females at the 10- $\mu$ g/kg dose level.

#### **2.3.4. Enzyme Induction or Inhibition**

There was no induction of hepatic microsomal enzymes in male or female cynomolgus monkeys after administration of teriparatide at doses up to 40  $\mu$ g/kg for 3 months, or in rats given teriparatide at doses up to 300  $\mu$ g/kg for 6 weeks.

#### **2.3.5. Distribution, Metabolism, and Excretion**

Distribution, metabolism, and excretion studies have not been performed with recombinant teriparatide. The ultimate fate of this peptide is expected to be metabolism into individual constituent amino acids, which are then reincorporated into the normal protein pool. However, considerable data are published that describe the metabolism and clearance of PTH, teriparatide, and related peptides (*Bringham et al. 1982*; *Martin et al. 1979*; *Daugaard 1996*; *Goltzman et al. 1986*; *Habener et al. 1984*). These studies indicate that liver, kidney, and bone are the major sites of metabolism and clearance for PTH and its amino- and carboxy-terminal fragments. Despite extensive efforts, the PTH(1-34) fragment has not been unequivocally identified as a natural metabolite that circulates at detectable levels in animals or humans. In rat, dog, cow, and man, sites of proteolytic cleavage have been identified at amino acids 33 and 37, consistent with generation of peptide metabolites similar in structure to the bioactive amino-terminal domain, PTH(1-34) (*Canterbury et al. 1973*; *Goltzman et al. 1986*; *Hock et al. 1997*). Like endogenous PTH, teriparatide is not expected to accumulate in bone or other tissues.

### 3. Nonclinical Safety

Teriparatide has been extensively tested in a variety of nonclinical safety studies that evaluated safety pharmacology, acute, subchronic, and chronic toxicity, genotoxicity, carcinogenicity, and developmental and reproductive toxicity. The primary findings from these studies are summarized in the following bullet points.

- Consistent with compound-induced vasodilation and compensatory physiological homeostatic mechanisms, rats and dogs given a single dose of 4 to 6  $\mu\text{g}/\text{kg}$  teriparatide showed a transient decrease in arterial blood pressure and increase in heart rate.
- Teriparatide did not produce any treatment-related ECG changes, such as prolongation of the QT interval, in monkeys that would indicate any effects on cardiac conduction, repolarization, or production of cardiac arrhythmias.
- Teriparatide is not acutely toxic to rodents at subcutaneous doses up to 10,000  $\mu\text{g}/\text{kg}$ .
- The primary effects in rats and monkeys in studies up to 1 year in duration were either directly or indirectly related to the known pharmacological actions of PTH on bone and mineral ion regulation. At the NOAEL of 2  $\mu\text{g}/\text{kg}$  in the chronic toxicity studies, systemic exposure of rats and monkeys to teriparatide was approximately five to six times greater than for humans given a dose of 20  $\mu\text{g}/\text{day}$ .
- Subtle renal histopathologic changes were observed in young cynomolgus monkeys treated for 3 months or 1 year at teriparatide doses that produced exposures that were up to 100 times greater than for humans given a dose of 20  $\mu\text{g}/\text{day}$ . The changes were correlated with the magnitude and duration of increases in blood ionized calcium, were largely reversible, and had a limited impact on kidney function. However, no treatment-related histopathologic changes in the kidney were observed in ovariectomized, female, cynomolgus monkeys (>9 years old) provided a 0.3% calcium diet and administered teriparatide daily for 18 months at systemic exposure levels that were approximately eight times greater than for humans given a dose of 20  $\mu\text{g}/\text{day}$ .
- Teriparatide was not genotoxic in a variety of in vitro and in vivo assays.
- In a 2-year rat carcinogenicity study, highly exaggerated increases in bone mass occurred that were associated with an increased incidence of bone tumors, including osteosarcoma. The increased incidence of bone tumors in rats is unlikely to be predictive of an increased risk of bone tumors in humans receiving teriparatide for osteoporosis for the following reasons (expanded upon in Section 3.6):
  - Sensitivity of the rat skeleton to the pharmacologic effects of PTH resulted in dose-dependent increases in bone mass that were highly exaggerated in comparison with the effects observed in monkeys and humans.

- There are fundamental differences in bone physiology between rats and humans, including near-lifetime skeletal growth and lack of haversian remodeling in rats.
- Near-lifetime duration of treatment in rats, compared with the relatively brief exposure in humans, resulted in prolonged and continual stimulation of osteoblasts.
- Chronic hormonal stimulation of a target tissue is known in some instances to induce tumors in rats that are not predictive of increased risk in humans.
- No bone tumors were observed in monkeys treated for up to 18 months.
- There is no clinical association between hyperparathyroidism and osteosarcoma.
- Teriparatide did not affect the fertility of male or female rats, and did not cause any developmental toxicity in pregnant rats or mice.

### 3.1. Introduction

In nonclinical safety evaluations, teriparatide has been tested in a wide variety of toxicology studies including the following: safety pharmacology studies; single-dose acute studies in rodents; subchronic and chronic studies in rats and monkeys; a special renal function study in monkeys; an extensive battery of in vivo and in vitro genotoxicity assays; and a 2-year carcinogenicity study in rats. In addition, numerous studies were conducted in rats, mice, and rabbits to evaluate the developmental and reproductive toxicity potential of teriparatide, primarily to generate information for assessing workplace safety.

### 3.2. Safety Pharmacology

In adult male rats, the NOEL for cardiovascular changes (measured as decreased blood pressure and increased heart rate) was 4.3 µg/kg of teriparatide. In female beagle dogs, a consistent and reproducible decrease in arterial pressure and increase in left ventricular inotropic state and heart rate were observed after treatment with 6 µg/kg teriparatide. These changes were consistent with PTH-induced vasodilation and compensatory physiological homeostatic mechanisms (*Pang 1989*). In the dog study, no treatment-related electrocardiograph changes were observed that would indicate any effects on cardiac conduction, repolarization, or production of cardiac arrhythmias. In adult male mice, teriparatide doses up to 100 µg/kg did not produce any secondary pharmacological effects related to the central nervous system or behavioral functions such as changes in body temperature, ambulatory and nonambulatory activity levels, central nervous system depression, and convulsive thresholds.

### 3.3. Acute Toxicity

No mortality occurred in rats given a single dose of 300 µg/kg intravenously or 1000 µg/kg subcutaneously, or in mice given a daily subcutaneous dose of 10,000 µg/kg for 2 consecutive days during an in vivo genotoxicity test.

### 3.4. Repeated-Dose Toxicity

In repeated-dose toxicity studies using subcutaneous administration, rats and monkeys were treated for 6 weeks to 1 year with teriparatide doses that ranged from 0.5 to 300 µg/kg/day.

#### Rats

In a 6-week rat study using daily subcutaneous doses up to 300 µg/kg and a 6-month rat study at daily doses up to 100 µg/kg, the primary effects produced by teriparatide were either directly or indirectly related to the known pharmacologic actions of PTH. Notable findings from these studies included slight-to-marked, dose-related increases in trabecular bone of all treated animals; slight increases in serum alkaline phosphatase activity and calcium concentration; increased urinary excretion of calcium; redness in the ears and paws attributed to vasodilation; increased serum cholesterol and triglycerides; slight-to-moderate decreases in neutrophil counts; increased spleen weights and extramedullary hematopoiesis in the spleen; and reduced pituitary weights. Essentially all of these changes were seen at teriparatide doses of at least 30 µg/kg in males and/or females, and the magnitude of the changes generally followed a dose-response pattern. The NOAEL for rats chronically treated with teriparatide was considered to be 10 µg/kg. The serum concentrations (AUC) of teriparatide in rats given 10 µg/kg was approximately five times greater than for humans given a dose of 20 µg/day (0.3 µg/kg).

#### Monkeys

In a 3-month study with cynomolgus monkeys (3 or 4/sex/group) using daily doses of 2 to 40 µg/kg, teriparatide produced effects that were attributed to the known pharmacologic actions of PTH. In animals from all treated groups, findings included minimal-to-marked, dose-related increases in trabecular bone and transient postdose elevation of blood ionized calcium. In addition, kidney weight was increased in females given 20 or 40 µg/kg, and histological evaluation of the tissues at the end of the study indicated minimal-to-moderate changes in the medullary interstitium and renal tubules at doses at or above 10 µg/kg. In animals with the most severe (moderate) lesions, the increases in blood ionized calcium at 4 and 8 hours postdose were frequently up to 40% to 50% above the baseline value. The only histological change in the 2-µg/kg group was observed in females and consisted of minimal expansion of the medullary interstitium. Other than ionized calcium, no substantive changes in clinical chemistry or urinalysis parameters were correlated with the renal histopathologic findings. A daily teriparatide dose of 2 µg/kg was considered to be the NOAEL in this subchronic study.

Similar changes to those observed in the 3-month study occurred in a 1-year study in male and female cynomolgus monkeys (4/sex/group) given daily subcutaneous doses of 0.5, 2, or 10 µg/kg. Minimal-to-moderate, dose-related increases in trabecular bone were observed in animals from all treated groups. In the high-dose group, transient elevations in blood ionized calcium were observed 4 hours postdose, and renal histologic changes occurred in 6 out of 8 animals in this group. As in the 3-month study, the most severe (moderate) lesions occurred in animals that had the highest blood ionized calcium values at 4 and 8 hours postdose. Minimal renal changes were noted in 1 female at 0.5 µg/kg and 1 female at 2 µg/kg. Other than ionized calcium, no substantive clinical chemistry or urinalysis changes were correlated with the renal changes. The average daily intake of calcium during this study (based on an estimated food intake value of 25 g/kg and an average dietary calcium content of 0.7%) was approximately 175 mg/kg. (Note: the average daily calcium intake is about 30 mg/kg for a postmenopausal woman receiving calcium supplementation.) No treatment-related, ECG changes (for example, prolongation of the QT interval) were observed in either the 3-month or 1-year study that would indicate any effects on cardiac conduction, repolarization, or production of cardiac arrhythmias. The number of animals with teriparatide-specific antibodies increased between 6 months and 1 year of treatment. Based on the minimal magnitude of the response, teriparatide was considered to be a weak immunogen in chronically treated cynomolgus monkeys. As in the 3-month monkey study, the NOAEL for the 1-year study was considered to be 2 µg/kg. The serum concentrations (AUC) of teriparatide in monkeys given 2 µg/kg was approximately six times greater (based on AUC) than for humans given a dose of 20 µg/day (0.3 µg/kg).

***Further Evaluation of Renal Changes.*** The potential functional effects of the renal histopathology findings in cynomolgus monkeys were further investigated using female animals in a special 4-month study with a 3-month reversibility period. In addition to routine clinical chemistry or urinalysis parameters, renal function parameters including urine-concentrating capacity, urine acidification, fractional electrolyte excretion, and glomerular filtration rate were evaluated. The previously identified histopathologic changes in the kidney were reproduced in 7 of the 8 monkeys administered 40 µg/kg in this study. Systemic exposure to teriparatide at this dose was more than 100 times higher (based on  $C_{max}$ ) than for humans given a dose of 20 µg/day (0.3 µg/kg). The expected transient increases in blood ionized calcium were observed, and marked hypercalcemia occurred in the 2 monkeys with the most severe renal lesions. In 1 monkey, signs of renal failure and marked hypercalcemia were observed after 82 days of treatment. However, renal function in this monkey returned to near normal after teriparatide treatment was discontinued. Except for this 1 animal, the compound-induced renal histologic changes did not affect renal function and were largely resolved by the end of the 3-month reversibility period. It was not conclusively determined if the observed renal histopathologic changes resulted from a direct effect of teriparatide on the kidney or merely represented a secondary response to the effect of teriparatide on calcium metabolism. However, the degree (magnitude and duration) of hypercalcemia appeared

to correlate reasonably well with the severity of the renal lesions observed in the 3-month and 1-year studies. Hypercalcemia has profound functional and morphologic effects on the kidney, and it appears likely that renal lesions in the monkey were due, at least in part, to the substantial elevations in serum calcium. In contrast to the findings in the toxicology studies, no treatment-related histopathologic changes were observed in a long-term primate pharmacology study in which ovariectomized female cynomolgus monkeys (greater than 9 years old) were administered teriparatide daily at subcutaneous doses of 1 or 5  $\mu\text{g}/\text{kg}$  for 18 months. Although the calcium content of the diet provided to the ovariectomized monkeys (0.3%) was less than that of the diet used in the 3- and 12-month toxicology studies (0.75%), the average daily calcium intake during the 18-month study (75 mg/day) still greatly exceeded that of a calcium-supplemented postmenopausal woman (30 mg/day). The dose of 5  $\mu\text{g}/\text{kg}$  produced serum concentrations (AUC) of teriparatide that were approximately eight times greater than for humans given a dose of 20  $\mu\text{g}/\text{day}$  (0.3  $\mu\text{g}/\text{kg}$ ). The fact that aged, ovariectomized monkeys given 5  $\mu\text{g}/\text{kg}$  daily for 18 months did not exhibit the renal histopathologic changes observed in younger, ovary-intact monkeys further suggests that this kidney lesion has limited relevance for the intended clinical population.

### 3.5. Genotoxicity

Teriparatide was not genotoxic in any of the following assays: the in vitro bacterial mutagenesis assay with and without metabolic activation, the mouse lymphoma assay for mammalian cell mutation, the chromosomal aberration assay in Chinese hamster ovary cells, and the in vivo micronucleus test in mice.

### 3.6. 2-Year Rat Study

Fischer 344 rats (60/sex/group, 6 to 7 weeks of age) were given daily subcutaneous injections of teriparatide for 2 years (80% to 90% of their lifetime) at doses of 0, 5, 30, or 75  $\mu\text{g}/\text{kg}$ . Serum concentrations of teriparatide were dose related and there was no clear difference between genders. The serum concentrations of teriparatide observed in the treated rats at 6 and 12 months were about twice as high as those measured at 18 months. Based on the the teriparatide concentrations measured at all three time points, systemic exposure in the rats was approximately 3 to 58 times higher than the AUC values observed in postmenopausal women administered 20  $\mu\text{g}$  (0.3  $\mu\text{g}/\text{kg}$ ). Anti-teriparatide antibody production was not observed.

It should be noted that the teriparatide blood levels observed at the 18-month time point in that study were the lowest PTH blood levels observed in that study (as noted in section 1.3 below) and may not be the most accurate representation of the teriparatide levels that occur in rats given a subcutaneous dose of 5 mcg/kg. At the 6- and 12-month time points in the 2-year study, the exposure multiples were both 3.6 at 5 mcg/kg.

The most representative and accurate exposure multiples are probably those that incorporate blood level data collected throughout the study (for example, 6-, 12-, and

18-month time points), rather than only blood levels observed at the 18-month time point. Exposure multiples based on this broader data set range from 3.0-58 for AUC and 8.8-136 for Cmax.

There were no compound-related effects on survival in male rats at the end of the study. A 12% decrease in survival occurred in the high-dose female rats, but could not be attributed to fatal neoplasia or to any single nonneoplastic cause of death.

Consistent with the expected pharmacologic effects on bone, teriparatide administration produced substantial dose-dependent increases in bone mass. Teriparatide-related bone changes included: substantial stimulation of new bone formation that resulted in significant reduction of marrow spaces in all treated groups; significant periosteal expansion that resulted in altered bone architecture in the 30- and 75- $\mu\text{g}/\text{kg}$  groups; and trabecular hypertrophy that was characterized by increased thickness and connectivity of trabecular bone. Biomechanical analyses showed that teriparatide treatment induced significantly stronger and stiffer femurs that were less flexible.

Focal cellular proliferative lesions, including osteosarcomas, were observed in the bones of rats in all teriparatide-treated groups. Focal hyperplastic lesions and benign neoplasms occurred at low incidence and included focal osteoblast hyperplasia, osteoma, and osteoblastoma. Malignant bone neoplasms (osteosarcomas) occurred in males and females in a dose-responsive manner, and reached an incidence of approximately 50% in high-dose male rats. Osteosarcoma occurred in 3, 21, and 31 male rats and in 4, 12, and 23 female rats in the 5-, 30-, and 75- $\mu\text{g}/\text{kg}$  treatment groups, respectively. These neoplasms were first detected by gross examination in the 75- $\mu\text{g}/\text{kg}$  group at approximately 17 months and in the 5- and 30- $\mu\text{g}/\text{kg}$  groups by approximately 20 months of treatment. Osteosarcomas arose in a variety of sites in the appendicular and axial skeleton, but were most prevalent in the tibia and vertebra. Osteosarcoma metastatic to soft tissue sites occurred in 36% of the rats diagnosed with osteosarcoma. Teriparatide treatment did not increase the incidence of neoplasms of nonosseous tissues.

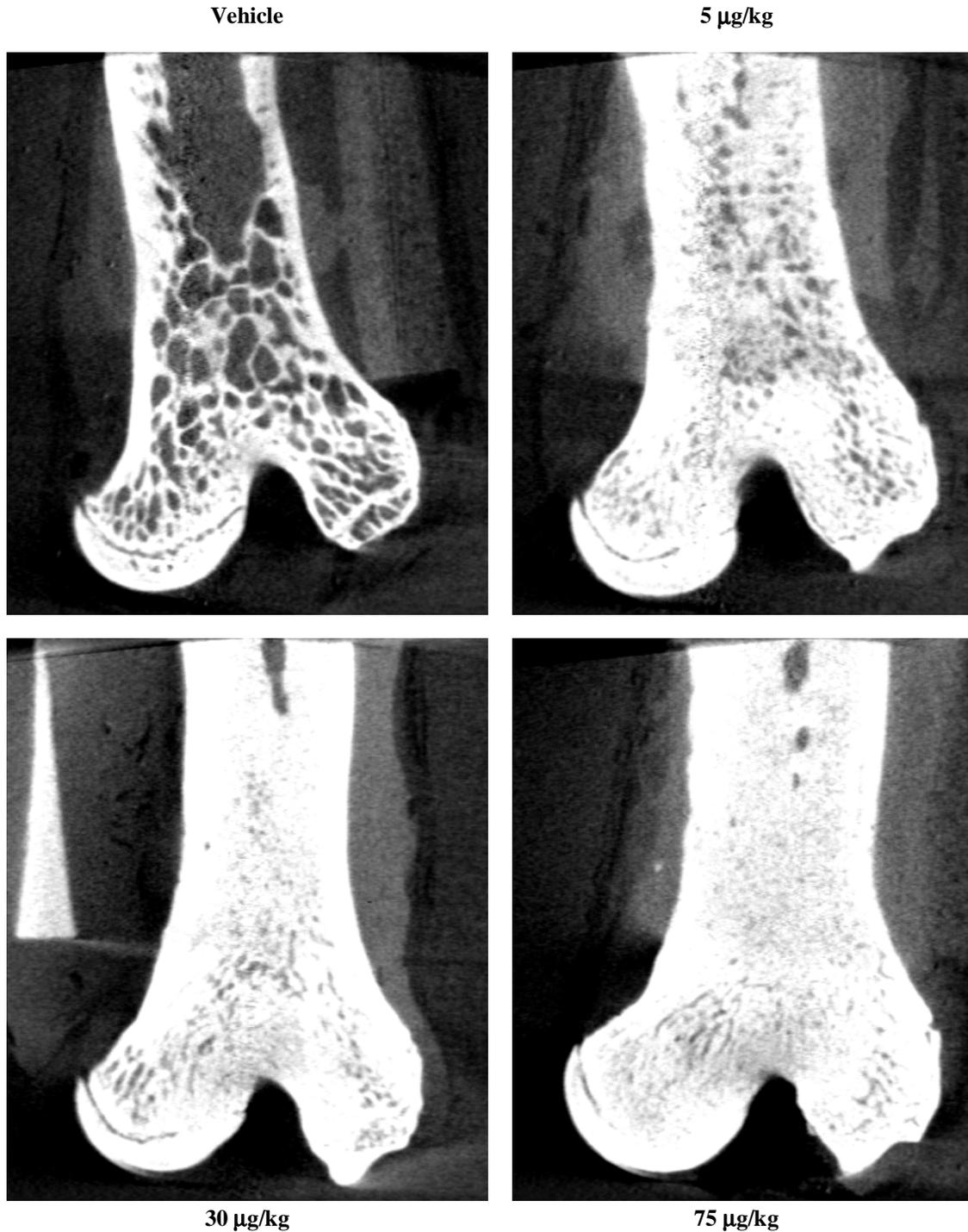
In summary, important effects of teriparatide were limited to the skeleton and included pharmacologically mediated, exaggerated bone formation and a spectrum of focal hyperplastic and neoplastic bone lesions, including osteosarcoma. These effects occurred at all dose levels in both males and females. The lowest dose tested resulted in bone anabolic effects in the rat that were in marked excess of the clinical response in humans.

### **Relevance of the Osteosarcoma Findings**

Based on the animal pharmacology studies with teriparatide, increases in bone mass in the femur and vertebra were expected; however, the extreme magnitude of the increases in bone mass, as well as the focal hyperplastic and neoplastic bone lesions observed in the 2-year study, were not anticipated. Although specific cellular or molecular mechanisms responsible for the rodent bone tumors are not currently understood, based on numerous factors discussed in the following text, the findings in rats are unlikely to be

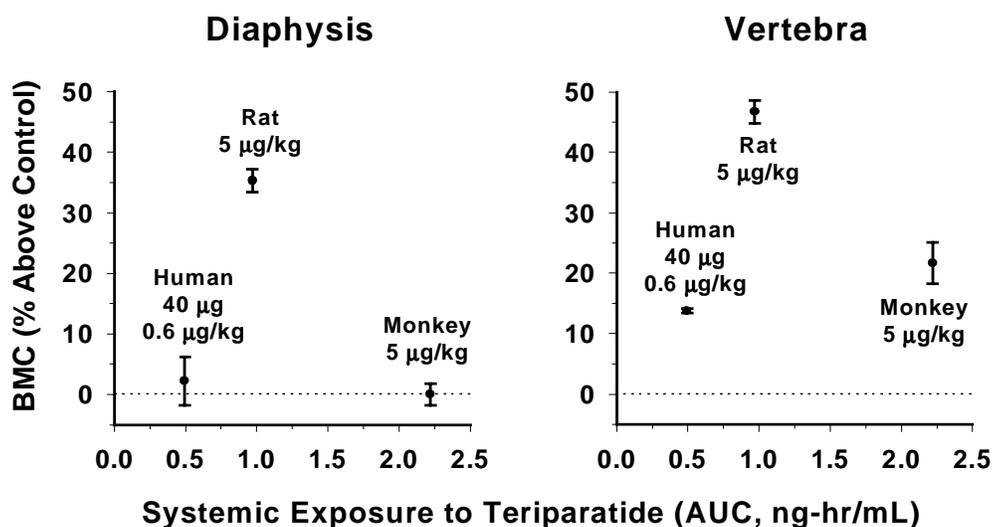
predictive of an increased risk of osteosarcoma in humans receiving teriparatide treatment for osteoporosis.

***Profound Pharmacologic Effects of Teriparatide on Rat Bone.*** Increases in both trabecular and cortical bone mass were expected pharmacologic responses; however, results from the QCT, histomorphometry, histopathology, and biomechanical evaluations verified that the pharmacologic effects on the skeleton in this 2-year rat study, even at 5 µg/kg, greatly exceeded those previously observed in rats treated with 5 µg/kg of teriparatide (Kimmel et al. 1993; Kishi et al. 1998). Teriparatide stimulated trabecular and endocortical apposition at 5 µg/kg, and reduced marrow space that was followed by periosteal expansion and alterations in bone size and shape at higher doses. The response was so dramatic (Figure 3.1) that the BMD for the whole femur of rats (BMD = 1350 to 1418 mg/cc) was quantitatively similar to that of a rod of pure cortical bone from a bovine femoral midshaft (BMD = 1393 mg/cc).

**Figure 3.1.****High-Resolution QCT Images of the Rat Proximal Femur**

Representative coronal images at 24x24x24  $\mu$ m resolution are shown of the vehicle, 5, 30, and 75  $\mu$ g/kg groups of female F344 rats after 2 years of treatment with teriparatide. Images show significant loss of marrow space due to increased trabecular apposition and increased cortical thickness at all doses of teriparatide.

As shown in Figure 3.2, 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. This agrees with previous high-dose studies in rats (Gasser and Jerome 1992; Jerome 1994). The greater sensitivity of the rat is due to, at least in part, fundamental differences in bone physiology (Kimmel 1996). In species with haversian remodeling (for example, humans and monkeys), PTH stimulates apposition onto existing bone surfaces and bone turnover. This osteonal remodeling results in increased porosity, and thus cortical bone mass does not increase dramatically. Due to the inherent inability of rats to replace cortical bone via osteonal remodeling, rats respond to PTH primarily by mineral apposition onto existing surfaces with little intracortical remodeling (Dempster et al. 1993; Gasser and Jerome 1992; Jee et al. 1990; Qi et al. 1995). In addition, the rat skeleton continues to grow longitudinally for most of their lives, while longitudinal growth in humans ceases between 18 and 30 years of age (Kimmel 1996; Compston 2001). In rats, PTH stimulates longitudinal and radial skeletal growth, so extreme gains in bone mass were induced by daily injections of PTH throughout their life (Fig. 3.1) Changes of comparable magnitude were not observed in osteonal remodeling species (for example, humans) administered PTH daily for a relatively short proportion of their life span (Lindsay et al. 1997; Neer et al. 2001).



**Figure 3.2. Effects of Teriparatide on Cortical (Diaphysis) and Trabecular (Vertebra) Bone Sites in Rats, Monkeys, and Humans Treated for 18 to 24 Months**

**Relevance of Chronic Hormone-Induced Neoplasia in Rats.** Chronic hormonal stimulation of a target cell population can lead to cell proliferation, clonal expansion, and ultimately neoplasia. Certain kinds of tumors can be drug-induced in rats, but have no clinical relevance. For example, phenobarbital indirectly causes elevations in circulating levels of thyroid-stimulating hormone (TSH) in the rat. Chronic elevation of TSH results in continual stimulation of thyroid follicular cells that subsequently leads to thyroid

follicular hyperplasia and neoplasia (Capen 1996, 1997; McClain 1989). In humans, chronically elevated levels of TSH do not appear to result in an increased incidence of thyroid neoplasia (Curran and DeGroot 1991). Therefore, rats are susceptible to phenobarbital-induced thyroid neoplasia that has no relevance to human safety. A second example is the neoplasia of gastric enterochromaffin-like cells induced in rats treated with omeprazole and other proton pump inhibitors (Ekman et al. 1985). These molecules indirectly lead to increased gastrin levels which, in the rat, result in hyperplasia and neoplasia of gastric enterochromaffin cells. Similar findings are not seen in humans receiving chronic therapy with proton pump inhibitors (Massoomi et al. 1993).

These examples provide evidence that chronic hormonal stimulation of a target tissue in the rat can lead to induction of hyperplastic and proliferative lesions. Similar to TSH and gastrin in the models above, PTH and teriparatide have direct, receptor-mediated effects on osteoblasts, where these peptides bind with high affinity to a specific PTH/PTHrP receptor. Parathyroid hormone and related peptides have numerous effects on osteoblast activity, including stimulating the differentiation of precursors (Dempster et al. 1993; Dobnig and Turner 1995; Potts et al. 1995; Schmidt et al. 1995).

It is a plausible hypothesis that compounds causing a profound bone anabolic response in the rodent via receptor-mediated effects on the osteoblast would produce bone proliferative lesions following near-lifetime treatment. A draft FDA Guidance for Industry on the development of PTH for the treatment and prevention of osteoporosis indicates that osteosarcomas have been observed in studies in two strains of rats and one strain of mice with PTH and related peptides. Because PTH and PTH-related peptides [including PTH(1-38), (1-34), (1-31); and PTHrP(1-34) and (1-36)] were shown to be anabolic in the rat skeleton through interactions with the PTH/PTHrP receptor (Whitfield and Morley 1998), it is likely that these peptides will produce the same spectrum of biological responses.

***Results From Other Nonclinical Studies With Teriparatide.*** Additional data supporting the conclusion that rat bone tumors are not predictive for other nonrodent species are available from other animal studies. A study in which teriparatide was given daily to skeletally mature (greater than 9 years old), ovariectomized, cynomolgus monkeys (20/group) at doses up to 5 µg/kg for 18 months demonstrated the marked differences in bone physiology between primates and rats. Although teriparatide produced increased bone mass, the magnitude of the skeletal effect was much less prominent than that observed in rats and was more similar to that seen in humans (Figure 3.2). Based on qualitative histologic observations, no neoplastic, cellular proliferative lesions or treatment-related bone anomalies of any kind were reported. In addition, the teriparatide used in the present study was negative in a battery of in vitro and in vivo genotoxicity tests, which further supports the conclusion that the bone proliferative lesions observed in the 2-year rat study were produced through a nongenotoxic mechanism.

***Primary Skeletal Tumors Are Not Increased in Humans With Hyperparathyroidism.*** An important model for PTH excess in humans is the group of disorders termed primary and secondary HPT. In HPT, chronic elevation of plasma PTH concentrations results

from neoplasia or hyperplasia of the parathyroid glands and over-secretion of the hormone. In all such cases, osteoblasts are stimulated with increased bone formation activity, due to the continuously elevated levels of PTH (Heath 1996).

Hyperparathyroidism is characterized by elevated bone turnover and net loss of bone, especially cortical bone, due to increased resorption activity which exceeds formation activity. The temporal differences in daily exposure between HPT and intermittent teriparatide administration often result in greater stimulation of the osteoclast in HPT. However, the stimulation of osteoblast activity is similar in HPT and intermittent teriparatide administration. This stimulation of osteoblasts often persists for 5 to 10 years or more in HPT, yet has not been associated with increased risk of primary skeletal tumors (Palmer et al. 1988).

### **3.7. Developmental and Reproduction Toxicity**

In Segment I reproduction (fertility) studies in male and female rats, no important effects were observed after administration of subcutaneous doses of 30 to 300 µg/kg/day. In Segment II developmental toxicity studies, there were no important effects observed in pregnant rats or mice administered teriparatide subcutaneously at daily doses of 30 to 1000 µg/kg. However, in a pilot study, pregnant rabbits administered teriparatide subcutaneously had vaginal bleeding and total resorption of all fetuses at doses of 10 to 100 µg/kg. At 100 µg/kg, 2 pregnant animals died and the remaining 3 animals were euthanized due to excessive reductions in food consumption and body weight. Fetal resorption in 1 of 5 animals and reduced litter size occurred at a dose of 3 µg/kg. The embryotoxicity observed in pregnant rabbits was considered to have resulted from the substantial elevations in blood ionized calcium observed in this species following teriparatide administration. The dramatic difference between the responses of pregnant rodents and rabbits to teriparatide treatment most likely is related to the rabbit's much greater sensitivity to the effects of PTH on blood-ionized calcium compared with the rat and mouse. It is generally accepted that the adverse pregnancy outcomes following sustained elevations of PTH in animals and humans result from hypercalcemia (Graham et al. 1998; Horii et al. 1992). Since teriparatide is not intended for use in pregnant women and sustained hypercalcemia is not expected to be a side effect of teriparatide therapy in humans, these findings in rabbits are not considered to represent a relevant clinical safety concern for nonpregnant women or for men.

In a combined Segment II/Segment III perinatal and postnatal study with teriparatide in CD rats, the NOAEL for F<sub>0</sub> maternal and reproductive toxicity was 1000 µg/kg/day, the highest dose level tested. For the F<sub>1</sub> generation, the NOAEL for developmental toxicity was a maternal dose of 30 µg/kg/day. Developmental toxicity in the F<sub>1</sub> progeny was characterized by mild growth retardation in female rats at 225 µg/kg/day, and by growth retardation and reduced motor activity in both male and female rats at 1000 µg/kg/day.

## 4. Clinical Pharmacology

The clinical pharmacology program used a combination of classic pharmacology studies, population pharmacokinetics, and population pharmacodynamics. The clinical pharmacology studies have focused principally on pharmacokinetics in the pivotal studies, in healthy older men and women, and in subjects with mild to severe renal insufficiency, hypertension, or mild or moderate heart failure, and on the effects of teriparatide on mineral metabolism. This section summarizes the following points:

- the scope of the pharmacokinetic and pharmacodynamic analyses
- for subcutaneous dosing, teriparatide is rapidly absorbed ( $T_{\max} = 30$  minutes), highly bioavailable (95%), and rapidly eliminated (duration of exposure less than 3 hours)
- exposure to PTH is less in patients with osteoporosis treated with teriparatide 20 µg/day than in patients with mild primary hyperparathyroidism
- teriparatide pharmacokinetics are independent of injection site (abdominal wall or thigh)
- dosing adjustment is not required on the basis of age, gender, or ethnic origin
- dosing adjustment is not required in patients with renal dysfunction, hepatic dysfunction, or heart failure
- based on the mechanism for teriparatide metabolism, clinically significant pharmacokinetic drug interactions are not anticipated.

### 4.1. Introduction

Population pharmacokinetic and pharmacodynamic analyses were performed in Phase 3 studies and GHAI to delineate relationships between pharmacokinetics and the patient population as well as effects on mineral metabolism, lumbar spine and/or femoral neck BMD, and biochemical markers of bone formation and resorption. The pharmacodynamic analyses sought to describe the time course of each response and to evaluate the relationship between early changes in biochemical markers and subsequent gains in lumbar spine BMD. The analyses were prospectively designed to assess important clinical and demographic factors such as the effects of age, gender, ethnicity, site of subcutaneous injection, smoking status, and alcohol use on the pharmacokinetics and pharmacodynamics of teriparatide. Additionally, the effects of renal function and congestive heart failure on the pharmacokinetics of teriparatide were assessed. Table 4.1 lists the clinical pharmacology studies.

**Table 4.1. List of Clinical Pharmacology Studies**

<b>Clinical Pharmacology Studies Investigating Teriparatide by Subcutaneous Administration</b>	
B3D-LC-GHAB	LY333334: Single-Dose Dose-Ranging Study, Pharmacokinetics and Pharmacodynamics Properties
B3D-LC-GHAD	Effect of LY333334 on Calcium Homeostasis in Healthy Postmenopausal Women
B3D-LC-GHAE	Safety of LY333334 in Hypertensive Women
B3D-MC-GHAM <sup>a</sup>	Assessment of Renal Effects of LY333334 Alone or in Combination with Raloxifene HCl or Continuous Combined Hormone Replacement Therapy
B3D-LC-GHAW	Pharmacokinetics and Acute Pharmacodynamics of LY333334 When Administered Alone and with Furosemide in Stable Chronic Renal Insufficiency
B3D-LC-GHBA	Thiazide Diuretic Interaction Trial
B3D-LC-GHBC	Safety, Pharmacokinetics, and Acute Pharmacodynamics of LY333334 in Patients with Stable Heart Failure
B3D-LC-GHBI	Absolute Bioavailability of LY333334 Administered by Subcutaneous Injection
B3D-FW-GHBO	Assessment of LY333334 on Cardiac Conduction and Repolarization
B3D-LC-GHBR	Randomized, Single-Blind, Crossover, Interaction Study of LY333334 and Digoxin Pharmacodynamics in Healthy Volunteers
<b>Clinical Pharmacology Studies Investigating Subcutaneous and Alternative (Nonsubcutaneous) Routes of Administration</b>	
B3D-EW-GHAK	Relative Bioavailability Administered by Inhalation and Subcutaneous Injection with Scintigraphic Evaluation of Lung Deposition
B3D-EW-GHAN	A Relative Bioavailability Study of the Buccal Route of Administration Compared with Subcutaneous Delivery in Healthy Subjects
B3D-MC-GHAO <sup>a</sup>	Effects of Pulmonary Inhalation of Teriparatide on Biochemical Markers of Bone Metabolism and Pulmonary Function Tests in Healthy Postmenopausal Women
B3D-EW-GHAS	A Relative Bioavailability Study of Pulmonary Route of Administration Compared with Subcutaneous Route and Single and Multiple Dose Safety and Pharmacokinetics of LY333334 by Inhalation
B3D-EW-GHAT	Evaluation of Nasal Absorption and Tolerability of Teriparatide Following Administration of a Novel Nasal Formulation in Healthy Volunteers
B3D-EW-GHBF	Multiple Dose Safety Study of Inhaled LY333334 and Relative Bioavailability to the Subcutaneous Route

<sup>a</sup> Phase 1b study terminated by sponsor decision before completion; data included in clinical trial safety database.

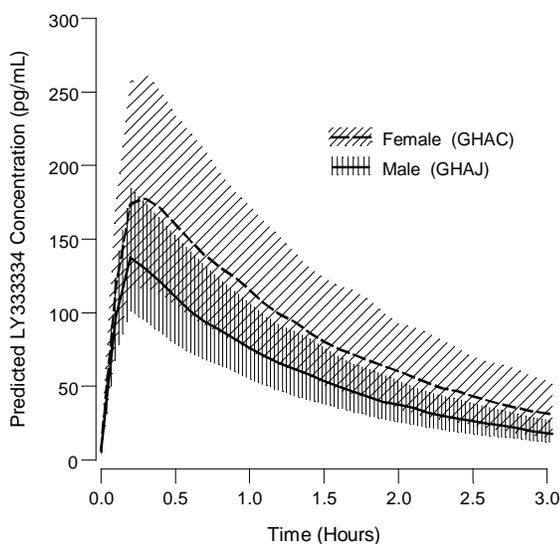
Conclusions from the cardiovascular safety assessments and pharmacodynamic analyses of mineral metabolism responses to teriparatide are discussed in Section 7: Clinical Safety. Highlights of the pharmacodynamic analyses of lumbar spine BMD and biochemical marker responses to teriparatide treatment are discussed in Section 6: Effectiveness of Teriparatide.

## 4.2. Summary of Pharmacokinetics and Bioavailability

Pharmacokinetic data were obtained via traditional methods from approximately 200 men and women who received at least one subcutaneous dose of teriparatide that ranged from 5 to 100 µg. Pharmacokinetic data were obtained from 36 postmenopausal women with low bone mass and from 611 men and postmenopausal women with osteoporosis who participated in one Phase 2 study (GHAA) and two Phase 3 studies (GHAC and GHAJ),

respectively. The dose of teriparatide ranged from 6 to 60  $\mu\text{g}$  in Study GHAA, whereas 20 and 40  $\mu\text{g}$  doses were investigated in Studies GHAC and GHAJ.

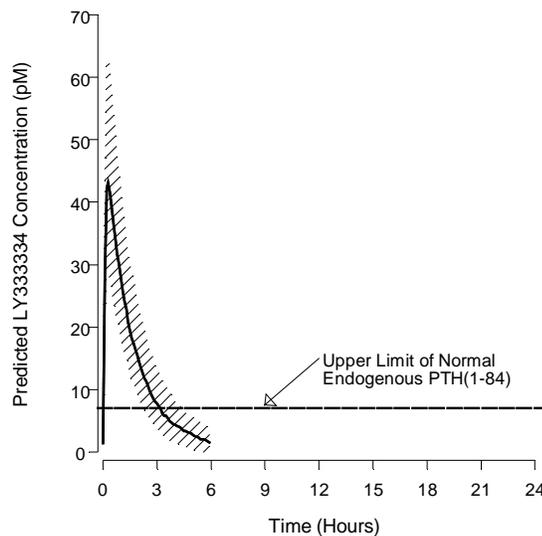
Teriparatide was extensively absorbed from the subcutaneous tissue; the absolute bioavailability averaged 95%. Serum concentrations of teriparatide increased linearly and proportionately with increasing dose. The pharmacokinetic profile was characterized by rapid absorption and elimination. Serum concentrations of immunoreactive teriparatide peaked approximately 30 minutes after injection of a 20- $\mu\text{g}$  dose and, in most subjects, declined to nonquantifiable concentrations within 3 hours (Figure 4.1). Systemic clearance of teriparatide (approximately 94 L/hr) exceeded the rate of normal liver plasma flow, consistent with both hepatic and extra-hepatic clearance. Volume of distribution was approximately 1.8 L/kg. The resultant disappearance half-life from the systemic circulation was approximately 1 hour. This half-life was influenced by the rate of absorption from the subcutaneous tissue, as the true elimination half-life following intravenous administration was approximately 5 minutes. Drug accumulation did not occur with daily dosing, and total systemic exposure in patients treated with teriparatide for up to 2 years was similar to the exposure in healthy subjects who received single doses of the drug. Between-subject coefficient of variation for the pharmacokinetic disposition of teriparatide ranged from 30% to 50%. As discussed in Section 4.2.1, there were no factors identified that produced clinically important changes in the pharmacokinetics of teriparatide.



Shaded regions represent the 25th to 75th percentile teriparatide concentrations calculated from 1000 iterations for a 20- $\mu\text{g}$  injection in the abdominal wall.

**Figure 4.1. Range of Population Predicted Teriparatide Concentrations in Men and Postmenopausal Women B3D-MC-GHAJ and B3D-MC-GHAC**

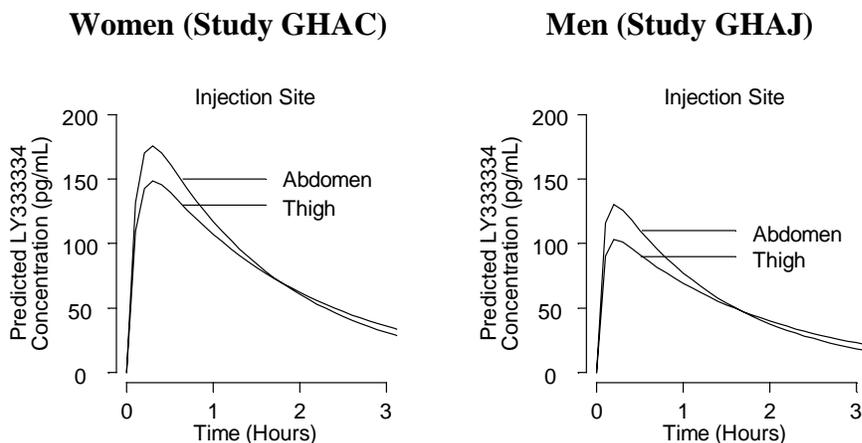
On a molar basis, peak concentrations of teriparatide measured in long-term clinical trials briefly (minutes) exceeded the upper limit of normal for endogenous PTH by 4- to 5-fold (Figure 4.2). However, the rapid disappearance of the peptide from serum, and subsequent slight suppression of endogenous PTH for a few hours, resulted in a 24-hour total PTH (teriparatide plus endogenous PTH) exposure that was less than the 24-hour exposure of a subject who maintained endogenous PTH concentrations at the upper limit of normal (65 pg/mL [7.0 pM]). Therefore, the average 24-hour exposure to endogenous and exogenous PTH peptides following the therapeutic administration of teriparatide was less than the 24-hour exposure occurring in patients with mild hyperparathyroidism (PTH concentrations greater than 65 pg/mL).



Shaded regions represent the 25th to 75th percentile teriparatide concentrations calculated from 1000 simulation iterations.

**Figure 4.2. Range of Population Predicted Teriparatide Concentrations in Postmenopausal Women B3D-MC-GHAC**

Approximately 60% of the patients in Studies GHAC and GHAI chose the abdominal wall as the site of injection and approximately 40% chose to inject themselves in the thigh. Volume of distribution increased 21% in women and 30% in men when the peptide was injected in the thigh, thereby resulting in lower peak concentrations (Figure 4.3), but no differences in total systemic exposure. There were no apparent differences based on the site of injection with regard to adverse events, serum and urine calcium responses, or serum uric acid responses. Furthermore, population pharmacodynamic analyses demonstrated no statistically significant differences in lumbar spine BMD or biochemical marker responses based upon site of injection. Therefore, teriparatide can be administered in either the abdominal wall or thigh without having a clinically significant impact on systemic exposure.



**Figure 4.3. Effect of Injection Site on Teriparatide Concentrations in Postmenopausal Women and in Men B3D-MC-GHAC and B3D-MC-GHAJ**

#### **4.2.1. Special Populations**

There were no differences in pharmacokinetics with respect to age (range: 31 to 85 years). Although systemic exposure to teriparatide was approximately 20% to 30% lower in men than in women, there were no gender differences with respect to safety, tolerability, or BMD responses. Thus, the same dose may be administered to both men and women. Neither smoking nor alcohol consumption in either gender affected teriparatide disposition.

The influence of ethnic origin on teriparatide disposition was examined in the population pharmacokinetic analyses. Although the studies were unrestricted with respect to race or ethnic background, the populations included in the pharmacokinetic analyses were predominantly Caucasian with less than 1.5% representing Hispanic, Asian, and other origins. Although there were no major differences in serum teriparatide concentrations among these ethnic groups, there were insufficient data to identify smaller shifts in the distributions of pharmacokinetic parameters that might be attributable to ethnic factors. However, the protein shows none of the characteristics that might be influenced by ethnic factors (nonlinear pharmacokinetics, a steep pharmacodynamic curve for safety and efficacy, a narrow therapeutic range, metabolism by enzymes associated with genetic polymorphism, administration as a pro-drug, or low bioavailability).

In subjects with mild, moderate, or severe chronic renal insufficiency, the clearance of teriparatide was inversely correlated with creatinine clearance between the range of 13 mL/min to 161 mL/min. The magnitude of these differences was not clinically relevant and dosage adjustment based on renal function is not required; however, long-term safety and efficacy have not been evaluated in patients with serum creatinine concentrations greater than 177  $\mu\text{mol/L}$  (2 mg/dL). The presence of stable mild or

moderate heart failure did not result in clinically relevant changes in the pharmacokinetics of teriparatide.

No significant association was found between teriparatide clearance and measures of hepatic function. This is not surprising because the principal site of clearance in the liver is not the hepatocyte, but is specific phagocytic cells in the hepatic sinusoidal capillaries, called Kupffer cells (*Daugaard 1996*; Segre et al. 1981b). Animal studies have shown that severely reduced hepatic blood flow decreased presentation of PTH to the Kupffer cells and consequently clearance of PTH (Segre et al. 1981a). Since clearance would only be affected by severe restriction in hepatic blood flow, safety and efficacy have not been evaluated in patients with hepatic impairment. Patients with mild or moderate liver disease would be expected to have relatively normal hepatic blood flow. Patients with severe cirrhosis might be expected to have significant reductions in hepatic blood flow.

#### **4.2.2. Drug Interactions**

There is no basis for suspecting a pharmacokinetic interaction between teriparatide and other drugs. The high-capacity Kupffer cells, responsible for cleavage of the PTH(1-34) peptide, are unlikely to be affected by the coadministration of other drugs. Furthermore, a change in clearance would be unlikely to result in a substantial change in the systemic exposure to teriparatide, as absorption from the subcutaneous tissue is the critical process that determines the duration of peptide exposure. Serum teriparatide concentrations are in the low picomolar range and can only be measured in the systemic circulation for less than 4 hours following administration of the proposed therapeutic dosage of 20 µg/day. These characteristics make it highly unlikely that the pharmacokinetics of teriparatide administered once daily will be affected by another drug, or that the systemic concentrations of this protein could substantially affect the pharmacokinetics of other drugs. When formally tested with intravenous furosemide, the diuretic drug did not alter the pharmacokinetics of teriparatide.

#### **4.3. Conclusions**

In conclusion, as a result of the examination of approximately 30 patient factors and laboratory values in men and postmenopausal women, no effects necessitating modifications in the dosing regimen were identified. Overall, the pharmacokinetic and pharmacodynamic analyses support the administration of teriparatide to postmenopausal women and to men without regard to age, body weight, cigarette smoking, alcohol consumption, or site of injection (abdominal wall or thigh). Dosage adjustment based on the presence of mild or moderate heart failure is not required. Dosage adjustment is also not required based on renal function; however, long-term safety and efficacy have not been evaluated in patients with serum creatinine concentrations greater than 177 µmol/L (2 mg/dL).

## 5. Overview of Phase 3 Clinical Studies

The Phase 3 clinical program was designed to evaluate the fracture efficacy of teriparatide in postmenopausal women and the effects on BMD and bone markers in postmenopausal women and in men. It was also designed to comprehensively evaluate the effects of long-term teriparatide administration on safety parameters. Because the clinical development was stopped, an observational follow-up study was used to obtain posttreatment safety and efficacy data.

This section summarizes the following:

- the clinical studies conducted with teriparatide
- the demographics of the long-term Phase 3 clinical studies (Studies GHAC, GHAJ, GHAF, and GHAH)
- the study design and eligibility criteria for Study GHAC, the pivotal study of osteoporosis treatment in women
- the study design and eligibility criteria for Study GHAJ, the pivotal study of osteoporosis treatment in men
- the study design and eligibility criteria for Study GHAF, a study designed to compare changes in lumbar spine BMD after treatment with either teriparatide and HRT or HRT monotherapy
- the study design and eligibility criteria for Study GHAH, a study designed to compare changes in lumbar spine BMD after treatment with either teriparatide or alendronate
- the study design for the observational follow-up study GHBJ, an ongoing study that enrolled most of the patients who were treated with placebo or teriparatide in any of the long-term Phase 3 studies.

### 5.1. Overview of the Clinical Plan

The clinical development of teriparatide began in September 1995. Since then, the safety of teriparatide has been evaluated in 25 clinical studies that enrolled over 2800 women and men. The four Phase 3 clinical studies of greater than 1-year duration included 2030 postmenopausal women and 437 men. Teriparatide doses ranged from 5 to 100 µg/day in short-term studies and 20 to 40 µg/day in the long-term studies. A total of 1943 patients received teriparatide, including 815 patients at 20 µg/day and 1107 patients at 40 µg/day. In the long-term clinical studies, 1137 patients were exposed to teriparatide for greater than 1 year (500 at 20 µg/day and 637 at 40 µg/day). Total exposure to teriparatide was more than 1967 patient-years.

The two placebo-controlled pivotal studies, (Studies GHAC and GHAJ), summarized in Table 5.1 included 1637 postmenopausal women and 437 men. The two

active-controlled, long-term studies, (Studies GHAF and GHAH), summarized in Table 5.2 enrolled 393 postmenopausal women.

On 8 December 1998, the sponsor suspended administration of injectable study drug in all ongoing clinical studies involving teriparatide because of an unexpected skeletal finding in an ongoing rat study. Investigators were advised to have all study patients continue their oral study medications and return for all scheduled study visits. On 17 December 1998, the sponsor stopped the studies and instructed the study investigators to have all patients complete the Early Discontinuation Visit. In 1999, the sponsor offered all patients who had enrolled in any Phase 3 study the option to enroll in an observational, posttreatment, follow-up study, Study GHBJ. Approximately 77% of eligible patients elected to enroll in this follow-up study.

**Table 5.1. Placebo-Controlled Pivotal Studies of Teriparatide**

<b>Number of Centers/ Study Identifier/ Short Title</b>	<b>Phase Design</b>	<b>Number of Subjects/ Ages</b>	<b>Criteria for Inclusion</b>	<b>Duration of Treatment/ Start Dates</b>	<b>Test Product/ Dosage/ Regimen/ Route of Administration</b>
99 centers in North and South America, Europe and Australia <b>B3D-MC-GHAC</b> Effects of LY333334 in the Treatment of Postmenopausal Women With Osteoporosis	Phase 3 Double-blind Randomized Parallel	N = 1637 F = 1637 42 to 86 years	F w/vert fx; Minimum of 5 years post- menopausal	Planned: 3 years Actual: up to 24 months Start: July 1996	Placebo; teriparatide: 20, 40 µg sc injection in lower abdomen or lateral thigh once daily
36 centers in North America, Europe, and Australia <b>B3D-MC-GHAJ</b> Effects of LY333334 in the Treatment of Men With Osteoporosis	Phase 3 Double-blind Randomized Parallel	N = 437 M = 437 28 to 85 years	M w/ low BMD	Planned: 2 years Actual: up to 14 months Start: July 1997	Placebo; teriparatide: 20, 40 µg sc injection in lower abdomen or lateral thigh once daily

Abbreviations: BMD = bone mineral density; F = females; vert = vertebral; fx = fracture; sc = subcutaneous; M = males; N = number of patients.

**Table 5.2. Active-Controlled Supportive Studies of Teriparatide**

Number of Centers/ Study Identifier/ Short Title	Design	Number of Subjects/ Ages	Criteria for Inclusion	Duration of Treatment Start Date	Test Product/ Dosage Regimen/ Route of Administration	Reference Therapy/ Dosage Regimen/ Route of Administration
14 centers in North America, Europe, and Africa <b>B3D-MC-GHAF</b> Effects of LY333334 in Women on Estrogen and Progestin Therapy	Double-blind Randomized Parallel	N = 247 F = 247 36 to 81 years	F w/ low BMD; Minimum of 5 years post-menopausal	Planned: 2 years Actual: up to 17 months Start: May 1997	Placebo; teriparatide: 40 µg sc injection in lower abdomen or lateral thigh once daily	Medically accepted HRT regimen (CEE 0.625 mg / MPA 2.5 mg or other) daily by mouth
12 centers in North America, Europe <b>B3D-MC-GHAH</b> Teriparatide Compared With Alendronate in Women With Osteoporosis	Double-blind Randomized Parallel	N = 146 F = 146 35 to 85 years	F w/ low BMD; Minimum of 5 years post-menopausal	Planned: 2 years Actual: up to 17 months Start: May 1997	Teriparatide: 40 µg sc injection in lower abdomen or lateral thigh once daily	Alendronate sodium 10 mg once daily by mouth

Abbreviations: BMD = bone mineral density; N = number of patients; F = females; sc = subcutaneous; CEE = conjugated equine estrogens; MPA = medroxyprogesterone acetate.

In addition to these long-term studies, one Phase 2 and three Phase 3 clinical studies have been conducted.

- Phase 2 Study GHAA was a double-blind, randomized, placebo-controlled, parallel design study which consisted of 51 postmenopausal women randomized to between 6 and 60 µg/day of teriparatide for 6 weeks. The primary endpoints of the study were serum biochemical markers of bone formation and resorption and spine BMD.
- Three small Phase 3 studies (GHAL; GHAU, and GHAV) enrolled a total of 18 postmenopausal women prior to study termination in December 1998. These women were treated with either placebo, teriparatide 20 µg/day, or teriparatide 40 µg/day. The maximum duration of treatment completed in these studies when they were stopped was less than 4 months, and no efficacy results are available.
- In this document, Studies GHAO and GHAM are considered clinical pharmacology studies.

Because these studies were limited in size and duration, they will not be further discussed in this document other than to note that all Phase 3 study participants were encouraged to participate in the observational, follow-up study, GHBJ. Safety data from all studies was used in the overall safety assessment.

## 5.2. Demographics of Long-Term Phase 3 Clinical Studies

### 5.2.1. Study GHAC

Table 5.3 summarizes the demographic and selected baseline characteristics of the patients at study enrollment. The majority of the patients were Caucasian (98.7%). At baseline, the majority of the patients were nonsmokers (83.0%), used caffeine (84.3%), and many used alcoholic beverages (37.3%). The demographics of the three treatment groups were well balanced at baseline.

**Table 5.3. Baseline Characteristics of Postmenopausal Women B3D-MC-GHAC**

	Placebo	PTH20	PTH40
N	544	541	552
Caucasian (%)	98.9	98.9	98.4
Age (years) <sup>a</sup>	69.0 ± 7.0	69.5 ± 7.1	69.9 ± 6.8
Years postmenopausal <sup>a</sup>	20.9 ± 8.5	21.5 ± 8.7	21.8 ± 8.2
Body mass index (kg/m <sup>2</sup> ) <sup>a</sup>	26.6 ± 4.8	26.7 ± 4.2	26.5 ± 4.2
Prior calcium intake (g/day) <sup>a</sup>	0.76 ± 0.44	0.77 ± 0.44	0.76 ± 0.45
Smokers (% Yes)	18.8	16.5	15.9
Previous osteoporosis therapy (% Yes)	14.9	15.5	13.0
Vertebral fractures <sup>a</sup>	2.3 ± 1.8	2.3 ± 1.8	2.3 ± 1.8
Lumbar spine BMD (g/cm <sup>2</sup> ) <sup>a</sup>	0.82 ± 0.17	0.82 ± 0.17	0.82 ± 0.17

Abbreviations: N = number of patients in treatment group; n = number of patients with vertebral fractures.

<sup>a</sup> Mean ± standard deviation.

### 5.2.2. Study GHAJ

The demographic characteristics (racial origin, age, height, weight, and body mass index ([BMI]) of the patients were not statistically significantly different among the three treatment groups at baseline (Table 5.4). At study entry, the mean age was 58.7 years, the mean weight was 75.7 kg, and most of the patients were Caucasian (99.1%). The treatment groups were comparable at baseline with respect to smoking habits, alcohol use, and caffeine consumption. The treatment groups also were comparable at baseline with respect to type of osteoporosis (idiopathic [51%] or hypogonadal [49%]).

**Table 5.4. Baseline Characteristics of Men with Osteoporosis B3D-MC-GHAJ**

	Placebo	PTH20	PTH40
N	147	151	139
Caucasian (%)	100	98.7	98.6
Age (years) <sup>a</sup>	58.7 ± 12.9	59.3 ± 13.4	58.1 ± 12.7
Osteoporosis type			
Idiopathic (%)	50.3	51.7	51.1
Hypogonadal (%)	49.7	48.3	48.9
Body mass index (kg/m <sup>2</sup> ) <sup>a</sup>	25.2 ± 3.6	25.4 ± 3.7	24.9 ± 3.6
Prior calcium intake (g/day) <sup>a</sup>	0.86 ± 0.57	0.84 ± 0.54	0.80 ± 0.50
Smokers (% Yes)	32.0	29.8	27.3
Previous osteoporosis therapy (% Yes)	11.6	14.6	18.0
Previous nonvertebral fractures (% Yes)	53.7	66.2	56.8
Lumbar spine BMD (g/cm <sup>2</sup> ) <sup>a</sup>	0.85 ± 0.14	0.89 ± 0.15	0.87 ± 0.14

Abbreviations: BMD = bone mineral density; N = number of patients.

<sup>a</sup> Mean ± standard deviation.

### 5.2.3. Study GHAF

For both strata (patients with previous use of HRT and patients with no previous use of HRT), the two therapy groups were not different with respect to baseline demographic characteristics (age, origin, BMI, height, and weight). Other baseline characteristics (dietary calcium intake, years postmenopausal, hysterectomy status, baseline lumbar spine BMD, and previous use of osteoporosis therapies) also did not differ significantly between therapy groups. Patients in the stratum “previous use of HRT” had a slightly higher baseline BMD in the lumbar spine (0.92 g/cm<sup>2</sup>, T-score = -1.76) than patients with “no previous use of HRT” (0.89 g/cm<sup>2</sup>, T-score = -2.00). In addition, all patients in the stratum “previous use of HRT” had previous use of osteoporosis drug, as expected, whereas no patients in the stratum “no previous use of HRT” had previous use of osteoporosis drug. Patients with “previous use of HRT” seemed to be more likely to have undergone a hysterectomy (54.1%) when compared with patients with “no previous use of HRT” (34.4%). The origin of patients appeared to be different between the two strata as well. Almost 88% of the patients with “previous use of HRT” were Caucasian, and approximately 11% were Hispanic, whereas these percentages were approximately 46% and 52%, respectively, for patients with “no previous use of HRT”.

### 5.2.4. Study GHAH

The two therapy groups comprising all randomly assigned patients were not different with respect to baseline demographic characteristics (age, origin, BMI, height, and weight). Other baseline characteristics (dietary calcium intake, years postmenopausal, etc.), except hysterectomy status, also did not differ significantly between therapy groups. Significantly more women in the alendronate group (34.2%) had undergone a hysterectomy than women in the teriparatide 40-μg group (19.2%, (p=0.040)). As there

were no significant differences in any other baseline characteristics, it is unlikely that these findings biased the outcomes of the study.

Most of the randomly assigned patients were Caucasian (82.2%), with the remaining mostly of Hispanic origin (16.4%). The mean age was approximately 65.4 years, and the mean number of years since last menstrual period was approximately 19 years (median = 18 years). A total of 39 (26.7%) patients had previously undergone a hysterectomy, and 17 (43.6%) of those underwent bilateral oophorectomy (surgical menopause). At baseline, only 12 patients (8.2%) had previously used osteoporosis therapy medications.

### **5.2.5. Observational Study GHBJ**

For each subset of patients in the follow-up study (Study GHBJ), the demographic and other baseline characteristics of the patients in the previous Phase 3 study were examined for evidence of enrollment bias. In general, baseline characteristics of the patients were representative of the previous study population and were well balanced across treatment groups.

## **5.3. Study Design of Long-Term Phase 3 Clinical Studies**

### **5.3.1. Study GHAC**

Study GHAC was the pivotal Phase 3 study supporting the indication of treatment of osteoporosis in postmenopausal women. Eligible patients were ambulatory women 30 to 85 years of age who were at least 5 years postmenopausal. The baseline spine radiograph was used to identify prevalent fractures; a minimum of one moderate or two mild atraumatic vertebral fractures was required for enrollment. Hip BMD or lumbar spine BMD measurement was required to be at least 1.0 standard deviation (SD) below the average bone mass for young, healthy women in patients with fewer than two moderate fractures, or in patients previously treated with therapeutic doses of bisphosphonates or fluorides.

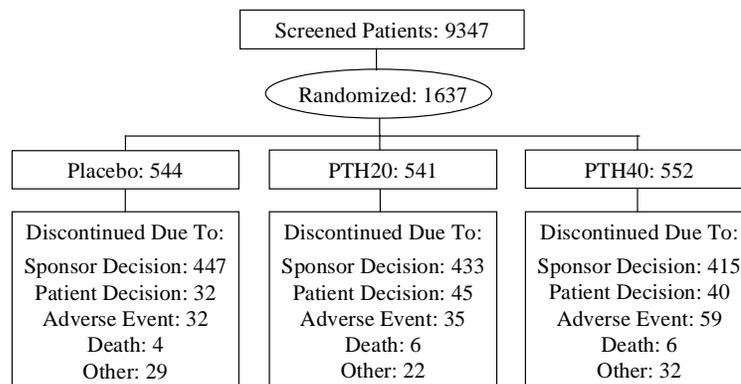
Women were not entered into the study if they had a history of bone disorders other than postmenopausal osteoporosis (for example, Paget's disease), a history of carcinoma in the previous 5 years, impaired hepatic or renal function, a history of nephrolithiasis, or were treated with corticosteroids in the 6 months prior to randomization. Laboratory values for serum calcium, PTH, and urine calcium were to be within normal limits at baseline.

All patients received 1000 mg/day of calcium and at least 400 IU/day of vitamin D for 1 to 6 months before randomization and during the study and demonstrated proficiency with the injection device before randomization. The planned duration of the study was 3 years, with interim analyses at 1 year (safety) and 2 years (safety and efficacy). Because the study was discontinued early, patients' actual treatment duration was up to 2 years, the median time on study drug was 19 months, and the median study duration was 21 months.

Most of the patients completed 18 to 23 months of treatment prior to their study closeout visits. Of the 544 patients randomly assigned to placebo, 384 (70.6%) patients were exposed for 18 to 23 months. Of the 541 patients randomly assigned to the 20- $\mu\text{g}$  group, 375 (69.3%) patients were exposed for 18 to 23 months. Of the 552 patients randomly assigned to the 40- $\mu\text{g}$  group, 362 (65.6%) patients were exposed for 18 to 23 months. Overall, 1121 of the 1637 (68.5%) patients received placebo or teriparatide from 18 to 23 months.

The total patient-year exposure by treatment group for all randomly assigned patients was 798 patient-years in the placebo group, 779 patient-years in the 20- $\mu\text{g}$  group, and 774 patient-years in the 40- $\mu\text{g}$  group.

Figure 5.1 lists the principal reasons for study discontinuation.



**Figure 5.1. Patient Disposition  
B3D-MC-GHAC**

### 5.3.2. Study GHAJ

Study GHAJ was the pivotal Phase 3 efficacy study supporting the indication of treatment of osteoporosis in men. Eligible patients were ambulatory men 30 to 85 years of age with primary osteoporosis (hypogonadal [49%] or idiopathic [51%]), defined by a posterior-anterior lumbar spine BMD or hip BMD measurement at least 2.0 SD below the mean for young, healthy men. Baseline spine radiographs were used to confirm that L-2 to L-4 vertebrae were intact and without artifacts, crush fractures, or other abnormalities that would have interfered with the BMD analysis.

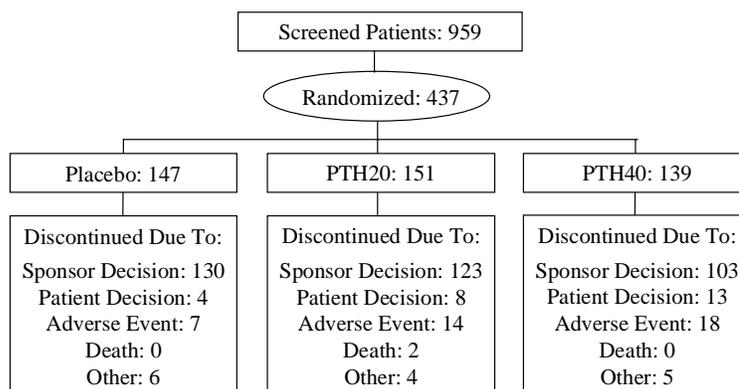
Men were not entered into the study if they had a history of bone disorders other than osteoporosis (for example, Paget's disease), renal osteodystrophy or osteomalacia, a history of carcinoma in the previous 5 years, impaired hepatic or renal function, a history of nephrolithiasis, or were treated with androgens or anabolic steroids in the 6 months prior to randomization.

All patients received 1000 mg/day of calcium and at least 400 IU/day of vitamin D for 1 to 2 months before randomization and during the study and demonstrated proficiency with the injection device before randomization. The planned duration was 2 years, but because the study was terminated early, patients were treated for up to 14 months, and the median study drug exposure was 11 months.

Of the 147 patients randomly assigned to placebo, 114 (77.6%) patients were exposed at least 9 months. Of the 151 patients randomly assigned to the 20- $\mu$ g group, 105 (69.5%) patients were exposed at least 9 months. Of the 139 patients randomly assigned to the 40- $\mu$ g group, 90 (64.7%) patients were exposed at least 9 months. Overall, 145 of the 437 patients (33.2%) received placebo or teriparatide for more than 11 months.

The total patient-year exposure by treatment group for all randomly assigned patients was 126 patient-years in the placebo group, 122 patient-years in the 20- $\mu$ g group, and 107 patient-years in the 40- $\mu$ g group. The 40- $\mu$ g group had a somewhat lower mean drug exposure than the placebo group ( $p=0.014$ ).

Figure 5.2 lists the principal reasons for study discontinuation.



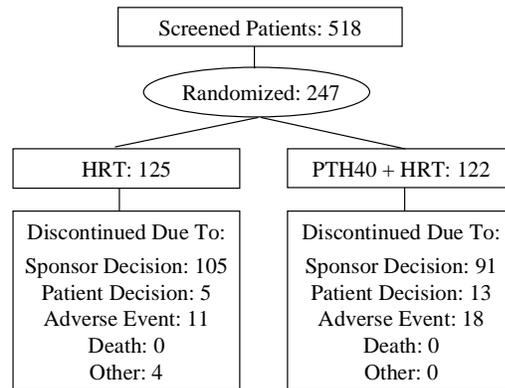
**Figure 5.2. Patient Disposition  
B3D-MC-GHAJ**

### 5.3.3. Study GHAF

Study GHAF was a global, multicenter, Phase 3, double-blind, randomized study in postmenopausal women from 30 to 85 years of age, diagnosed with osteopenia or osteoporosis. The study design called for the creation and analysis of two strata: women treated with systemic HRT for a minimum of 1 year prior to random assignment to study drug, and women not treated with HRT in the year preceding random assignment to study drug. Because the studies were stopped, patients completed up to 17 months of the study (median of 14 months). This study was designed to compare changes in lumbar spine

BMD after treatment with either teriparatide 40 µg/day and HRT plus calcium and vitamin D or HRT plus calcium and vitamin D.

Figure 5.3 provides a summary of the primary reasons for study discontinuation.

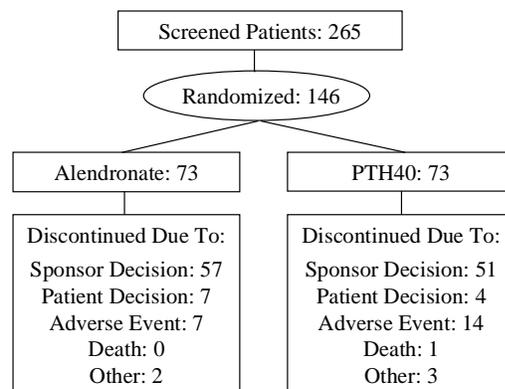


**Figure 5.3. Patient Disposition B3D-MC-GHAF**

#### 5.3.4. Study GHAH

Study GHAH was a global, multicenter, Phase 3, double-blind, randomized study in postmenopausal women 30 to 85 years of age diagnosed with osteoporosis. Because the studies were stopped, patients completed up to 17 months of the study (median of 14 months). This study was designed to compare changes in lumbar spine BMD following treatment with teriparatide 40 µg/day plus calcium and vitamin D compared with alendronate 10 mg/day plus calcium and vitamin D.

Figure 5.4 provides a summary of the primary reasons for study discontinuation.

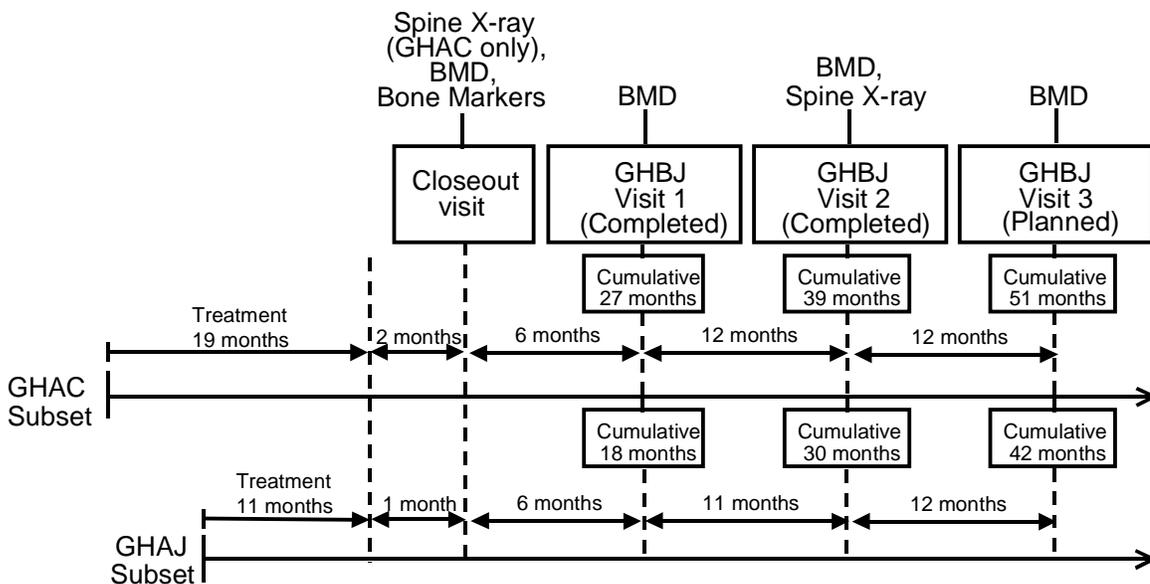


**Figure 5.4. Patient Disposition B3D-MC-GHAF**

### 5.3.5. Observational Study GHBJ

Study GHBJ is an ongoing observational, posttreatment study that has enrolled 1925 women and men who were treated with teriparatide or injectable placebo in any of the long-term, Phase 3 studies (Studies GHAC, GHAF, GHAH, GHAI, GHAL, GHAN, and GHAV). This study is collecting additional safety and efficacy information after the discontinuation of study material, including a systematic assessment of vertebral fractures in women and men. The design of this study accommodates discussions with regulatory agencies and the input of experts in oncology and epidemiology.

Figure 5.5 illustrates the total observation period during Study GHBJ for patients previously enrolled in Studies GHAC and GHAI (GHAC and GHAI subsets, respectively). The initial observation phase of the follow-up study (Visits 1 through 3) will be followed by a 30-month extension phase. This extension phase will result in monitoring of serious adverse events for 5 years after study drug was discontinued in active clinical studies. By the end of year 2005, it is estimated that there will be over 7000 cumulative patient-years of observation in patients who received teriparatide.



All durations are median number of months.

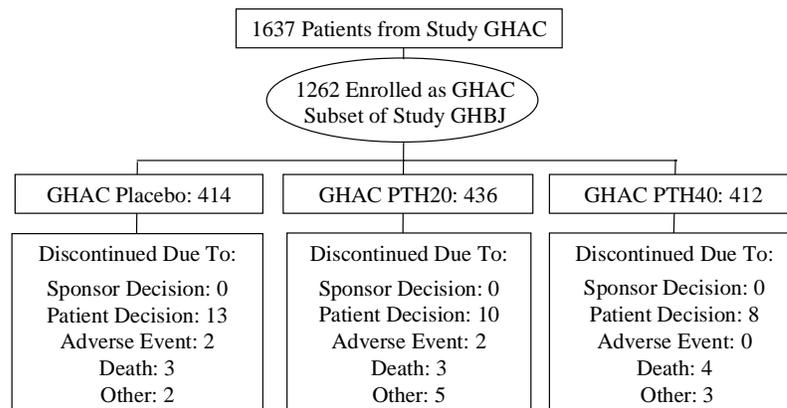
**Figure 5.5. Illustration of Total Observation Period for Patients in GHAC and GHAI Subsets of B3D-MC-GHBJ**

An interim analysis was done after GHBJ Visit 2, a median of 18 months after the previous study closeout visit. This analysis provided over 36 months of data (3981 patient-years) for Study GHAC (Figure 5.4) and over 30 months of data (866 patient-years) for Study GHAI (Figure 5.5). For the subset of patients from

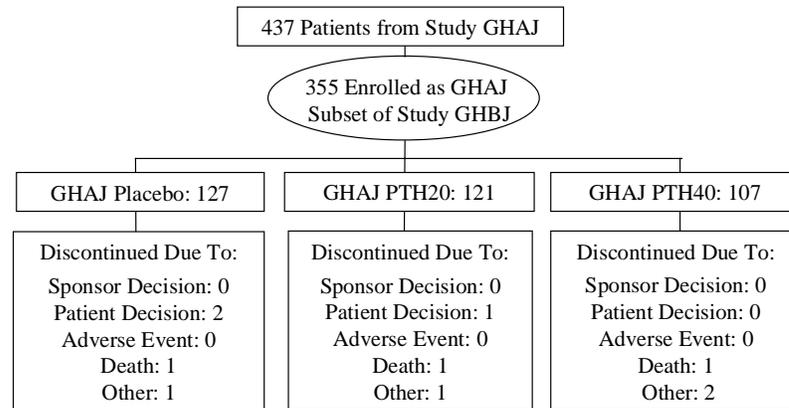
Study GHAF, this analysis included more than 33 months (527 patient-years) of safety observations, and for patients from Study GHAH there were more than 34 months of data (288 patient-years).

Patients in Study GHBJ were provided, at the discretion of their physician, with calcium and vitamin D supplements and also were allowed to take therapies approved for the treatment of osteoporosis. Patients were categorized as “with osteoporosis treatment” if they used any osteoporosis drug for at least 1 day. Approximately 29% of patients previously in the GHAC subset had taken one or more osteoporosis drugs by Visit 1, and 54% of patients in the GHAC subset had taken one or more of these agents by Visit 2. Most patients receiving an osteoporosis therapy were prescribed a bisphosphonate. Notably, at each visit there were no significant differences among treatment groups in the proportion of patients who had taken an approved osteoporosis therapy (not including teriparatide) overall, or within any class of osteoporosis drugs. Therefore, the primary analyses combined all patients, regardless of whether they received another osteoporosis treatment.

For Study GHBJ, the principal reasons for study discontinuation are listed in Figures 5.6 and 5.7 and were similar across treatment groups.



**Figure 5.6. Patient Disposition  
GHAC Subset of B3D-MC-GHBJ**



**Figure 5.7. Patient Disposition  
GHAJ Subset of B3D-MC-GHBJ**

## 6. Effectiveness of Teriparatide

The effectiveness of teriparatide 20 and 40 µg/day was evaluated in Phase 3 studies by assessment of incident vertebral and nonvertebral fractures in postmenopausal women with a prevalent vertebral fracture, and of BMD and biochemical markers of bone metabolism in both postmenopausal women and in men with osteoporosis. This section describes:

- the measures used to assess the effectiveness of teriparatide in the pivotal studies
- the highly significant 65% and 69% reductions in the occurrence of one or more new vertebral fractures (the primary endpoint in Study GHAC), in women treated with teriparatide 20 and 40 µg
- as supportive observations in Study GHAC, the 77% and 86% reductions in the risk of two or more vertebral fractures in women treated with teriparatide 20 and 40 µg, and the 90% and 78% reductions, respectively, in the occurrence of moderately severe or severe vertebral fractures
- as a clinical correlate of vertebral fracture, the significant reduction in the incidence and severity of the adverse event back pain in women treated with teriparatide
- the significant 53% and 54% reductions in the incidence of all nonvertebral fragility fractures in women treated with teriparatide 20 and 40 µg
- the continued significant reductions in the occurrence of one or more new vertebral fractures (40% and 45%), and the sustained benefits in nonvertebral fracture reduction in women during 18 months of follow-up after completion of treatment with teriparatide 20 and 40 µg in Study GHAC
- the clinically relevant, but not statistically significant, 52% and 48% reductions in the risk of one or more incident vertebral fractures in men who were treated with teriparatide 20 and 40 µg in Study GHAJ, and then followed posttreatment for 18 months
- the statistically significant, dose-related increases in lumbar spine and hip BMD and in total body BMC in women treated with teriparatide 20 and 40 µg, with significant changes in lumbar spine BMD as early as 3 months and increases in BMD in 96% of women treated with teriparatide 20 µg
- the statistically significant, dose-related increases in lumbar spine BMD in men treated with teriparatide 20 and 40 µg, with significant increases as early as 3 months and increases in BMD in 93% of men treated with teriparatide 20 µg
- the statistically significant increases in total body BMC and femoral neck BMD in men treated with teriparatide 20 and 40 µg and changes that were similar in

magnitude but that did not achieve statistical significance, for the total hip and other hip subregions

- the supportive study result that teriparatide 40 µg plus HRT increased BMD more than HRT alone regardless of previous use of HRT
- the supportive study result that treatment with teriparatide 40 µg was significantly more efficacious than alendronate 10 mg with respect to increases in lumbar spine and hip BMD
- the evidence that teriparatide rapidly stimulated the formation of normal bone, as shown by increases in biochemical markers of bone formation and resorption, and by the histology and histomorphometry of iliac crest bone biopsies.

## 6.1. Introduction

In this section, results of the clinical studies that have established the efficacy of teriparatide in the treatment of osteoporosis in postmenopausal women and in men are presented. The primary efficacy conclusions are based on the analysis of data from 1637 women in Study GHAC, 437 men in Study GHAJ, and in the subsets of 1262 patients from Study GHAC and 355 patients from Study GHAJ who were enrolled in Study GHBJ. Two additional supporting studies of 393 women, Studies GHAF and GHAH were performed to further evaluate the impact of teriparatide on lumbar spine BMD.

## 6.2. Efficacy Measures in the Studies

The efficacy measures were those required by regulatory guidelines (US FDA 1994; CPMP 1997) to establish teriparatide as an effective agent for the treatment of osteoporosis.

In Study GHAC, the protocol-defined primary efficacy endpoint was the proportion of patients with new vertebral fractures in each treatment group. Fractures were adjudicated by radiologists at a central location who knew the temporal sequence of baseline and endpoint spine radiographs, but not the treatment assignment. Each vertebra was graded as normal (normal height) or as mildly, moderately, or severely deformed (a decrease in height of approximately 20% to 25%, 26% to 40%, or more than 40%, respectively). A new vertebral fracture was reported if a normal vertebra became deformed; worsening of preexisting fractures was not analyzed. The secondary endpoints included the proportion of patients with new nonvertebral fragility fractures, change in lumbar spine, hip, and forearm BMD and in total body bone mineral, changes in biochemical markers of bone formation and resorption, and standing height loss as a clinical correlate of vertebral fracture.

The primary efficacy analysis in Study GHAC included all randomly assigned patients, but new vertebral fracture results were also analyzed for two protocol-defined substudies

(Substudy 1, N = 619 patients; Substudy 2, N = 707 patients). The inferences for each substudy were the same as for the primary analysis.

In Study GHAJ, the protocol-defined primary efficacy endpoint used to establish the effectiveness of teriparatide in men was change in lumbar spine BMD. The secondary endpoints of the study included changes in BMD at the hip and forearm, in total body bone mineral, and in biochemical markers of bone formation and resorption. An efficacy objective of a protocol addendum to the follow-up Study GHBJ was to determine the incidence of vertebral fractures in men who participated in Study GHAJ, and then were followed for approximately 18 months in Study GHBJ. Incident fractures were assessed in the manner described for Study GHAC, using spine radiographs obtained at Study GHAJ baseline (that is, prerandomization to treatment), and at the GHBJ 18-month follow-up visit.

In Study GHAF, a primary efficacy objective of the study was to assess vertebral BMD in postmenopausal women with osteopenia or osteoporosis, who were treated with HRT for at least 1 year preceding randomization, following 18-month treatment with teriparatide 40- $\mu$ g/day given in combination with HRT, calcium, and vitamin D, compared with patients treated with placebo injections in combination with HRT, calcium, and vitamin D.

The other primary efficacy objective of the study was to assess vertebral BMD in postmenopausal women with osteopenia or osteoporosis not treated with HRT in the year preceding randomization following 18-month treatment with teriparatide 40  $\mu$ g/day given in combination with HRT, calcium, and vitamin D, compared with patients treated with placebo injections in combination with HRT, calcium, and vitamin D.

In Study GHAH, the primary objective was to demonstrate a greater increase in vertebral BMD in postmenopausal women with osteoporosis following 2-year treatment with teriparatide 40- $\mu$ g/day plus calcium and vitamin D, compared with patients treated with alendronate 10 mg/day plus calcium and vitamin D.

### **6.3. Efficacy Results**

In the pivotal study of fracture reduction (Study GHAC), postmenopausal women with osteoporosis were treated for up to 2 years; the median treatment duration was 19 months. In the study of men with osteoporosis (Study GHAJ), patients were treated for up to 14 months, with a median treatment duration of 11 months.

Compared with placebo, teriparatide significantly and substantially decreased the incidence of new vertebral fractures and nonvertebral fractures, and increased lumbar spine and hip BMD and total body BMC, as summarized in the following sections.

### 6.3.1. Vertebral Fracture Efficacy

#### Teriparatide Reduced the Risk of Vertebral Fractures in Postmenopausal Women

Study GHAC established that, compared with placebo, each dose of teriparatide was effective in reducing the risk of new vertebral fractures. Treatment with teriparatide 20 and 40 µg resulted in highly significant 65% and 69% reductions in the occurrence of new vertebral fractures (Table 6.1). The two doses were comparable with respect to fracture risk reduction.

**Table 6.1. Effect of Teriparatide on Risk of Vertebral Fracture B3D-MC-GHAC**

	Number of Patients With Fracture (%)			Absolute Risk Reduction		Relative Risk Reduction	
	Placebo N=448	PTH20 N=444	PTH40 N=434	PTH20 (%)	PTH40 (%)	PTH20 (%)	PTH40 (%)
Overall Analysis							
New fractures	64 (14.3)	22 (5.0) <sup>a</sup>	19 (4.4) <sup>a</sup>	9.3	9.9	65	69

Abbreviations: N = number of patients with evaluable baseline and endpoint x-ray films.

<sup>a</sup> Pairwise comparison statistically significant (p<0.001) compared with placebo.

The number of women who would have to be treated (number needed to treat ) in order to prevent at least one new vertebral fracture was calculated. Overall, 11 patients receiving 20 µg and 10 patients receiving 40 µg of teriparatide would need to be treated to prevent a new vertebral fracture.

Additional supportive analyses (Table 6.2) established that treatment with teriparatide 20 and 40 µg resulted in 77% and 86% reductions in the risk of two or more new vertebral fractures, respectively. Each dose of teriparatide also reduced the risk of vertebral fractures classified as moderate or severe.

**Table 6.2. Effect of Teriparatide on Risk of Multiple, Moderately Severe, and Severe Vertebral Fractures B3D-MC-GHAC**

	Number of Patients With Fracture (%)			Absolute Risk Reduction		Relative Risk Reduction	
	Placebo N=448	PTH20 N=444	PTH40 N=434	PTH20 (%)	PTH40 (%)	PTH20 (%)	PTH40 (%)
Overall Analysis							
Multiple new fractures	22 (4.9)	5 (1.1) <sup>a</sup>	3 (0.7) <sup>a</sup>	3.8	4.2	77	86
New moderate or severe fractures	42 (9.4)	4 (0.9) <sup>a</sup>	9 (2.1) <sup>a</sup>	8.5	7.3	90	78
New severe fractures	14 (3.1)	0 (0.0) <sup>a</sup>	3 (0.7) <sup>b</sup>	3.1	2.4	100	77

Abbreviations: N = number of patients with evaluable baseline and endpoint x-ray films.

<sup>a</sup> Pairwise comparison statistically significant ( $p \leq 0.001$ ) compared with placebo; <sup>b</sup> Pairwise comparison statistically significant ( $p = 0.009$ ) compared with placebo.

### **Durability of Reductions in Vertebral Fracture Risk in Women Treated with Teriparatide for a Median of 19 months**

Study GHBJ provided extended follow-up of 77% of all patients randomized in Study GHAC. Patients continued to have a significant reduction in fracture risk after completing treatment with teriparatide. Compared with placebo significantly fewer patients who received teriparatide during Study GHAC had at least one new vertebral fracture between GHAC endpoint and GHBJ Visit 2 (Table 6.3). Both the 40% reduction in the proportion of patients with a minimum of one new vertebral fracture in the 20- $\mu$ g group, and the 45% reduction in the 40- $\mu$ g group were significant. As shown in the table, additional analyses indicated that teriparatide also reduced the incidence of multiple vertebral fractures and moderate or severe vertebral fractures.

**Table 6.3. Effect of Teriparatide on Risk and Severity of Vertebral Fracture from GHAC Endpoint to GHBJ Visit 2**

Proportion of Patients With Fracture (%) from GHAC Endpoint to GHBJ Visit 2							
				Absolute Risk Reduction		Relative Risk Reduction	
	Placebo (N=344)	PTH20 (N=361)	PTH40 (N=338)	PTH20 (%)	PTH40 (%)	PTH20 (%)	PTH40 (%)
New fracture (≥1)	19.5%	11.6% <sup>a</sup>	10.7% <sup>a</sup>	7.9	8.8	40	45
Multiple fractures (≥2)	5.8%	3.6%	2.4% <sup>b</sup>	2.2	3.4	38	59
Moderate or severe fracture (≥1)	10.2%	4.4% <sup>a</sup>	3.0% <sup>a</sup>	5.8	7.2	56	71

Abbreviations: N = number of patients in the GHAC subset with spine x-ray film at GHAC endpoint and GHBJ Visit 2.

<sup>a</sup> Pairwise comparison statistically significant ( $p < 0.01$ ) compared with placebo; <sup>b</sup> Pairwise comparison statistically significant ( $p < 0.05$ ) compared with placebo

After patients discontinued from Study GHAC, investigators chose to administer drugs approved for osteoporosis treatment to some patients. Approximately 29% of patients in the GHAC subset had taken one or more osteoporosis drugs by GHBJ Visit 1, and 54% of patients in the GHAC subset had taken one or more of these agents by GHBJ Visit 2. The patient subgroups with and without osteoporosis drug treatment were found to differ significantly at Study GHAC baseline with respect to weight, BMI, use of osteoporosis drugs prior to randomization in Study GHAC, baseline lumbar spine BMD, proportion of patients with >1 prevalent vertebral fracture at baseline, and vertebral fracture incidence. Considering these differences, the risk of osteoporotic fractures in these subgroups would not be expected to be comparable.

### Favorable Effects on Clinical Correlates of Vertebral Fracture

Teriparatide reduced the incidence of new or worsened back pain reported as an adverse event. There was a significant 26% reduction in spontaneous reports of new or worsened back pain in the 20- $\mu$ g group in Study GHAC, and a 29% reduction in the 40- $\mu$ g group.

Treatment with teriparatide was also associated with a significant reduction in the severity of back pain. These findings were consistent with the reduced incidence and severity of new vertebral fractures observed in women treated with teriparatide.

In Study GHAC, there were no statistically significant differences among treatment groups in change in height at study endpoint, which was analyzed by last observation carried forward (LOCF) and included all patients, even those who discontinued from the study within the first few months after randomization.

For the patients from study GHAC who are followed in Study GHBJ, mean height decreased by 8.0 mm in the placebo group, 6.6 mm in the 20- $\mu$ g group, and 5.6 mm in the 40- $\mu$ g group between GHAC baseline and GHBJ Visit 2. This represented a positive trend towards a difference among treatment groups ( $p = 0.063$ ), and the decreases in height were significantly smaller in the 40- $\mu$ g group, compared with placebo ( $p = 0.019$ ). The

results suggest that treatment with teriparatide may reduce the severity of incident vertebral fractures, as measured by decrease in height.

### Teriparatide Reduced the Incidence of Vertebral Fractures in Men

Radiographs of the spine obtained at baseline in Study GHAJ were repeated at Visit 2 in Study GHBJ, and the films were compared to identify new vertebral fractures. Treatment with teriparatide reduced the proportion of men with incident vertebral fractures (Table 6.4) between GHAJ baseline and GHBJ Visit 2, an interval of approximately 30 months. For the combined teriparatide treatment groups, the risk of new vertebral fractures was reduced by 50% compared with placebo ( $p=0.086$ ). This establishes a positive trend for vertebral fracture risk reduction in males. As shown in Table 6.4, teriparatide also reduced the incidence of moderate or severe vertebral fractures. The men in this study were not required to have a prevalent vertebral fracture at baseline; however, the absolute risk reduction for new fractures was approximately 6% in both treatment groups and compared favorably with data from women in Study GHAC, especially considering the men were treated for 8 months less than the women.

**Table 6.4. Effect of Teriparatide on Risk and Severity of Vertebral Fracture from GHAJ Baseline to GHBJ Visit 2**

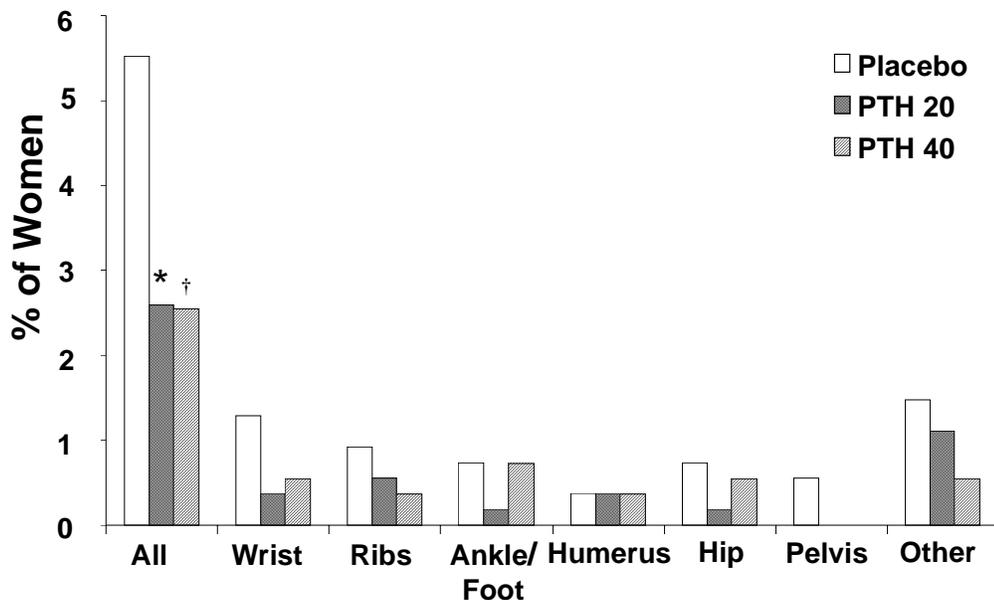
Proportion of Patients With Fracture from GHAJ Baseline to GHBJ Visit 2							
				Absolute Risk Reduction		Relative Risk Reduction	
	Placebo (N=101)	PTH20 (N=87)	PTH40 (N=81)	PTH20	PTH40	PTH20	PTH40
	n (%)	n (%)	n (%)	(%)	(%)	(%)	(%)
New fracture ( $\geq 1$ )	12 (11.9)	5 (5.7)	5 (6.2)	6.2	5.7	52	48
Moderate or severe fracture ( $\geq 1$ )	7 (6.9)	1 (1.1) <sup>a</sup>	1 (1.2) <sup>a</sup>	5.8	5.7	83	82

Abbreviations: N = number of randomized patients; n = number of patients with fracture.

<sup>a</sup> Pairwise comparison showing positive trend ( $p < 0.10$ ) compared with placebo.

### 6.3.2. Nonvertebral Fracture Efficacy

In Study GHAC, information on all nonvertebral fractures was recorded. At the time of study visits, the sites were asked to determine whether the associated trauma would have fractured a normal bone. Teriparatide treatment resulted in 35% and 40% reductions in the risk of any nonvertebral fracture for the 20- and 40- $\mu\text{g}$  groups, respectively, regardless of whether it was associated with excess trauma. When taking into account the investigator's assessment of trauma, treatment with teriparatide reduced the risk of fragility fracture by 53% and 54% in the 20- and 40- $\mu\text{g}$  groups, respectively. While the number of fractures at any specific site was low (Figure 6.1), the incidences of nonvertebral fractures at each site were similar or lower in the teriparatide groups than in placebo group.

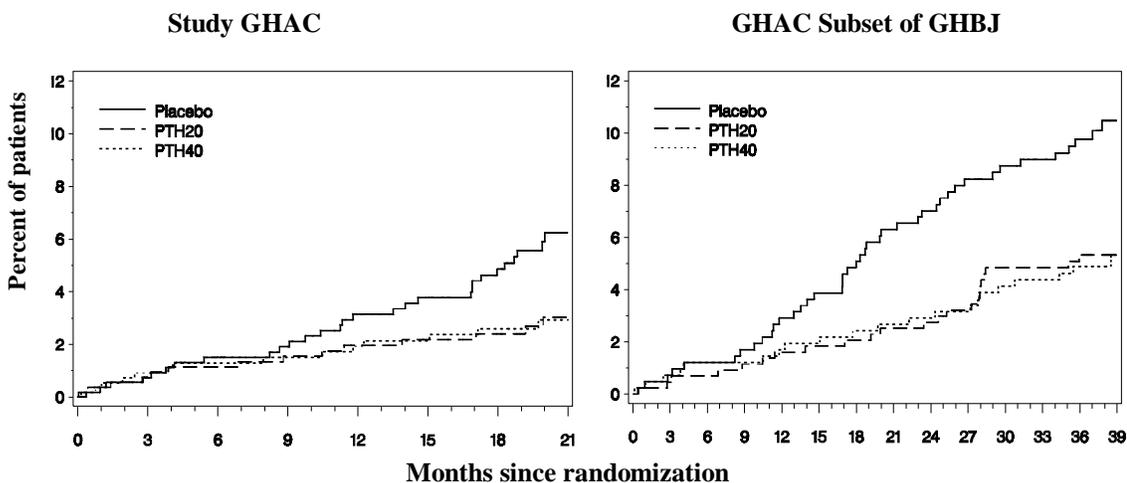


**Figure 6.1. Percent of Patients with New Nonvertebral Fragility Fractures  
All Randomly Assigned Patients  
B3D-MC-GHAC**

\*Pairwise comparison statistically significant ( $p=0.015$ ) compared with placebo; †Pairwise comparison statistically significant ( $p=0.012$ ) compared with placebo.

A significant reduction in nonvertebral fracture risk continued after treatment with teriparatide was stopped. For the combination of treatment for up to 2 years in Study GHAC and 6-months of observational follow-up (GHB Visit 1), the risk of nonvertebral fragility fracture was reduced by 62% and 63% in the 20- and 40- $\mu\text{g}$  groups, respectively. For the combination of treatment for up to 2 years in Study GHAC and 18-months of observational follow-up, the risk of nonvertebral fragility fracture was reduced by 48% for the 20- $\mu\text{g}$  dose and 52% for the 40- $\mu\text{g}$  dose of teriparatide.

Kaplan-Meier plots (Figure 6.2) of time to first nonvertebral fragility fracture in Study GHAC and in the GHAC subset of patients followed in Study GHBJ demonstrated that: 1) teriparatide treatment did not result in increased skeletal fragility at any time, 2) there is evidence for separation of the incidence curves at less than 1 year, and 3) the benefit is durable for at least 18 months after cessation of treatment (the median duration of treatment in study GHAC was 19 months).



**Figure 6.2. Percent of Patients with Nonvertebral Fragility Fractures B3D-MC-GHAC and GHAC Subset of B3D-MC-GHBJ**

The number of patients with nonvertebral fractures in Study GHAJ was too small (3 patients in the placebo group, 2 patients in the 20- $\mu$ g group and 1 patient in the 40- $\mu$ g group) for meaningful analysis.

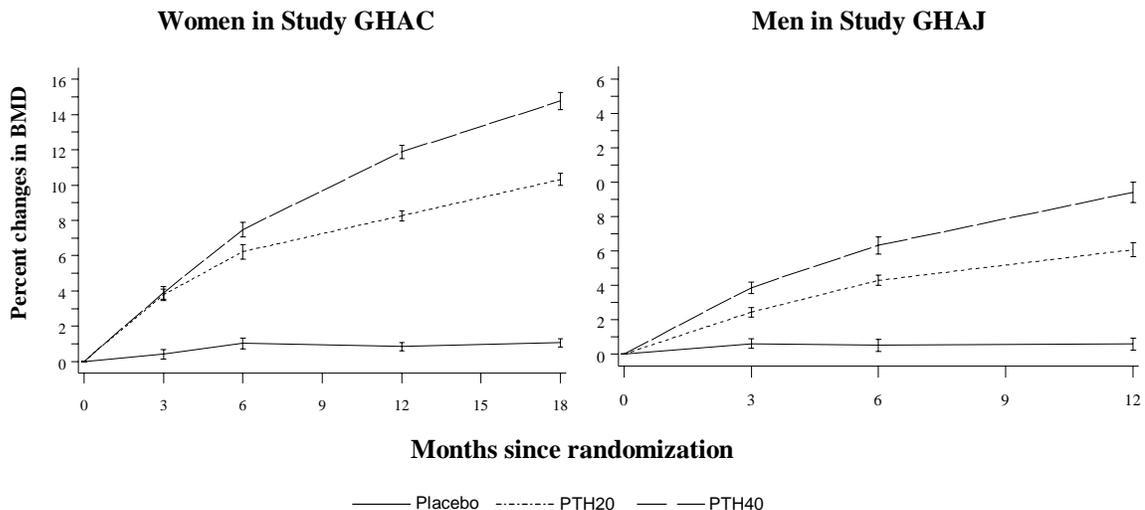
### **6.3.3. Bone Mass**

#### **Teriparatide Increased BMD in Postmenopausal Women and in Men**

In postmenopausal women (Study GHAC), treatment with teriparatide 20 or 40  $\mu$ g for up to 2 years produced statistically significant, dose-related increases in lumbar spine, total hip, and hip subregion BMD, and in total body BMC, but not in radius BMD (Table 6.5). Men with osteoporosis (Study GHAJ) treated with these doses of teriparatide for up to 14 months had significant, dose-related increases in lumbar spine BMD compared with placebo (Table 6.6). In men this duration of treatment with teriparatide 20 or 40  $\mu$ g significantly increased BMD at the femoral neck and total body bone mineral. The 40- $\mu$ g dose also produced statistically significant increases in BMD at the total hip and intertrochanter region, compared with placebo.

Only 3 months of treatment were needed to demonstrate significant increases in lumbar spine BMD in postmenopausal women and in men (Figure 6.3). The magnitude of the

vertebral BMD response in women was the same in both teriparatide treatment groups at 3 months. Thereafter, significantly greater increases in BMD were seen in the 40- $\mu$ g group, which was consistent with the BMD dose-response relationship previously reported for teriparatide administered with concomitant HRT (Hodsman et al. 1997; Lindsay et al. 1997) and observed in men in Study GHAJ. Although there was a greater increase in BMD in the 40- $\mu$ g group, there was no clinical difference in fracture efficacy between the two doses of teriparatide. Our results confirm that teriparatide is efficacious as a monotherapy for increasing bone density at the spine, hip, and total body.



**Figure 6.3. Time Course of Percent Changes in Lumbar Spine (L-1 Through L-4) BMD Observed Cases in Women and Men All Randomly Assigned Patients B3D-MC-GHAC and B3D-MC-GHAJ**

Statistically significant increases in BMD compared with placebo were found at all skeletal sites evaluated in Study GHAC except at the radius. The density of the distal radius did not differ significantly among the three treatment groups. At the midshaft (distal 1/3) radius, no significant change versus placebo was observed in BMD for the 20- $\mu$ g group. A small decrease in BMD was observed at the midshaft radius in the 40- $\mu$ g group. This change was statistically significant, compared with placebo, and was consistent with published data from a smaller study for a similar dose of teriparatide (Neer et al. 1993).

Although BMD at the radial midshaft decreased during the first year of treatment in Study GHAC compared with placebo (significant for the 40- $\mu$ g dose only), there was no evidence of increased fragility at the site. A pilot study conducted in a subset of patients in Study GHAC indicated that peripheral quantitative computed tomography (pQCT) provided additional information, not reflected in the dual energy x-ray absorptiometry (DXA) measurements, about therapeutic effects of teriparatide on the distal radius. In

these patients, the BMD and mineral content of the radius measured by pQCT was consistent with the DXA bone densitometry results. However, analysis of the cross-sectional geometry of the distal radius by pQCT suggested that teriparatide has favorable effects which are predictive of increased bone strength (Ferretti et al. 1996). The numerically lower incidence of wrist fractures in the teriparatide treatment groups compared with placebo, as well as the improvements in cross-sectional geometry on pQCT, suggest that the changes in BMD observed on DXA are not indicative of an adverse effect of teriparatide on cortical bone. This position is further strengthened by an analysis of time to first distal radius fracture in the GHAC subset Study GHBJ, which shows that at no time is there increased fragility of the distal radius compared with placebo.

**Table 6.5. Measurements of BMD<sup>a</sup> and Total Body Bone Mineral in Women  
B3D-MC-GHAC**

PTH(1-34) (µg per day)	Baseline (mean ± SD)			Percent Change at Endpoint (mean ± SD)					
	Placebo	PTH20	PTH40	N	Placebo	N	PTH20	N	PTH40
Lumbar spine (mg/cm <sup>2</sup> )	820 ± 170	820 ± 170	820 ± 170	504	1.1 ± 5.5	498	9.7 ± 7.4 <sup>b</sup>	497	13.7 ± 9.7 <sup>b</sup>
Femoral neck (mg/cm <sup>2</sup> )	640 ± 110	640 ± 110	640 ± 110	479	-0.7 ± 5.4	479	2.8 ± 5.7 <sup>b</sup>	482	5.1 ± 6.7 <sup>b</sup>
Trochanter (mg/cm <sup>2</sup> )	570 ± 120	570 ± 120	570 ± 120	479	-0.2 ± 6.3	479	3.5 ± 6.8 <sup>b</sup>	482	4.4 ± 7.5 <sup>b</sup>
Intertrochanter (mg/cm <sup>2</sup> )	860 ± 160	850 ± 160	850 ± 140	257	-1.3 ± 4.5	250	2.6 ± 5.5 <sup>b</sup>	254	4.0 ± 6.0 <sup>b</sup>
Total hip (mg/cm <sup>2</sup> )	710 ± 120	700 ± 120	700 ± 110	230	-1.0 ± 4.3	222	2.6 ± 4.9 <sup>b</sup>	232	3.6 ± 5.4 <sup>b</sup>
Distal radius (g/cm <sup>2</sup> )	0.32 ± 0.08	0.31 ± 0.07	0.32 ± 0.07	154	-1.6 ± 8.3	152	-0.1 ± 7.2	145	-1.5 ± 8.4
Radius shaft (g/cm <sup>2</sup> )	0.58 ± 0.11	0.58 ± 0.10	0.59 ± 0.11	154	-1.3 ± 3.3	152	-2.1 ± 4.2	145	-3.2 ± 4.5 <sup>b</sup>
Total body bone mineral (g)	1373 ± 305	1351 ± 289	1401 ± 288	140	-0.7 ± 5.6	134	1.9 ± 5.6 <sup>b</sup>	131	2.8 ± 5.5 <sup>b</sup>

**Table 6.6. Measurements of BMD<sup>a</sup> and Total Body Bone Mineral in Men  
B3D-MC-GHAJ**

PTH(1-34) (µg per day)	Baseline (mean ± SD)			Percent Change at Endpoint (mean ± SD)					
	Placebo	PTH20	PTH40	N	Placebo	N	PTH20	N	PTH40
Lumbar spine (g/cm <sup>2</sup> )	0.85 ± 0.14	0.89 ± 0.15	0.87 ± 0.14	143	0.52 ± 3.90	141	5.87 ± 4.50 <sup>b</sup>	129	9.03 ± 6.46 <sup>b</sup>
Femoral neck (g/cm <sup>2</sup> )	0.70 ± 0.11	0.71 ± 0.10	0.70 ± 0.11	137	0.31 ± 4.11	135	1.53 ± 3.95 <sup>c</sup>	125	2.93 ± 6.34 <sup>b</sup>
Trochanter (g/cm <sup>2</sup> )	0.65 ± 0.11	0.66 ± 0.10	0.65 ± 0.12	137	1.09 ± 3.30	136	1.33 ± 4.15	125	2.08 ± 5.32
Intertrochanter (g/cm <sup>2</sup> )	0.96 ± 0.13	0.98 ± 0.13	0.97 ± 0.14	137	0.61 ± 2.87	136	1.18 ± 3.09	125	2.34 ± 4.41 <sup>b</sup>
Total hip (g/cm <sup>2</sup> )	0.83 ± 0.11	0.84 ± 0.10	0.83 ± 0.11	137	0.54 ± 2.70	135	1.17 ± 2.94	125	2.33 ± 4.41 <sup>b</sup>
Distal radius (g/cm <sup>2</sup> )	0.43 ± 0.06	0.44 ± 0.07	0.43 ± 0.06	93	-0.29 ± 3.17	89	-0.48 ± 3.21	85	0.22 ± 5.82
Radius shaft (g/cm <sup>2</sup> )	0.78 ± 0.12	0.78 ± 0.12	0.77 ± 0.11	93	-0.15 ± 1.87	89	-0.46 ± 2.39	85	-0.56 ± 2.36
Total body bone mineral (g)	2415 ± 350	2463 ± 368	2396 ± 357	87	-0.45 ± 2.75	84	0.64 ± 3.65 <sup>c</sup>	83	0.87 ± 3.65 <sup>c</sup>

Abbreviations: SD = standard deviation; N = Number of patients.

<sup>a</sup> Results for standardized BMDs are presented as mg/cm<sup>2</sup>, and for nonstandardized BMDs as g/cm<sup>2</sup>; <sup>b</sup> Pairwise comparison statistically significant (p<0.001) compared with placebo; <sup>c</sup> Pairwise comparison statistically significant (p<0.05) compared with placebo.

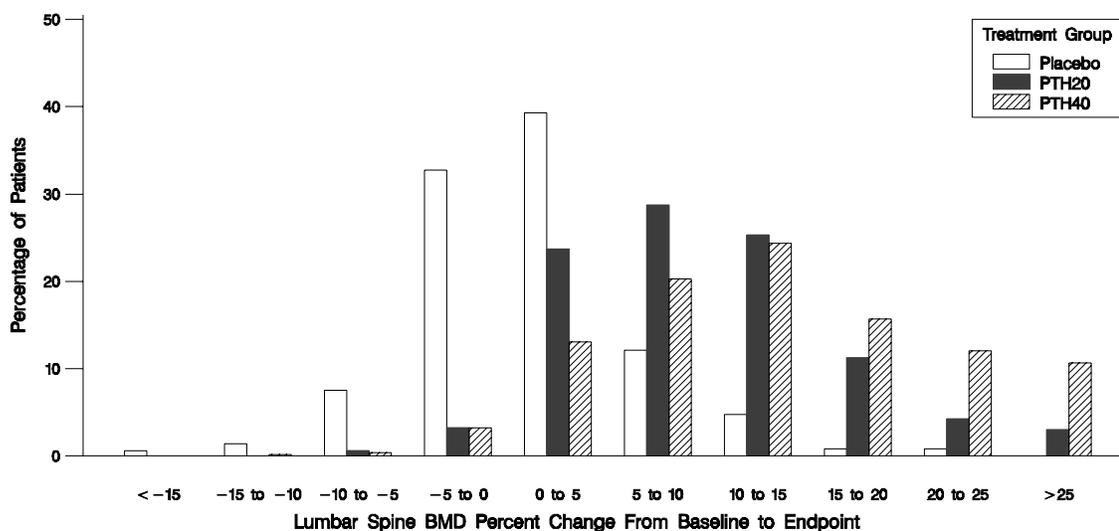
## Patient Characteristics and Lumbar Spine BMD Response

In women treated with teriparatide 20- $\mu$ g, baseline lumbar spine BMD was not a significant predictor of change in BMD. In contrast, men having higher baseline lumbar spine BMD values were more likely to have a greater change in BMD.

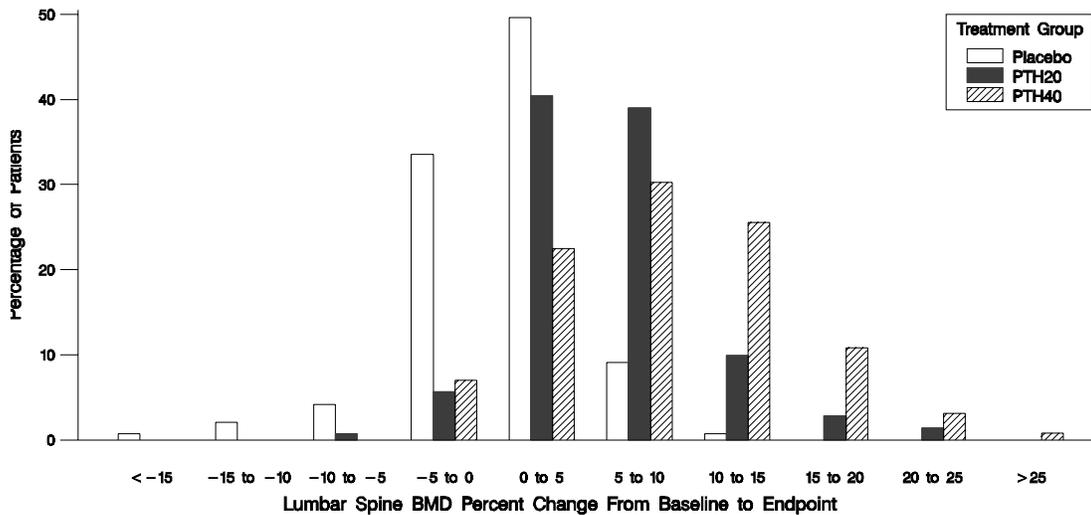
Lumbar spine BMD response to teriparatide was not related to 1) baseline serum 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, or testosterone, 2) body weight or BMI, alcohol consumption, or cigarette smoking, 3) site of injection (abdominal wall or thigh), or 4) number of previous vertebral or nonvertebral fractures (in women, insufficient data for men).

In Study GHAC, an increase in lumbar spine BMD occurred in 96% of patients treated with either teriparatide 20 or 40  $\mu$ g, compared with 58% of patients in the placebo group who took only calcium and vitamin D (Figure 6.4). At endpoint, a 10% or more increase in lumbar spine BMD was observed in approximately 44% of those in the 20- $\mu$ g group and in 63% of those in the 40- $\mu$ g group, but rarely in the placebo group (6%). In Study GHAJ, an increase in lumbar spine BMD occurred in 93% of men treated with teriparatide 20 or 40  $\mu$ g. At least a 10% increase in lumbar spine BMD was seen at endpoint in 15% of patients in the 20- $\mu$ g group and in 41% of patients in the 40- $\mu$ g group ( $p < 0.001$  compared with placebo, Figure 6.5).

The therapeutic effect of teriparatide was greater in patients with higher baseline concentrations of serum BSAP and urinary NTX. These findings suggest that the anabolic effect of teriparatide is enhanced in patients who already have a high rate of bone turnover at initiation of treatment.



**Figure 6.4. Categories of Total Lumbar Spine (L-1 - L-4) BMD Percent Change from Baseline to Endpoint B3D-MC-GHAC**

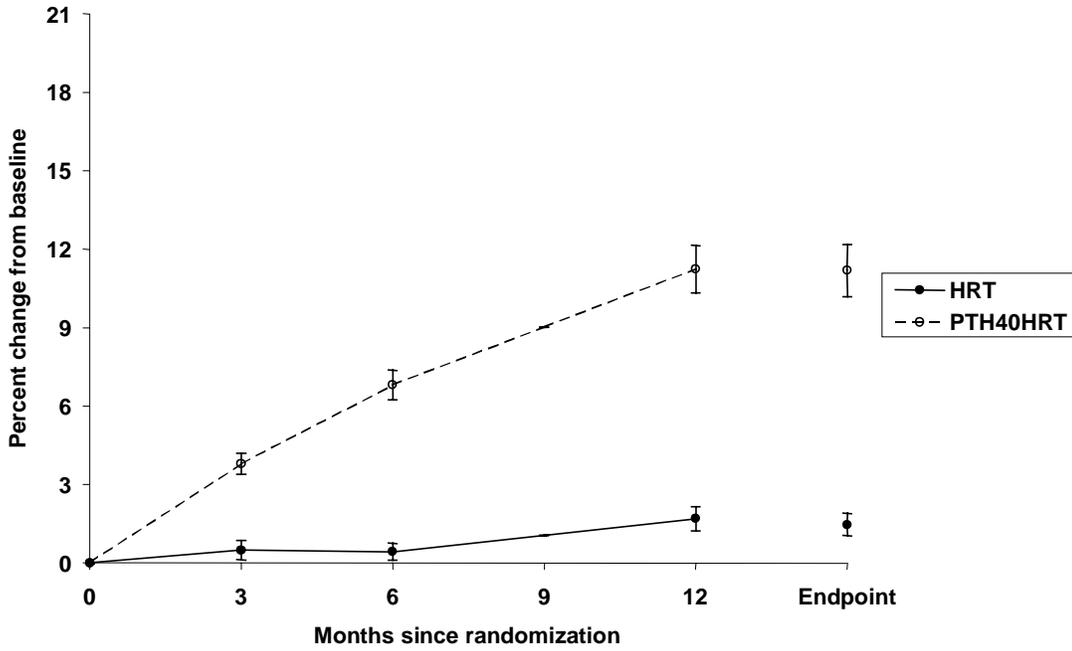


**Figure 6.5. Categories of Total Lumbar Spine (L-1 - L-4) BMD Percent Change from Baseline to Endpoint B3D-MC-GHAJ**

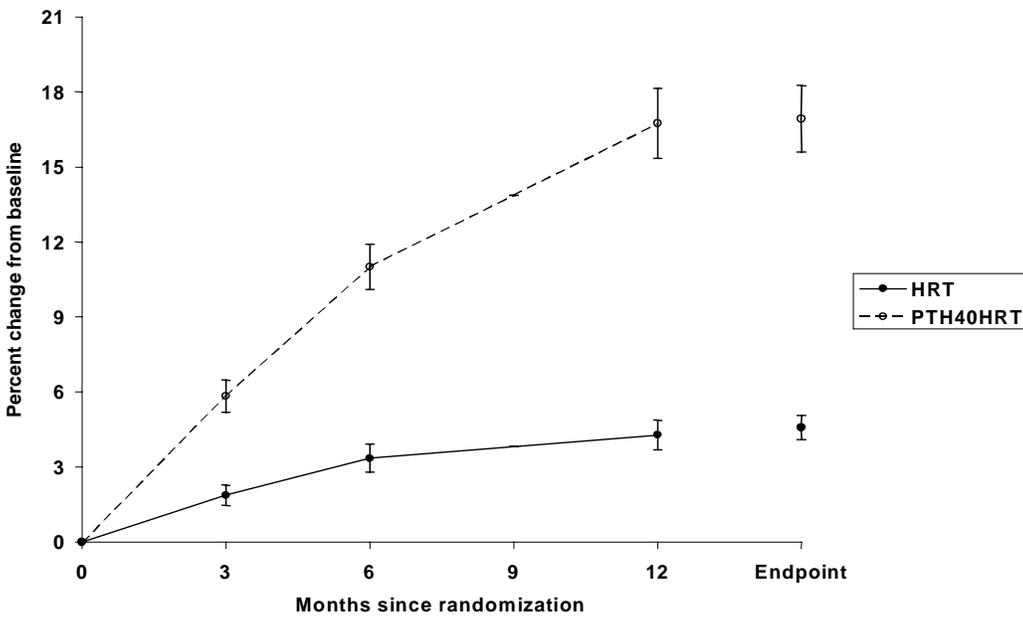
### **Teriparatide Plus HRT Increased BMD More than HRT Alone, Regardless of Previous Use of HRT**

In women treated with systemic HRT for a minimum of 1 year prior to random assignment to study drug (“previous use of HRT”), the patients in the 40- $\mu$ g plus HRT group had significant increases in lumbar spine BMD of approximately 11% at endpoint, and in hip (femoral neck) BMD of approximately 3% at study endpoint. These increases were statistically significant compared with the approximately 1.5% mean increase in lumbar spine BMD at endpoint and no change in mean hip (femoral neck) BMD at endpoint observed in the HRT group. Figure 6.6 shows BMD change by visit, using the observed data at each visit, as well as change at endpoint.

In women not treated with HRT in the year preceding random assignment to study drug (“no previous use of HRT”), the patients in the 40- $\mu$ g plus HRT group had significant increases in lumbar spine BMD of approximately 17% at endpoint, and in hip (femoral neck) BMD of approximately 7% at study endpoint. These increases were statistically significant in comparison to the approximately 5% mean increase in lumbar spine BMD at endpoint, and 3% increase in hip (femoral neck) BMD at endpoint observed in the HRT group. Figure 6.8. shows BMD change by visit, using the observed data at each visit, as well as change at endpoint.



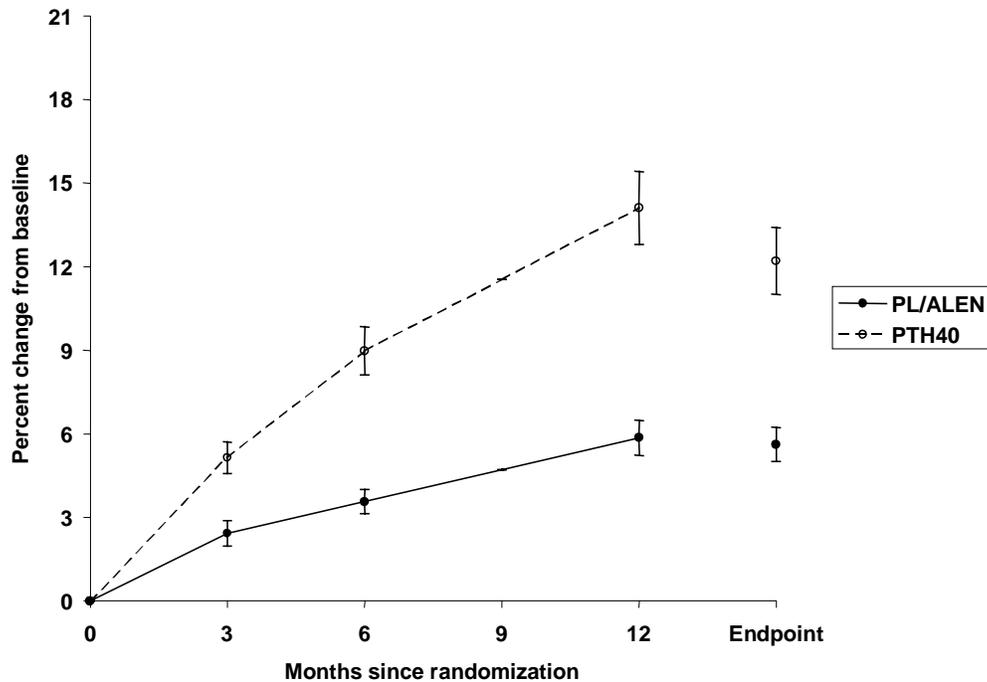
**Figure 6.6.** Lumbar Spine BMD - Mean Percent Change From Baseline Endpoint and Observed Cases By Visit  
All Randomly Assigned Patients – Previous Use of HRT  
B3D-MC-GHAF



**Figure 6.7.** Lumbar Spine BMD - Mean Percent Change From Baseline Endpoint and Observed Cases By Visit  
All Randomly Assigned Patients – No Previous Use of HRT  
B3D-MC-GHAF

### Teriparatide 40 µg/day Increased Lumbar Spine and Hip BMD More Than Alendronate 10 mg/day

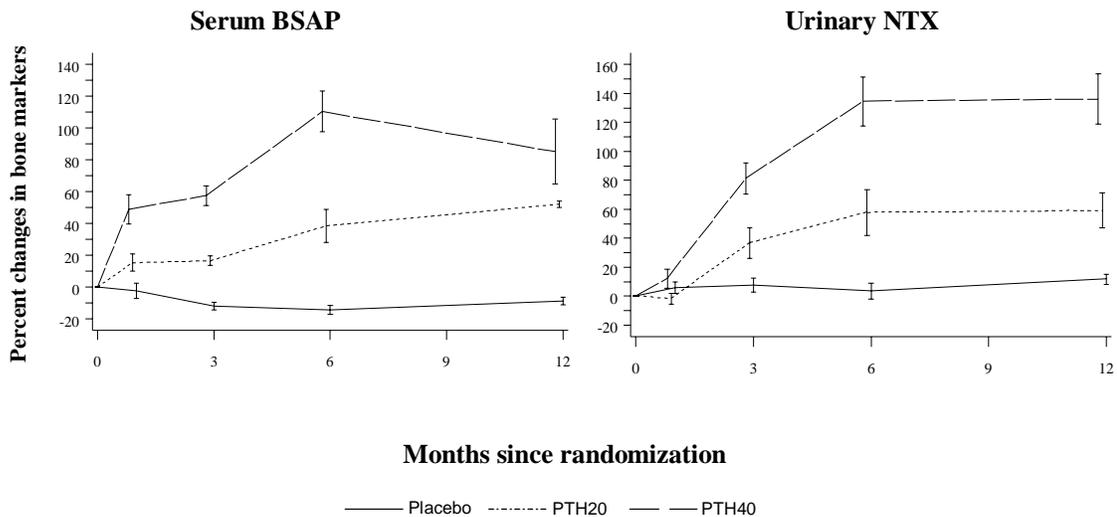
Patients in the 40-µg group in Study GHAH had significant increases in lumbar spine BMD of approximately 12% at endpoint, and in femoral neck BMD of approximately 5% at study endpoint. These increases were significantly greater than the significant increases in lumbar spine and femoral neck BMD (approximately 6% and 2%, respectively) observed at endpoint in the alendronate-treated patients. Figure 6.8 shows BMD change by visit, using the observed data at each visit, as well as change at endpoint.



**Figure 6.8. Lumbar Spine BMD - Mean Percent Change From Baseline Endpoint and Observed Cases By Visit  
All Randomly Assigned Patients  
B3D-MC-GHAH**

#### 6.3.4. Bone Markers

Administration of teriparatide 20 or 40 µg to postmenopausal women and to men with osteoporosis in placebo-controlled studies (Studies GHAJ and GHAC, respectively) rapidly stimulated bone formation as shown by early increases in the markers of bone formation, BSAP (Figure 6.9) and PICP. The increases in formation markers were accompanied by secondary increases in the markers of bone resorption, urinary NTX (Figure 6.10) and DPD, consistent with the physiological coupling of bone formation and resorption in skeletal remodeling. Changes in BSAP, NTX, and DPD were 25% to 50% lower in men than in women, possibly because of lower systemic exposure to teriparatide in men.



**Figure 6.9. Time Course of Percent Changes in Serum BSAP and Urinary NTX in Postmenopausal Women Observed Cases at Each Visit All Randomly Assigned Patients with Bone Marker Assessments B3D-MC-GHAC**

Serum PICP concentrations had declined to near-baseline values after 1 year of treatment in Studies GHAC and GHAI, but at endpoint in Study GHAC serum BSAP concentrations remained significantly increased, compared with placebo. At GHB Visit 1, or about 6 months after treatment was stopped, serum BSAP concentrations had returned to Study GHAC baseline concentrations in both the 20- and 40- $\mu$ g groups. The return of the concentrations of these surrogate markers of bone formation to baseline by GHB Visit 1 was consistent with resolution of the anabolic effect of teriparatide on bone after withdrawal of treatment.

The concentration of serum NTX in the teriparatide groups at Study GHAC endpoint was significantly higher than placebo, which was consistent with a treatment-related increase in bone resorption. In contrast, at GHB Visit 1 there was no statistically significant difference among treatment groups in serum-NTX concentration. These changes suggest that the pharmacologic effects of teriparatide treatment on bone remodeling and biochemical markers had resolved by the time of this follow-up visit.

### 6.3.5. Bone Quality

Histomorphometric findings from iliac crest biopsies of women with osteoporosis treated with teriparatide for up to 2 years indicated that teriparatide-treated women had increased trabecular bone volume, wall width, mean orthogonal intercept length, and mineral apposition rate. No significant histological safety concerns (such as woven bone,

osteomalacia, or marrow fibrosis) were identified in the 19 evaluable bone biopsy samples obtained after 1 year of treatment, or in the evaluable 36 samples obtained at endpoint. No adverse effects were observed in the treatment groups. There appeared to be a transient increase at 12 months in cortical and trabecular remodeling in the 40- $\mu$ g group that was not present in the 20- $\mu$ g group, or in either group at the final study visit. There was no evidence of excessive osteoblast stimulation in either the 20 or 40  $\mu$ g group at 12 months or at endpoint.

#### **6.4. Efficacy Conclusions**

Overall, the benefits of teriparatide on the skeleton have been demonstrated by large-scale clinical studies conducted in postmenopausal women and in men. Teriparatide demonstrated rapid increases in BMD and highly significant fracture efficacy. Treatment for up to 2 years with teriparatide significantly reduced the risk of new vertebral and nonvertebral fractures and rapidly increased vertebral and hip BMD. Teriparatide also reduced height loss and back pain, representing clinical correlates of vertebral fractures.

## 7. Clinical Safety

Treatment with teriparatide was safe and well tolerated. There were no serious adverse effects, and mortality was not increased in patients treated with teriparatide. All the adverse effects were mild and resolved upon discontinuation of treatment. This section of the briefing document summarizes the following points:

- The teriparatide and placebo groups did not differ significantly with respect to mortality or the number of patients reporting a serious adverse event (SAE). There was no apparent relationship of teriparatide use to any patient death.
- No primary skeletal malignancies or osteosarcomas have occurred in patients treated with teriparatide, and the incidence of carcinoma in these patients was lower than in patients treated with placebo.
- The adverse events nausea, headache, and leg cramps were considered treatment related, and were infrequent and mild.
- The serum calcium concentration increased transiently in patients treated with teriparatide, but typically remained within the normal range. The increase began approximately 2 hours after dosing and reached a peak concentration between 4 to 6 hours after dosing. The serum calcium concentration began to decline approximately 6 hours after dosing and returned to baseline by 16 to 24 hours after each dose.
- Treatment with teriparatide did not affect renal function or the incidence of symptoms possibly related to urolithiasis, but produced small increases in 24-hour urinary calcium excretion during the first 3 to 6 months of treatment.
- Treatment with teriparatide increased serum uric acid, but this rarely produced hyperuricemia and was not associated with gout.
- Antibodies to teriparatide detected in a small proportion of women after up to 2 years of treatment did not produce hypocalcemia, reduce BMD response, or affect the incidence of adverse events.
- Adverse effects often associated with hyperparathyroidism, such as hypertension, atherosclerotic cardiovascular disease, and peptic ulcer disease, were observed at similar frequency across both teriparatide and placebo treatment groups.
- Transient symptomatic orthostatic hypotension was observed in a Phase 1 study in 1 subject treated with teriparatide 20 µg. Isolated episodes occurred at higher doses, but did not preclude continued treatment. Although it was not a clinically significant finding in Phase 3 studies, orthostatic hypotension is considered a treatment-related effect that might occur early in the course of treatment.
- Teriparatide did not adversely affect cardiac repolarization as determined by the QTc.

## 7.1. Introduction

The primary safety database consisted of data from the pivotal fracture prevention study, Study GHAC. Safety data from the pivotal study of osteoporosis in men, Study GHAJ, and from the safety follow-up study GHBJ, were considered supportive data. Data for deaths, SAEs, and treatment-emergent adverse events (TESS events) from the four large Phase 3 studies (Studies GHAC, GHAF, GHAH, and GHAJ) were tabulated, but no other integration of databases from individual studies was planned because of between-study differences in study length, control groups, doses of teriparatide administered, and number of patients enrolled.

In this section, information from the single-dose and short-term repeated dose clinical pharmacology studies has been integrated with the results of Phase 3 studies. In contrast to the Phase 3 studies, clinical pharmacology research staff administered the majority of teriparatide doses in an inpatient setting. As a result, the serum teriparatide concentrations and effects on parameters such as serum calcium, blood pressure, and the ECG could be carefully evaluated.

## 7.2. Discontinuations Due to Adverse Events

The reasons for study discontinuation for patients in Studies GHAC and GHAJ are summarized in the Patient Disposition figures (Section 5, Figures 5.1 and 5.2, respectively). In these placebo-controlled studies, early discontinuation due to adverse event occurred in 5.6% of patients in the placebo group, 7.1% of patients in the 20- $\mu$ g group, and 11.1% of patients in the 40- $\mu$ g group. In both studies, nausea resulted in discontinuation by significantly more patients in the 40- $\mu$ g group than in patients treated with placebo. No events caused discontinuation significantly more often in the 20- $\mu$ g group, compared with placebo. The results of the other supportive Phase 2 and Phase 3 studies were consistent with these data.

## 7.3. Deaths and Serious Adverse Events

### 7.3.1. Deaths

While participating in the studies, a total of 20 deaths are known to have occurred among the 2467 patients who enrolled in the following five Phase 3 studies: GHAC, GHAF, GHAH, GHAJ, and GHAL (Table 7.1). Of these, a total of 16 (1.0% of 1637) patients died while participating in Study GHAC. There was no significant difference in the number of deaths among treatment groups, with 4 (0.7% of 544) deaths in the placebo group, 6 (1.1% of 541) deaths in the 20- $\mu$ g group, and 6 (1.1% of 552) deaths in the 40- $\mu$ g group. Two (0.5% of 437) patients in the 20- $\mu$ g group died while participating in Study GHAJ, and there was no significant difference in the number of deaths among treatment groups. One patient died in Study GHAL in the 40- $\mu$ g group and another patient died in Study GHAH in the 40- $\mu$ g group. None of the deaths was causally related to study drug or study conditions as assessed by the investigators. Review of individual

event classifications and patient summaries did not reveal any trends in the cause of death.

**Table 7.1. Listing of Deaths During Participation in Teriparatide Studies  
B3D-MC-GHAC, B3D-MC-GHAF, B3D-MC-GHAH,  
B3D-MC-GHAJ, and B3D-MC-GHAL**

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

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

Between the end of the Phase 3 studies and 4 June 2001, an additional 27 deaths were reported for patients who had participated in any teriparatide trial (Table 7.2).

**Table 7.2. Listing of Deaths After Participation in Teriparatide Studies and Reported Prior to 4 June 2001  
B3D-MC-GHAC, B3D-MC-GHAF, B3D-MC-GHAH,  
B3D-MC-GHAJ, and B3D-MC-GHAL**

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

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

As of 4 June 2001, a total of 47 deaths are known to have occurred among patients who enrolled in Phase 3 studies (Table 7.3). There was no significant difference in the number of deaths among treatment groups, with 13 (1.9% of 691) deaths in the placebo group, 17 (2.5% of 692) deaths in the 20- $\mu$ g group, and 17 (1.9% of 886) deaths in the 40- $\mu$ g group. For the combined Phase 3 treatment studies, additional analyses showed no significant differences among treatment groups in mortality attributable to coronary artery disease or cancer.

**Table 7.3. Summary of Deaths of Patients Who Previously Participated in LY333334 Studies Reported Prior to 4 June 2001**  
**B3D-MC-GHAC, B3D-MC-GHAF, B3D-MC-GHAH, B3D-MC-GHAJ, and B3D-MC-GHAL**

	Placebo	PTH20	PTH40	HRT	Alendronate
Study	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
GHAC	12/544 (2.2)	14/541 (2.6)	14/552 (2.5)	—	—
GHAJ	1/147 (0.7)	3/151 (2.0)	1/139 (0.7)	—	—
GHAF	—	—	0/122 (0.0)	0/125 (0.0)	—
GHAH	—	—	1/73 (1.4)	—	0/73 (0.0)
GHAL <sup>a</sup>	—	—	1/6 (16.7)	—	—
Total	13/691 (1.9)	17/692 (2.5)	17/886 <sup>a</sup> (1.9)	0/125 (0.0)	0/73 (0.0)
Placebo- Controlled <sup>b</sup>	13/691 (1.9)	17/692 (2.5)	15/691 (2.2)	—	—

Abbreviations: n = number of deaths; N = number enrolled.

<sup>a</sup> The 6 patients in Study B3D-MC-GHAL were previously enrolled in Study B3D-MC-GHAC; therefore, they were not included in the total.

<sup>b</sup> Placebo-controlled trials are B3D-MC-GHAC and B3D-MC-GHAJ.

Focusing on the placebo-controlled studies, there was no significant difference in the number of deaths among treatment groups, with 13 (1.9% of 691) deaths in the placebo group, 17 (2.5% of 692) deaths in the 20- $\mu$ g group, and 15 (2.2% of 691) deaths in the 40- $\mu$ g group. The teriparatide treatment groups contained more older patients than the placebo groups (Table 7.4), which may account for the slightly smaller number of deaths in the placebo group.

**Table 7.4. Distribution of Patient Age at Randomization in Placebo-Controlled Studies**  
**B3D-MC-GHAC and B3D-MC-GHAJ**

	Placebo	PTH20	PTH40
Age	N (%)	N (%)	N (%)
<70 years	410 (59.3)	384 (55.5)	373 (54.0)
$\geq$ 70 years	281 (40.7)	308 (44.5)	318 (46.0)

Abbreviations: N = number enrolled.

Examining the deaths by age group shows more deaths occurred in patients  $\geq 70$  years of age in each treatment group, and no significant differences among the treatment groups either for deaths during participation in the placebo-controlled studies GHAC and GHAJ (Table 7.5), or for all deaths reported prior to 4 June 2001 among patients who had participated in the placebo-controlled studies (Table 7.6). In contrast, the relationship between age group and number of deaths was statistically significant (Table 7.6).

**Table 7.5. Summary of Deaths by Age at Randomization During Participation in Placebo-Controlled Studies B3D-MC-GHAC and B3D-MC-GHAJ**

Age	Placebo n/N (%)	PTH20 n/N (%)	PTH40 n/N (%)	Total n/N (%)
<70 years	1/410 (0.2)	3/384 (0.8)	2/373 (0.5)	6/1167 (0.5)
$\geq 70$ years	3/281 (1.1)	5/308 (1.6)	4/318 (1.3)	12/907 (1.3)

Abbreviations: n = number of deaths; N = number enrolled.

**Table 7.6. Summary of Deaths in Placebo-Controlled Studies by Age at Randomization All Reported Deaths Prior to 4 June 2001 B3D-MC-GHAC and B3D-MC-GHAJ**

Age	Placebo n/N (%)	PTH20 n/N (%)	PTH40 n/N (%)	Total n/N (%)
<70 years	4/410 (1.0)	6/384 (1.6)	5/373 (1.3)	15/1167 (1.3)
$\geq 70$ years	9/281 (3.2)	11/308 (3.6)	10/318 (3.1)	30/907 (3.3)

Abbreviations: n = number of deaths; N = number enrolled.

### 7.3.2. Serious Adverse Events

A total of 315 (19.2%) patients randomly assigned to treatment in Study GHAC reported a minimum of one SAE. There was no significant difference among treatment groups in the number of patients reporting at least one SAE. There were 113 (20.8% of 544) patients with SAEs in the placebo group, 93 (17.2% of 541) patients with SAEs in the 20- $\mu$ g group, and 109 (19.7% of 552) patients with SAEs in the 40- $\mu$ g group.

In Study GHAJ there was no significant difference in the number of patients reporting at least one SAE among treatment groups: 16 (10.9%) patients in the placebo group, 15 (9.9%) patients in the 20- $\mu$ g group, and 14 (10.1%) patients in the 40- $\mu$ g group reported an SAE.

All reports of cancer in patients treated with teriparatide were examined in detail. There were no reports of osteosarcoma in any patient treated with teriparatide. A summary of TESS events mapped to the Coding Symbol and Thesaurus for Adverse Reaction Terms (COSTART) terms related to cancer was compiled for patients in both placebo-controlled studies (GHAC and GHAJ). In order to include follow-up data on patients previously

enrolled in these two studies, the same analysis was done combining the GHAC and GHAI subsets in Study GHBJ. Tables 7.7 and 7.8 show the summary of cancer COSTART terms. Table 7.7 includes TESS events that occurred during the treatment studies. Table 7.8 includes events that occurred after the end of the treatment studies through Visit 2 of the GHBJ follow-up study. There was a consistent trend toward fewer cancers in the teriparatide-treated patients during treatment and follow-up.

**Table 7.7. Summary of TESS Events  
Cancer COSTART Terms  
B3D-MC-GHAC and B3D-MC-GHAJ**

Event Classification	Placebo (N=691) n (%)	PTH20 (N=691) n (%)	PTH40 (N=691) n (%)	Total (N=2073) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	19 (2.7)	10 (1.4)	6 (0.9)	35 (1.7)	.021
PATIENTS WITH NO TESS	672 (97.3)	681 (98.6)	685 (99.1)	2038 (98.3)	.021
BREAST CARCINOMA	7 (1.0)	1 (0.1)	1 (0.1)	9 (0.4)	.018
CARCINOMA	2 (0.3)	3 (0.4)	1 (0.1)	6 (0.3)	.606
CARCINOMA OF LUNG	3 (0.4)	1 (0.1)	2 (0.3)	6 (0.3)	.606
GASTROINTESTINAL CARCINOMA	2 (0.3)	2 (0.3)	0	4 (0.2)	
BLADDER CARCINOMA	2 (0.3)	1 (0.1)	0	3 (0.1)	
PATHOLOGICAL FRACTURE	1 (0.1)	0	2 (0.3)	3 (0.1)	
CARCINOMA OF LARYNX	0	1 (0.1)	0	1 (0.0)	
CERVIX CARCINOMA	0	0	1 (0.1)	1 (0.0)	
ENDOMETRIAL CARCINOMA	0	1 (0.1)	0	1 (0.0)	
LYMPHOMA LIKE REACTION	1 (0.1)	0	0	1 (0.0)	
MYELOMA	1 (0.1)	0	0	1 (0.0)	

Program stored as RMP.B3DP.SASMACRO(AES2A) AE25002B

Data from INTEGRATED DATABASE OF GHAC GHAJ

\* Frequencies are analyzed using a Chi-Square test.  
XAES0002

**Table 7.8. Summary of Cancer COSTART Terms in Follow-Up Observation Phase GHAC and GHAI Subsets of Study GHBJ**

Event Classification	Placebo (N=541)		PTH20 (N=557)		PTH40 (N=519)		Total (N=1617)		Chi-Square p-Value
	n	(%)	n	(%)	n	(%)	n	(%)	
Breast carcinoma	5	(0.9)	5	(0.9)	2	(0.4)	12	(0.7)	0.516
Carcinoma	4	(0.7)	2	(0.4)	1	(0.2)	7	(0.4)	0.378
Carcinoma lung	1	(0.2)	4	(0.7)	0	(0.0)	5	(0.3)	0.086
Gastrointestinal carcinoma	3	(0.6)	1	(0.2)	0	(0.0)	4	(0.2)	0.177
Bladder carcinoma	1	(0.2)	1	(0.2)	0	(0.0)	2	(0.1)	—
Prostate carcinoma	1	(0.2)	1	(0.2)	0	(0.0)	2	(0.1)	—
Carcinoma of mouth	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.1)	—
Endometrial carcinoma	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.1)	—
Carcinoma larynx	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.1)	—
Total	15	(2.8)	12	(2.2)	5	(1.0)	32	(2.0)	0.100

Abbreviations: N = number of randomly assigned patients in treatment group(s); n = number of patients in treatment group(s) reporting the adverse event; — = combined incidence rate less than 5 and Pearson's chi-square p-value not calculated.

Source: RMP.B3DSBJV2.SASPGM(AEL023MH), RMP.B3DP.SASMACRO(AEL1A) AE18002R.

#### 7.4. Treatment-Emergent Adverse Events

Teriparatide demonstrated a good safety profile when administered at doses of 5 to 100 µg during Phase 1 studies and 6 to 60 µg in Phase 2 studies. A dose-dependent increase in the incidence of nausea and headache was observed in the Phase 1 and 2 studies. In the clinical pharmacology studies, where the time of onset of the adverse event could be collected, headache and nausea typically began between 1 and 4 hours postdose. The frequencies of vomiting and postural hypotension were also increased with dose in Phase 1 studies. These events rarely occurred at 20 µg, and this dose was better tolerated than doses of 40 µg and above. No deaths or life-threatening toxicity occurred, and only 3 of the 265 subjects exposed to doses of teriparatide up to 100 µg were discontinued from a clinical pharmacology study because of an adverse event that was judged to be related to the study drug.

In Phase 3 studies, nausea, headache, and leg cramps were considered related to treatment. The seven TESS events that had an incidence of  $\geq 2.0\%$  in any treatment group in Study GHAC, and showed a significant difference among treatment groups at the  $\alpha=0.10$  level, are displayed in Table 7.9. In the 20-µg group, there was a significant reduction in the incidence of back pain, and there was a significant increase in the incidence of leg cramps compared with placebo. The significant reduction in the incidence of back pain was also observed in the 40-µg group, compared with placebo. There were significant increases in the incidence of headache and nausea compared with placebo that were consistent with previous studies evaluating doses higher than 20 µg/day.

A significant difference among treatment groups was found for syncope, but neither the 20- nor 40-µg group was significantly different from placebo, and the incidence in all teriparatide-treated patients was the same as the incidence in placebo-treated patients. Detailed analysis of the individual cases of syncope did not reveal any likely association with teriparatide. There were also observed increases in the teriparatide-treated groups in cyst and nail disorder compared with placebo, but the actual terms reported for cyst and nail disorder were very heterogeneous and did not suggest any relationship to teriparatide. Therefore, syncope, dry eyes, cyst, and nail disorders were not considered to be associated with teriparatide administration.

**Table 7.9. Summary of TESS Events  
Incidence  $\geq 2.0\%$  in Any Treatment Group and  $p \leq 0.10$   
All Randomly Assigned Patients  
B3D-MC-GHAC**

Event Classification	Placebo	PTH20	PTH40	Total	Overall	PTH20 vs Pbo
	N=544	N=541	N=552	N=1637		
	%	%	%	%		
Back Pain	22.6	16.8	15.8	18.4	0.007	0.017
Nausea	7.5	9.4	17.8	11.6	<0.001	0.264
Headache	8.3	8.1	13.0	9.8	0.008	0.934
Leg Cramps	1.1	3.1	2.4	2.2	0.069	0.020
Cyst	0.9	1.7	3.1	1.9	0.029	0.277
Syncope	1.7	3.1	0.7	1.8	0.011	0.109
Nail Disorder	0.4	1.3	3.1	1.6	0.001	0.093

Abbreviations: N = number of randomly assigned patients in treatment group(s); n = number of patients in treatment group(s) reporting the treatment-emergent adverse event; vs = versus; Pbo = placebo.

In men treated with teriparatide, the 20- $\mu\text{g}$  dose was very well tolerated, with a small increase in the incidence of depression being the only significant adverse event. Increased incidences of nausea, hernia, and nervousness, but not depression, were observed with the 40- $\mu\text{g}$  dose. There was a trend toward an increase in headache with the 40- $\mu\text{g}$  dose as well. Nausea occurred soon after starting treatment, and was the only adverse event that was a significant reason for discontinuation. The absence of a dose response for the event of depression, the low number of reported patients for this event, and the lack of a consistent effect in other Phase 3 studies suggest that depression is not associated with treatment. Likewise, hernia and nervousness were not observed in other studies and are not likely to be caused by teriparatide administration.

Table 7.10 lists, without attribution of causality, the TESS events reported in Studies GHAC and GHAJ at a frequency  $\geq 2.0\%$ , and in more patients in the 20- $\mu\text{g}$  group than in the placebo group. The incidence of many of these events (hypertension, angina pectoris, syncope, dyspepsia, tooth disorder, insomnia, rhinitis, pharyngitis and pneumonia) in patients in the 40- $\mu\text{g}$  group was equal to or lower than the incidence in placebo-treated patients.

**Table 7.10. Summary of TESS Events  
Incidence  $\geq 2.0\%$  in 20- $\mu\text{g}$  Group  
Listed without Attribution of Causality  
B3D-MC-GHAC and B3D-MC-GHAJ**

Event Classification	Placebo N=691 (%)	20- $\mu\text{g}$ N=691 (%)	40- $\mu\text{g}$ N=691 (%)
<b>BODY AS A WHOLE</b>			
Pain	20.5	21.3	22.9
Headache	7.4	7.5	12.6
Asthenia	6.8	8.7	10.4
Neck Pain	2.7	3.0	2.9
<b>CARDIOVASCULAR</b>			
Hypertension	6.8	7.1	5.6
Angina Pectoris	1.6	2.5	1.6
Syncope	1.4	2.6	0.7
<b>DIGESTIVE SYSTEM</b>			
Nausea	6.7	8.5	17.9
Constipation	4.5	5.4	5.1
Diarrhea	4.6	5.1	5.2
Dyspepsia	4.1	5.2	3.8
Vomiting	2.3	3.0	3.6
Gastrointestinal Disorder	2.0	2.3	2.7
Tooth Disorder	1.3	2.0	1.3
<b>MUSCULOSKELETAL</b>			
Arthralgia	8.4	10.1	8.4
Leg Cramps	1.3	2.6	2.0
<b>NERVOUS SYSTEM</b>			
Dizziness	5.4	8.0	7.7
Depression	2.7	4.1	4.5
Insomnia	3.6	4.3	3.6
Vertigo	2.7	3.8	4.5
<b>RESPIRATORY SYSTEM</b>			
Rhinitis	8.8	9.6	8.2
Cough Increased	5.5	6.4	6.1
Pharyngitis	4.8	5.5	3.6
Dyspnea	2.6	3.6	4.5
Pneumonia	3.3	3.9	3.3
<b>SKIN AND APPENDAGES</b>			
Rash	4.5	4.9	5.5
Sweating	1.7	2.2	3.0

In the supportive studies GHAF and GHAH, patients treated with teriparatide received 40- $\mu\text{g}/\text{day}$ , and nausea, headache, dizziness, and leg cramps appeared to be associated with this treatment. A reduction in back pain in the teriparatide-treated patients was also observed. There were 3 cases of syncope in studies GHAF and GHAH, 2 in the control groups and 1 in the teriparatide-treated groups, which supports the conclusion from the primary Phase 3 safety database that syncope is not related to study drug. No safety

considerations besides those evident in the primary safety database were detected in the supportive studies.

The data do not suggest that tolerance to the treatment-associated adverse events of headache, nausea, and leg cramps develops with continued treatment. Rather, these symptoms appear to persist until treatment is withdrawn.

In the observational follow-up study GHBJ, the incidence of headache, nausea, and leg cramps was no longer different among treatment groups. For the subset of patients from Study GHAC, Table 7.11 summarizes the five TESS events that had a total incidence of at least 4 and showed a significant difference among treatment groups during the follow-up period. Only back pain occurred in more patients in the placebo group than in either of the teriparatide treatment groups. Sinusitis and glaucoma were increased in the 40- $\mu$ g group, but occurred in <2% of patients in the 20- $\mu$ g group. The event terms cardiovascular disorder and anemia will be discussed in more detail.

**Table 7.11. Summary of TESS Events  
Incidence  $\geq 2.0\%$  in Any Treatment Group and  $p \leq 0.10$   
During Follow-up Period, All Randomly Assigned Patients  
GHAC Subset of B3D-MC-GHBJ**

Event Classification	Placebo	PTH20	PTH40	Total	Overall	PTH20 vs Pbo
	N=414	N=436	N=412	N=1262		
	%	%	%	%		
Back Pain	19.3	12.8	12.9	15.0	0.010	0.010
Sinusitis	0.5	0.9	2.9	1.4	0.007	0.450
Cardiovascular Disorder	1.7	3.4	4.9	3.3	0.040	0.108
Anemia	0.2	2.5	2.7	1.8	0.013	0.005
Glaucoma	0.7	1.4	3.2	1.7	0.022	0.354

Abbreviations: N = number of randomly assigned patients in treatment group(s); n = number of patients in treatment group(s) reporting the treatment-emergent adverse event; vs = versus; Pbo = placebo.

The most common cardiac problems mapped to the COSTART term cardiovascular disorder were cardiac murmurs and/or heart valve abnormalities. Coronary disease was mapped to this term in 4 patients. Approximately one-half of the events were cardiac murmurs reported by one investigator, who has concluded that there probably was no relationship between prior treatment with teriparatide and these murmurs. The maximum severity of cardiovascular disorder events in the follow-up period was “mild” in most cases (34 patients: 6 in the placebo group, 14 in the 20- $\mu$ g group, and 14 in the 40- $\mu$ g group), and moderate in the others (8 patients: 1 in the placebo group, 1 in the 20- $\mu$ g and 6 in the 40- $\mu$ g group).

The COSTART term anemia was reported during the follow-up period for more patients in the GHAC subset who had previously been treated with teriparatide than for patients who previously received placebo. Most of these patients had mild anemia (1 in the placebo group, 9 in the 20- $\mu$ g group and 10 in the 40- $\mu$ g group), 3 patients had moderate

anemia (2 in the 20- $\mu$ g group and 1 in the 40- $\mu$ g group), and none had severe anemia. Of the patients with the TESS event anemia, 6 patients in the 20- $\mu$ g group, and 3 patients in the 40- $\mu$ g group had no abnormally low hemoglobin or hematocrit values either during treatment (Study GHAC) or afterwards (Study GHBJ), suggesting the condition was very mild. None of the patients with anemia during follow-up had leukopenia or thrombocytopenia, and no significant relationship between treatment and the TESS event anemia was seen in the other clinical studies.

For the subset of patients from Study GHAJ, there were three TESS events (depression, amnesia, malaise) that had a total incidence of at least 4 and showed a significant difference among treatment groups during the follow-up period. Malaise was reported only in patients in the placebo group, and neither depression nor amnesia were reported in patients in the 40- $\mu$ g group. Since there was no dose-response for depression or amnesia, these findings may be due to chance and are probably not clinically important effects of withdrawal from teriparatide.

## 7.5. Clinical Laboratory Evaluation

The effects of PTH on serum and urine calcium, renal handling of other electrolytes and organic acids, and other laboratory parameters have been known for many years. There were no new or unexpected findings in the safety laboratory evaluations, and no clinical safety concerns. Sections 7.5.1, 7.5.2, and 7.5.3 provide greater detail regarding the effects of treatment on calcium, renal function, and uric acid. All laboratory changes observed during the Phase 3 studies appeared reversible, and most were no longer different from placebo at the study closeout visit.

In Study GHAC, there were no clinically significant changes in the hematology results in either of the teriparatide treatment groups, but there were statistically significant differences ( $p < 0.05$ ) or trends ( $p < 0.10$ ) in several erythrocyte and leukocyte indices. In the 20- $\mu$ g group, the median red blood cell (RBC) count, hematocrit, and hemoglobin were slightly decreased, compared with placebo, at some study visits without any apparent relationship to duration of treatment. The maximum observed decrease was 2.2% in the median RBC count, 2.4% in the median hematocrit, and 0.7% in the median hemoglobin. In the leukocyte indices, the median white blood cell (WBC), segmented neutrophil, and monocyte counts were increased ( $< 16\%$ ) during the study, but not at endpoint. The only significant difference in the frequencies of abnormal erythrocyte or leukocyte indices in the 20- $\mu$ g group, compared with placebo, was a reduction in the frequency of abnormally low leukocyte counts. Small increases ( $< 5\%$ ) in the median platelet count at Months 1 and 6 were not statistically significant.

Small but statistically significant decreases in serum magnesium were observed in Study GHAC. While it has been postulated that PTH may have an effect on renal reabsorption of magnesium similar to the effects it has on calcium, several studies have failed to demonstrate a significant effect of PTH on renal magnesium clearance (*Reeve et al. 1976*; *Roelen et al. 1989*). However, the skeleton contains the largest pool of total

body magnesium, and in patients with severe hyperparathyroidism, hypomagnesemia as well as hypocalcemia have occasionally been reported immediately following parathyroidectomy as part of the “hungry bones syndrome” (Strewler and Rosenblatt 1995). Thus, therapeutic administration of teriparatide may indirectly affect serum magnesium concentration by increasing skeletal uptake, although renal magnesium clearance is not altered.

Teriparatide demonstrated effects on vitamin D metabolism that were consistent with the known effects of endogenous PTH. Following administration of teriparatide 20 µg, the median increase in the serum concentration of 1,25-dihydroxyvitamin D was 19% at 12 months. The serum 25-hydroxyvitamin D concentration was reduced by 19% at 12 months, which may reflect the renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. The effect of teriparatide on serum 1,25-dihydroxyvitamin D may account for the small calciuric effects observed in the study.

The clinical and laboratory safety conclusions from the supportive Phase 2 and 3 studies were consistent with those from the primary Phase 3 safety database. There were no TESS events identified in the supportive Phase 2 and 3 studies that were not identified in the primary Phase 3 safety database. Most of the clinical laboratory changes were no longer detectable by the treatment study closeout visit.

In the follow-up study GHBJ, laboratory findings for each subset of patients were analyzed separately. In the GHAC subset, there was no statistically significant difference among treatment groups in frequency of abnormal serum uric acid at the 6-month follow-up visit, although there was still a small increase in the median serum uric acid, compared with placebo. Small increases (<3%, compared to pretreatment baseline) in median serum creatinine in the 20- and 40-µg groups were statistically significant in the GHAC subset, compared with placebo, but significant changes were not observed in measured creatinine clearance or serum urea nitrogen.

In the GHAC subset, the proportions of patients with an abnormally elevated serum creatinine (> 101 µmol/L) at pretreatment baseline in the placebo (1.5%), 20- and 40-µg groups did not differ significantly (2.1%, 1.0%). When serum creatinine was re-measured in Study GHBJ, fewer patients in placebo (1.7 %) than in the 20- and 40-µg groups (3.9% and 3.9%) had an abnormally elevated value. All patients with an elevated serum creatinine in Study GHBJ had pretreatment baseline values in Study GHAC which were in the upper 30% of all patients ( $\geq 75\mu\text{mol/L}$ ). Several of these patients in the 20- and 40-µg groups had an elevated serum creatinine at pretreatment baseline and at all subsequent visits (patients with baseline serum creatinine  $>177\mu\text{mol/L}$  were excluded from Study GHAC). Examination of case reports for the patients with elevated creatinine in Study GHBJ indicated that most patients in each group were treated for hypertension, diabetes, or heart failure, but no unusual study-related conditions were identified. The proportion of patients in each treatment group who displayed elevated serum creatinine in Study GHBJ was not increased in the patients who at any time during treatment or follow-up had an abnormally elevated serum calcium.

In the GHAC subset, small decreases in hemoglobin (compared with pretreatment baseline) were observed in the placebo (-0.062 mmol/L-Fe [-0.10 g/dL]) and the teriparatide treatment groups (-0.124 mmol/L-Fe[-0.20 g/dL]) at the follow-up visit. The magnitude of these changes was very small relative to the median hemoglobin concentration for the placebo (8.32 mmol/L-Fe [13.38 g/dL]), 20- $\mu$ g (8.25 mmol/L-Fe [13.26 g/dL]), and 40- $\mu$ g (8.19 mmol/L-Fe [13.17 g/dL]) groups. Although the overall difference among treatment groups for hemoglobin was statistically significant, the proportion of patients with abnormally low hemoglobin values in any group was small ( $\leq 2\%$ ), and not dose-related or statistically significant. The finding of  $< 1\%$  decreases in hemoglobin, compared with placebo, in the GHAC subset was not replicated in men who had been treated with teriparatide, and was probably not clinically relevant.

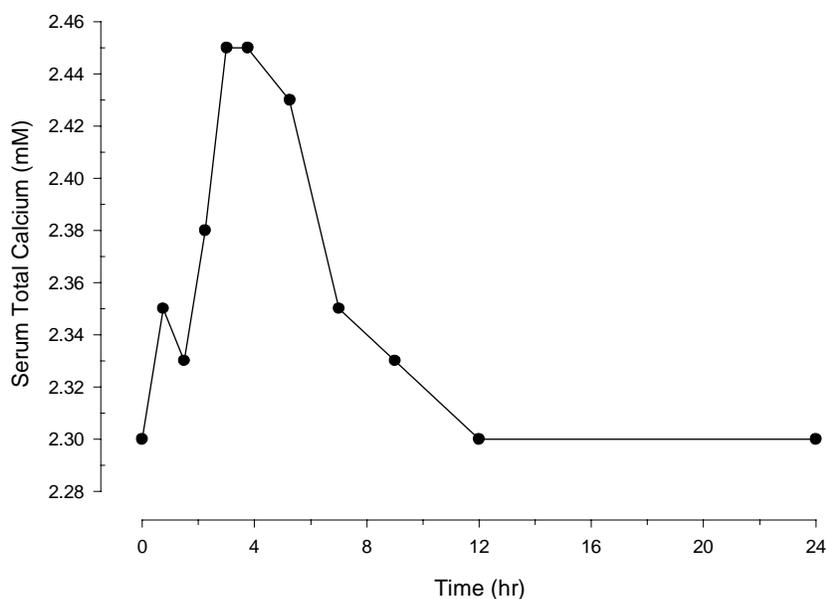
For the GHAJ subset in the follow-up study, there were no statistically significant laboratory findings for the 20- $\mu$ g group at the 6-month follow-up visit. For the 40- $\mu$ g group only a small increase (3%) in serum uric acid was significant, compared with placebo.

### 7.5.1. Serum Calcium

PTH is known to increase serum calcium. In Phase 1 studies, the effect of teriparatide on serum calcium was modest, even when a single dose as high as 100 µg was administered. During repeated dosing, the observed effects in the Phase 2 and 3 studies were dose dependent, resolved within the dosing interval, and not clinically important at the 20-µg dose. At the 40-µg dose, the magnitude of the effects was greater, but there were no adverse clinical outcomes associated with the laboratory changes.

#### Timing of Transient Postdose Increase in Serum Calcium

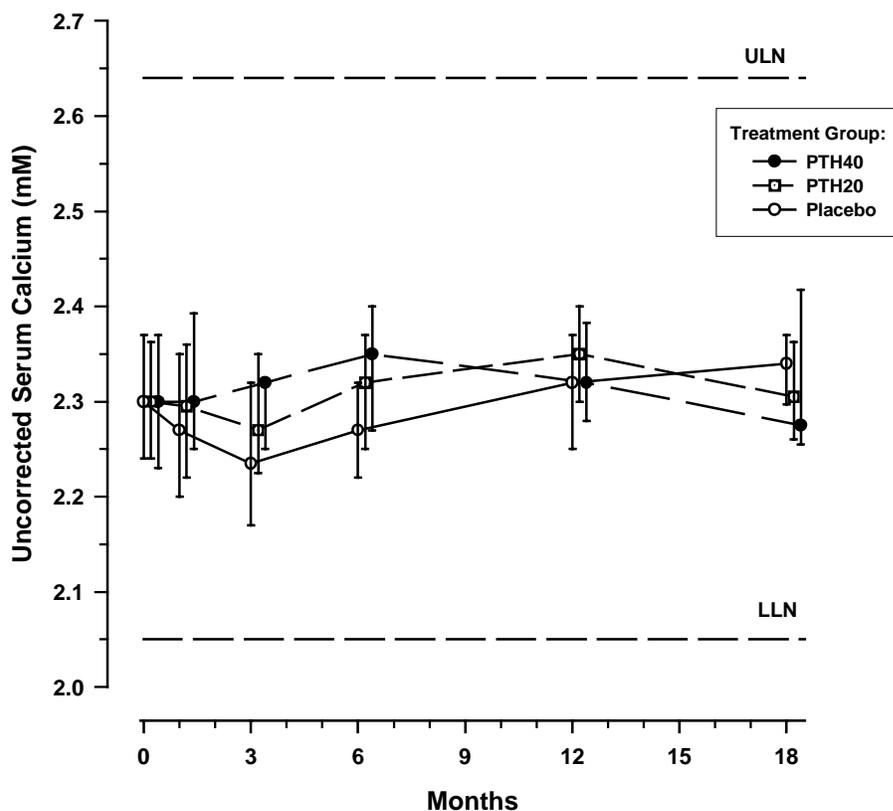
When teriparatide is administered once daily, the serum calcium concentration increases transiently, beginning approximately 2 hours after dosing and reaching a peak concentration between 4 to 6 hours after dosing. The serum calcium concentration begins to decline approximately 6 hours after dosing and returns to baseline by 16 to 24 hours after each dose (Figure 7.1).



**Figure 7.1** Serum Calcium Response from a Representative Subject following a Single Dose of Teriparatide 20 µg

## Predose Serum Calcium

In the placebo-controlled Phase 3 studies, there was no statistically significant change in the predose serum calcium compared with the study baseline value. Figure 7.2 presents results from Study GHAC.

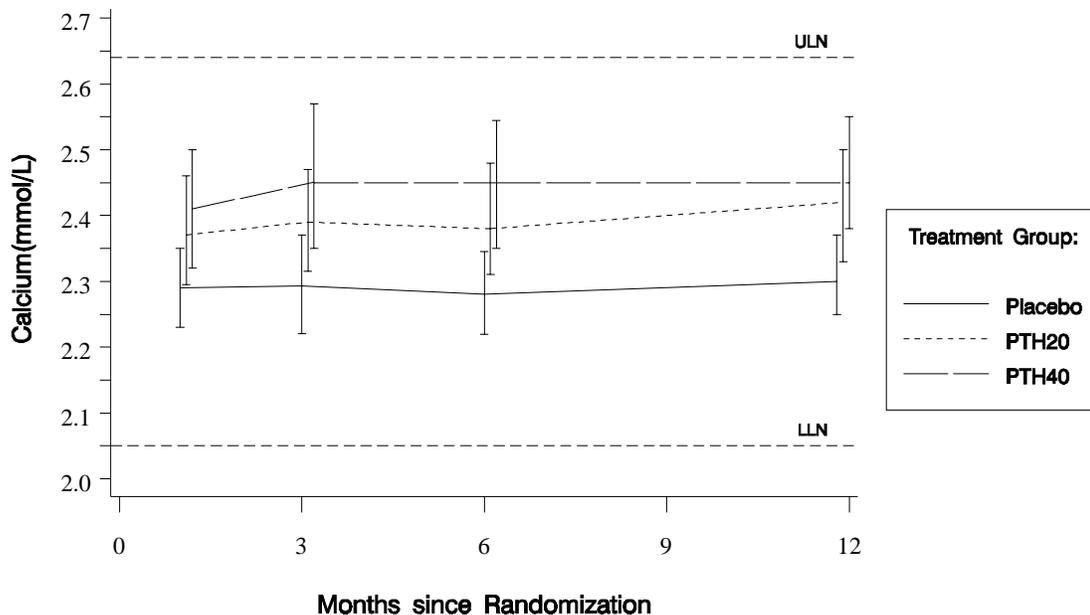


**Figure 7.2.** **Predose Serum Calcium**  
**Median Values with 25th to 75th Percentile**  
**All Randomly Assigned Patients**  
**B3D-MC-GHAC**

As part of the general chemistry testing in Study GHAC, serum calcium was assessed without regard to time relative to dosing. Approximately 70%, 30%, and 20% of the samples at Months 6, 12, and 18 were obtained between 8 hours prior to and 30 minutes after the current dose, and are the basis for the predose analysis. This analysis could also be described as the 24-hour postdose analysis. Because serum albumin was normal in the study population, total serum calcium was analyzed without adjustment for albumin.

## Postdose Serum Calcium

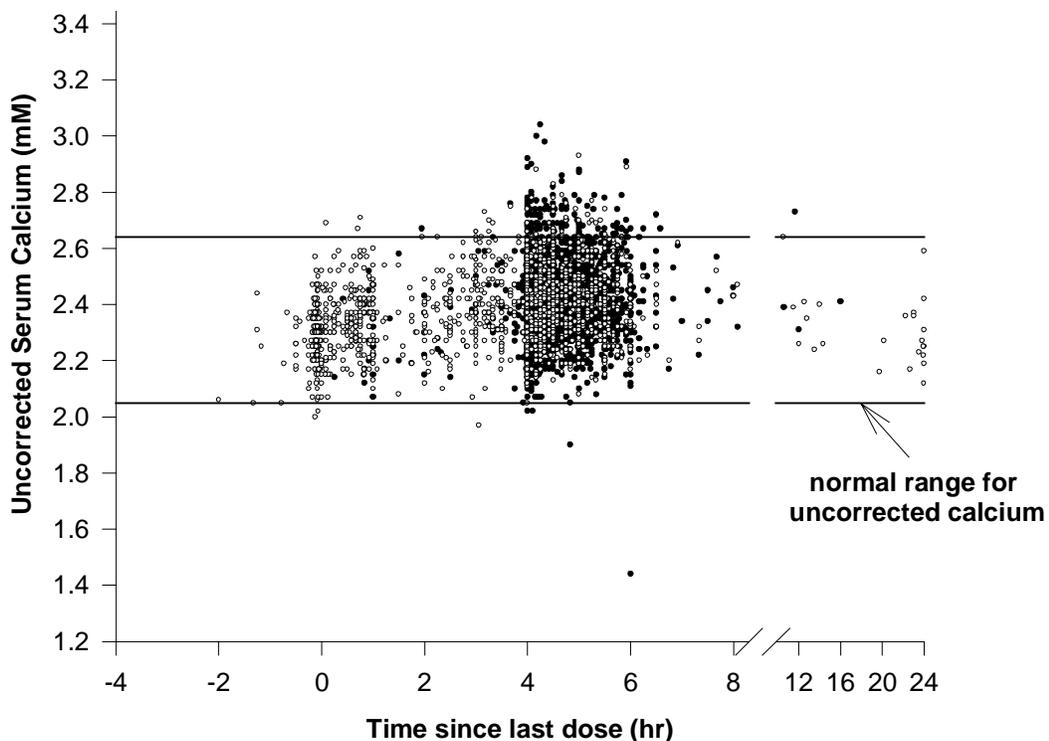
The effects of teriparatide treatment on the peak-effect, or postdose serum calcium were evaluated with samples obtained approximately 4 to 6 hours after each dose at each visit. Overall, the increase in the postdose serum calcium was dose-dependent and statistically significant (Figure 7.3). In the 20- $\mu$ g group, the magnitude of the increases in the postdose serum calcium was very small (0.08 to 0.12 mmol/L higher than placebo).



RMPB3DSGHAC.SASPGM(LAG018MH)

**Figure 7.3. Median Postdose (4- to 6-Hour) Serum Calcium  
Median Values with 25th to 75th Percentile  
All Randomly Assigned Patients  
B3D-MC-GHAC**

Figure 7.4 shows the serum calcium relative to the time of dosing for the 20- $\mu$ g treatment group. In this graph, every serum calcium observation for which the time of dose and the time of sample collection were recorded was plotted as a function of time relative to the dose. There is a greater density of observations in the 4- to 6-hour postdose interval because this was assessed at each visit. The serum calcium in both teriparatide-treated groups appeared to peak at about 4 hours postdose and then returned toward baseline within a few hours. This pattern was consistent with the observations made in the clinical pharmacology studies.



**Figure 7.4**

**Uncorrected Serum Calcium by Time Since Last Dose  
All Randomly Assigned Patients in the 20- $\mu$ g Group  
B3D-MC-GHAC**

Every serum calcium observation for which the time of dose and the time of sample collection were recorded is plotted as a function of time relative to the dose. Since this analysis incorporates data from all visits, several serum calcium observations from each patient are included.

## Frequency of Elevated Serum Calcium Levels

To help evaluate the clinical significance of the serum calcium results, the number of patients with either predose or peak postdose elevated (>ULN) serum calcium values at each visit, grouped by the magnitude of the elevation, is presented in Table 7.12.

**Table 7.12. Summary of Patients with Elevated Serum Calcium at Each Visit  
All Randomly Assigned Patients  
B3D-MC-GHAC**

	Month 1 (Visit 5)	Month 3 (Visit 6)	Month 6 (Visit 7)	Month 12 (Visit 9)	Month 18 (Visit 11)
	n	n	n	n	n
<b>Placebo (N=544)</b>					
>2.64, ≤2.76	1	0	2	2	0
>2.76, ≤2.90	0	1	0	1	1
>2.90	0	0	0	0	0
<b>Total</b>	<b>1</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>1</b>
<b>Teriparatide 20-μg/day (N=541)</b>					
>2.64, ≤2.76	13	13	23	14	7
>2.76, ≤2.90	3	1	4	2	0
>2.90	0	0	0	0	0
<b>Total</b>	<b>16</b>	<b>14</b>	<b>27</b>	<b>16</b>	<b>7</b>
<b>Teriparatide 40-μg/day (N=552)</b>					
>2.64, ≤2.76	31	38	35	34	14
>2.76, ≤2.90	8	16	14	16	2
>2.90	2	7	3	3	2
<b>Total</b>	<b>41</b>	<b>61</b>	<b>52</b>	<b>53</b>	<b>18</b>

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

In the 20-μg group, the magnitude of the increases in serum calcium was very small. Most of the patients remained below 2.76 mmol/L (11.0 mg/dL) at each visit and no patient exceeded 2.90 mmol/L (11.6 mg/dL). The increases in serum calcium were identified rapidly. The highest incidence occurred at Month 6 (Visit 7), and all observations above 2.81 mmol/L (11.2 mg/dL) were observed in Months 1 and 3 (Visits 5 and 6). In the 40-μg group, the magnitude of the increases in serum calcium was still small, but greater than observed in the 20-μg group. Most of the patients remained below 2.76 mmol/L, and only 1 or 2 patients exceeded 3.0 mmol/L (12.0 mg/dL) at each visit.

Less than 1% of patients in the placebo group, and 3.0% of patients in the 20-μg group had an elevated postdose serum calcium which was confirmed by repeat testing, and which resulted in subsequent reductions in study drug. One patient in the placebo and 1 patient in the 20-μg group discontinued due to elevated postdose serum calcium. In the 40-μg group, the frequency of elevated postdose serum calcium values was higher than in

the 20- $\mu$ g group, but still nearly 90% of patients did not have study drug adjustments due to elevated postdose serum calcium. As described above, the predose (24-hour postdose) serum calcium was unchanged from baseline in all groups, including the 40- $\mu$ g group (Table 7.13).

**Table 7.13. Summary of Patients with Elevated Serum Calcium on Repeat Testing Dose Adjustments of Calcium Supplements and Teriparatide All Randomly Assigned Patients B3D-MC-GHAC**

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

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

### Elevated Serum Calcium and Selected Adverse Events

To determine whether the transient increases in postdose serum calcium values were associated with any clinical adverse effects, a subgroup analysis was performed comparing adverse events in patients who did and who did not have a minimum of one elevated postdose serum calcium. The events nausea, headache, leg cramps, depression, asthenia, dizziness, and syncope were analyzed. Dizziness was the only event which had a significant treatment-by-subgroup interaction ( $p=0.041$ ). In the patients with at least one elevated 4- to 6-hour postdose total serum calcium at anytime in the study, dizziness was reported significantly less ( $p=0.027$ ) in the 40- $\mu$ g group (6.3%) than in the placebo (16.7%) or the 20- $\mu$ g (20.0%) groups. However, in the patients whose 4- to 6-hour postdose total serum calcium was not elevated at any time during the study, the incidence of dizziness was not significantly different among treatment groups ( $p=0.302$ ).

The changes in serum calcium in men treated with teriparatide were similar to those seen in women. In Study GHAJ, there was a significant increase in the peak effect (postdose) serum calcium, and the majority of men who experienced at least one elevated postdose

serum calcium were identified within the first 28 weeks after randomization. Beyond 28 weeks, the incremental incidence of new postdose serum calcium values above the ULN was similar to placebo. Only 1.0% of men in the 20- $\mu$ g group had a postdose serum calcium above the ULN that was confirmed by repeat testing, and only 3 men discontinued from the 20- $\mu$ g group as a result of elevated postdose serum calcium. The increase in mean postdose serum calcium in the 20- $\mu$ g group, compared with placebo, was 0.10 mmol/L (0.40 mg/dl) after 6 months of treatment.

### **Serum Phosphorous and Calcium-Phosphorous Product**

Changes in serum phosphorus concentrations associated with teriparatide were minor and consistent with the known effects of PTH. Teriparatide, like endogenous PTH, lowers the serum concentration by increasing the renal clearance of phosphorus. The effects are transient. The time course of the response to teriparatide 20 and 40  $\mu$ g was examined in clinical pharmacology studies. Serum phosphorus had returned to predose values by 9 hours after dosing. The Phase 3 clinical studies showed no clinically significant differences among treatment groups in serum phosphorus. There were no statistically significant differences or trends among treatment groups in frequency of abnormal serum phosphorus in Studies GHAC or GHAJ. Because survival is reduced in patients with end-stage renal disease whose calcium-phosphorus product is  $>72$  mg<sup>2</sup>/dL<sup>2</sup> (Block et al. 1998), the serum phosphorus-postdose serum calcium product was calculated in Study GHAC. One patient in the placebo group, but no patients in either teriparatide treatment group had a value  $>72$  mg<sup>2</sup>/dL<sup>2</sup>.

### **Coadministration of Teriparatide and Diuretics**

Teriparatide was investigated in combination with diuretic drugs that alter calcium homeostasis, and no clinically significant interactions were found. In 20 healthy men and women at least 50 years of age who received stable doses of supplemental calcium and vitamin D, and who were on hydrochlorothiazide (HCTZ), the coadministration of HCTZ 25 mg orally with teriparatide 40- $\mu$ g did not result in a clinically significant drug interaction. Neither the magnitude nor the time course of the serum calcium response was different as a result of the coadministration of HCTZ with teriparatide. The combined treatment was associated with a statistically significant decrease (15%) in 24-hour urine calcium excretion compared with the response of teriparatide given alone. The magnitude of this difference was not considered clinically relevant because the serum calcium response of teriparatide was not affected by the coadministration of HCTZ. Phosphorus response in serum and urine was also similar when teriparatide was administered alone or in combination with HCTZ.

Teriparatide 40  $\mu$ g and a rapidly infused intravenous dose of furosemide were coadministered to 9 subjects with normal renal function and to 17 subjects with significant renal impairment ( $Cl_{Cr}$  72 to 13 mL/min). Furosemide doses were relatively large and adjusted for the level of renal function. Small differences in serum and urine calcium responses occurred when teriparatide was administered alone versus in

combination with furosemide, but these changes were not considered clinically relevant. Importantly, the furosemide-containing regimen did not increase the maximum serum calcium concentration above the level observed during treatment with teriparatide. Total urine calcium excretion was higher during combined treatment, especially in study subjects with renal failure. The total amount excreted by these subjects was, however, substantially less than occurred in the healthy subjects when teriparatide was administered alone.

### **Relevance of Calcemic Effects to Safety**

The calcemic effects of teriparatide in these studies were consistent with the known physiologic effects of PTH. There were small but significant increases in the 4- to 6-hour postdose serum calcium, representing the peak effect on serum calcium. More importantly, the predose serum calcium was not increased, and there were no associated adverse clinical effects. This lack of an adverse effect is consistent with the findings in the literature from patients with hyperparathyroidism and mild hypercalcemia (*Heath et al., 1980*). The small and transient nature of the calcemic effects and the lack of associated adverse clinical effects indicate that routine monitoring of serum calcium is not required during treatment with teriparatide 20 µg.

### **7.5.2. Urinary Calcium, Renal Function, and Incidence of Urolithiasis**

The effects of teriparatide on urinary calcium were generally consistent with the known physiologic effects of PTH. The time course of urine calcium excretion was evaluated over 24 hours in clinical pharmacology studies. Consistent with the known anticalciuric actions of PTH, teriparatide was associated with a reduced rate of calcium excretion that lasted for 6 to 8 hours following the dose. Subsequently, urine calcium excretion tended to be similar to or higher than the excretion rate observed during placebo administration. Summation of calcium excretion in the serial urine collections revealed little difference in the amount excreted over 24 hours between active treatments and placebo.

In long-term clinical studies, teriparatide had no significant effect on renal function as measured by urinalysis and serial determinations of serum creatinine and creatinine clearance. In Study GHAC, small clinically insignificant, but statistically significant differences in the median 24-hour urine calcium excretion among treatment groups were evident for the first 6 months of the study. Compared with placebo, there were significant increases in the median 24-hour urine calcium excretion at Months 1 and 6 that ranged from 0.10 to 0.76 mmol/day (4.0 to 30.4 mg/day). At Month 12, median 24-hour urine calcium excretion was similar to placebo, even though patients were still on treatment. However, no significant differences or trends among treatment groups in the incidence of patients with abnormally high 24-hour urine calcium excretion (>7.5 mmol Ca/day or 300 mg/day) were found.

No obvious differences among treatment groups in the magnitude of urine calcium elevations were detected. There was a broad distribution in all treatment groups, with approximately 1% to 2% of patients in each treatment group excreting greater than 11.0 mmol/day at each visit. This is due, in part, to the variability in 24-hour urine calcium measurements. Although the protocol provided guidelines for adjustments in calcium supplements or in the dose of study drug on the basis of confirmed increases in urinary calcium, only 4 patients underwent reductions of calcium supplements. There was no study drug reduction and only one discontinuation due to elevated urine calcium and urinary calcium-to-creatinine ratio.

In men treated in Study GHAJ, there were small, but statistically significant differences in the mean 24-hour urine calcium excretion among treatment groups after one month, but not after 6 months of treatment. The increases in means in men treated with teriparatide ranged from 0.61 to 0.84 mmol/day compared with placebo.

### **Urine Phosphorus**

In single-dose studies, teriparatide produced transient phosphaturia. The rate of phosphorus excretion had returned to predose values by 9 hours after dosing. There were no significant differences among treatment groups in the 24-hour urine phosphorus excretion in Studies GHAC or GHAJ.

### **Analyses of Confirmed or Possible Urolithiasis**

To evaluate the potential effects of teriparatide on urolithiasis, all treatment-emergent adverse events possibly related to the urinary tract in Study GHAC were analyzed. In addition to 4 patients with a kidney calculus (2 in the placebo group, 2 in the 20- $\mu$ g group), 2 patients had calcifications (1 in the 20- $\mu$ g group, 1 in the 40- $\mu$ g group) that were assigned the COSTART term urinary tract disorder. Furthermore, 3 patients in the 20- $\mu$ g group and 1 patient in the 40- $\mu$ g group had reported kidney pain. Although this symptom is nonspecific, it is compatible with urolithiasis. A total of 2 patients in the placebo group, 6 in the 20- $\mu$ g group, and 2 in the 40- $\mu$ g group had confirmed or possible urolithiasis. The difference among treatment groups was not statistically significant ( $p=0.192$ ).

Similar analyses of confirmed or possible urolithiasis were completed for Study GHAJ and for 18 months of follow-up in all patients in Study GHB, again with no differences among treatment groups. Overall, there was no evidence of a significant increase in renal stone disease in patients treated with teriparatide.

### **Relevance of Calciuric Effects to Safety**

There were no adverse renal effects in the Phase 3 treatment studies. Urinary excretion of calcium was significantly increased in the Phase 3 studies, but the magnitude was small and the increases lasted only 1 to 6 months, even with continued treatment. There was no significant increase in the incidence of urolithiasis in the teriparatide-treated

patients in any Phase 3 study. Urolithiasis and renal insufficiency are known complications of severe chronic hyperparathyroidism, but neither of these adverse effects was associated with once daily administration of teriparatide.

### **7.5.3. Serum Uric Acid**

PTH affects the renal handling of organic acids. It increases the renal tubular reabsorption of uric acid (Kippen et al. 1977), and decreases uric acid clearance (Dunzendorfer and Schmidt-Gayk 1981). This results in increased serum uric acid concentrations in hyperparathyroidism, although gout or other clinical sequelae of hyperuricemia are not associated with mild hyperparathyroidism.

In women treated with teriparatide 20- $\mu$ g, there was a statistically significant 13% to 20% (0.6 to 0.9 mg/dL) increase in median serum uric acid levels that presumably reflected the physiologic action of PTH on the kidney. Approximately 1% of patients in the placebo group, 3% of patients in the 20- $\mu$ g group and 5% of patients in the 40- $\mu$ g group had at least one serum uric acid level above the ULN. There was no difference in the incidences of gout, arthralgia, urolithiasis or the use of allopurinol among treatment groups. There were similar but slightly smaller increases in serum uric acid concentrations in men treated with teriparatide compared with placebo.

#### **Relevance of Uric Acid Effects to Safety**

No increase in gout, arthralgia, or urolithiasis, which might be attributable to increases in serum uric acid, were observed in the Phase 3 treatment studies or in follow-up Study GHBJ. Although gout is uncommon in postmenopausal women, it is associated with sustained hyperuricemia in men. These excursions in uric acid are unlikely to be clinically relevant, except possibly in patients with inadequately controlled gout.

### **7.5.4. Antibodies to Teriparatide**

Indirect testing was performed for anti-teriparatide antibodies during Studies GHAC and GHAI. A positive finding was reported when the results from a radio-immunoprecipitation assay [binding of radio-iodinated rhPTH(1-34)] increased 2-fold during the study, exceeded a reference range generated in normal study subjects, and showed >40% inhibition in a competition with 100 ng of unlabeled PTH.

In Study GHAC, 1 (0.2%) patient in the placebo group, 15 (2.8%) patients in the 20- $\mu$ g group, and 44 (8%) patients in the 40- $\mu$ g group had at least one positive test. Follow-up testing was requested of all patients with positive results. Hypocalcemia should be a sensitive indicator of impairment of endogenous PTH activity by antibodies, and loss of BMD response is an indicator of clinically significant neutralization of teriparatide by antibodies. Subgroup analysis of the patients with and without antibody responses showed no differences in BMD response, serum calcium levels, or adverse events. These results indicate that the serum binding activity does not affect the biological activity of teriparatide or produce any detectable adverse effects. No men in

Study GHAJ were found to have abnormal tests, perhaps because of the shorter duration of exposure compared to study GHAC.

### **Relevance of Antibodies to Safety**

A small but significant number of patients developed antibodies to teriparatide. These antibodies did not appear to be associated with any adverse clinical outcomes.

## **7.6. Conditions Historically Associated with Hyperparathyroidism**

Hyperparathyroidism has been linked historically with hypertension, cardiovascular disease, renal impairment, urolithiasis, and peptic ulcer disease, although recent surveys have not supported many of these associations in patients who do not have severe or complicated disease (*Wermers et al. 1998*).

Once daily administration of teriparatide in Phase 3 studies was not associated with any significant changes in blood pressure or pulse. Examination of adverse events did not reveal an association of teriparatide with atherosclerotic cardiovascular disease. There were no significant increases in the incidence of individual COSTART terms describing cardiovascular disease, and grouping similar terms, such as angina and chest pain, also did not reveal any significant treatment-associated adverse effects. There were also no changes in renal function or an increase in the incidence of urolithiasis or peptic ulcers. Therefore, the cardiovascular, urinary tract, and acid-peptic effects thought to be associated with severe chronic hyperparathyroidism do not appear to be associated with once daily administration of teriparatide.

## **7.7. Cardiovascular Safety**

Chronic hyperparathyroidism, particularly secondary to renal failure, has historically been linked with hypertension and cardiovascular disease. Daily therapeutic administration of teriparatide did not result in hypertension or a worsening pattern of cardiovascular disease. In the clinical studies, once daily administration of teriparatide was not associated with any significant changes in blood pressure or pulse. Examination of TESS events in the Phase 3 studies did not reveal an association of teriparatide treatment with atherosclerotic cardiovascular disease. There were no significant increases in the incidence of individual COSTART terms describing cardiovascular disease, and grouping similar terms such as angina and chest pain also did not reveal any significant treatment-associated adverse effects. There was a baseline imbalance in coronary artery disease in Study GHAC; the number of patients reporting a coronary artery disease event prior to study entry was highest in the 20- $\mu$ g group. This was supported by a review of pretreatment use of nitrates that revealed a 30% greater likelihood of nitrate use in the 20- $\mu$ g group. This imbalance continued to be observed throughout the treatment and follow-up periods. However, there was no increase in coronary artery disease in the 40- $\mu$ g group or in either dose in the other Phase 3 studies.

Therefore, the cardiovascular effects thought to be associated with severe chronic hyperparathyroidism were not associated with teriparatide treatment.

Teriparatide did not alter the cardiovascular safety of digoxin as evidenced by data from the Phase 3 studies and a focused clinical pharmacology study. In the clinical pharmacology study, calcium and non-calcium mediated pharmacodynamic cardiac effects of digoxin were evaluated in 15 healthy volunteers by repeated measurements of systolic time intervals and heart rate, respectively. Digoxin, dosed daily to steady state, resulted in the expected changes in these parameters. The co-administration of teriparatide 20- $\mu$ g did not increase the cardiac sensitivity to digoxin. This lack of a potentiating effect of teriparatide is supported by safety results from patients receiving digoxin in Study GHAC. A total of 55 patients used a digitalis glycoside during the study. Adverse events were analyzed separately for patients who did and did not use digitalis glycosides. The adverse events in each subgroup were similar to the overall results and there were no clinically significant differences between groups in the incidence of any adverse event. Specifically, patients who used digitalis glycosides did not experience treatment-related arrhythmia or other cardiovascular adverse events which were not observed in the overall study population.

Teriparatide had modest effects on resting hemodynamics. A series of supine and standing pulse rate and blood pressure measurements were obtained following each teriparatide dose administered at the research unit in the clinical pharmacology studies. When evaluated across subjects, the 20- $\mu$ g dose was not associated with changes in blood pressure. Pulse rate was minimally affected during standing. The average postdose value was 3.2 bpm higher during treatment with 20  $\mu$ g when compared with placebo ( $p < 0.05$ ). Treatment with teriparatide did not differ statistically from placebo in regards to the maximum increase in standing pulse rate averaged across subjects (10 bpm vs 6.4 bpm during teriparatide and placebo administration). Higher doses were associated with small reductions in diastolic blood pressure and elevations in pulse rate in a dose-dependent fashion.

Although average changes in pulse rate and blood pressure following dosing with teriparatide were small, some subjects in the clinical pharmacology studies demonstrated an exaggerated blood pressure response and developed hypotension. There was one documented case of hypotension in the supine position (at the 60- $\mu$ g dose). There were several cases of symptomatic orthostatic hypotension, and this type of event was the most significant safety finding observed in the clinical pharmacology studies. These episodes typically began within 4 hours of dosing, lasted from a few minutes to less than 6 hours, and only required the subject to recline for treatment. No clinically important cardiac arrhythmias were found during the episodes. The frequency of symptomatic orthostatic hypotension was greater at the higher doses than at the 20- $\mu$ g dose. Several study subjects experienced dizziness upon standing following a 20- $\mu$ g dose, but there was only one documented case of symptomatic orthostatic hypotension among the study subjects

who received this dose. When study subjects with symptomatic orthostatic hypotension received subsequent doses, they usually did not experience orthostatic hypotension.

In the Phase 3 studies, patients' activities were not restricted following the initial dose, but they were required to remain at the study site for at least 3 hours to be evaluated if symptoms of orthostatic hypotension occurred. Under these circumstances more typical of clinical use than the conditions in the clinical pharmacology studies, there were no significant differences or trends among treatment groups in the incidence of the COSTART terms hypotension and postural hypotension. Hypotension was reported in 1.1% of patients in the placebo group, 0.9% of patients in the 20- $\mu$ g group, and 1.6% in the 40- $\mu$ g group in Study GHAC. Postural hypotension was reported in 0.2% of patients in the 20- $\mu$ g group and no patients in either the placebo or the 40- $\mu$ g groups. There was no difference among groups in systolic or diastolic blood pressure or heart rate, which were not timed in relation to dosing. The frequency of syncope was similar between patients assigned to teriparatide and placebo. Furthermore, there were no increases in the incidence of clinically significant outcomes, such as accidental injury or nonvertebral fractures, which might be indirectly related to orthostatic hypotension.

### **Relevance of Cardiovascular Data to Safety**

None of the cardiovascular effects thought to be associated with severe chronic hyperparathyroidism appear to be associated with once daily administration of teriparatide for up to 2 years. While orthostatic hypotension was not a clinically significant finding in the Phase 3 studies, it is considered a treatment-related effect and may occur early in the course of treatment in susceptible individuals or in the case of overdose.

## **7.8. Electrocardiogram Results**

Teriparatide did not have clinically important effects on the ECG when evaluated across five clinical pharmacology studies. Results from 12-lead surface ECGs pooled across subjects and submitted with the NDA were subsequently supplemented with additional ECG data from healthy volunteers and subjects with stable, mild or moderate heart failure. The final dataset included 118 subjects, of whom 98 were healthy volunteers, 7 had renal insufficiency, and 13 had stable heart failure. Subjects ranged from 21 to 84 years of age, and 75% were at least 50 years old. Exposure to teriparatide consisted of single subcutaneous administration at doses that ranged from 0 (placebo) to 80  $\mu$ g. The preponderance of data was obtained for placebo and the 20- $\mu$ g dose (104 of 118 subjects). Measurement times included the time associated with maximal serum teriparatide concentration. The ECGs obtained in these studies were reviewed by cardiologists associated with organizations under contract to interpret ECGs in Lilly-sponsored clinical studies. In an analysis of data combined across these 5 studies, there were no clinically important adverse effects of teriparatide on the ECG, including the QTc, even when 4 times the proposed therapeutic dose was administered. Dose-related shortenings in the RR, QT, and QTc intervals allay any concern in regard to adverse

effects on repolarization. These responses reflect the activity of teriparatide in modestly increasing heart rate. The lack of any effect on the PR and QRS intervals attests to the fact that there is no disruption in cardiac conduction. Although there is no evidence from the preclinical or existing clinical data to indicate any adverse effect of teriparatide on cardiac conduction or repolarization, Lilly intends to acquire additional ECG data in patients with osteoporosis treated with teriparatide.

## 7.9. Post-Approval Surveillance

The sponsor is committed to worldwide safety monitoring of its drug products before and after marketing approval. The sponsor is continuing to work with the FDA to refine the Fortéo™ (i.e., teriparatide) post-approval surveillance plan.

## 7.10. Safety Conclusions

Based upon the primary Phase 3 safety database, leg cramps were considered treatment associated and clinically relevant. Based upon the entire safety database, nausea and headache were considered treatment associated and clinically relevant. Hyperuricemia was statistically significant, although there was no increased incidence of gout, arthralgia, or urolithiasis associated with hyperuricemia in the clinical trials. Effects of teriparatide on serum and urine calcium were mild and transient in both the 20- $\mu$ g and 40- $\mu$ g groups. Orthostatic hypotension was observed in clinical pharmacology studies. One subject experienced symptomatic orthostatic hypotension after receiving a 20- $\mu$ g dose and other cases occurred with higher doses. None of these adverse events was severe enough to cause discontinuation from the 20- $\mu$ g group, although nausea was a significant cause of discontinuation from the 40- $\mu$ g group. None of the biochemical changes was associated with adverse clinical effects, and routine laboratory monitoring is not indicated.

Continued follow-up of 1930 patients for approximately 18 months following discontinuation of the randomized treatment studies demonstrated that there were no short-term or long-term adverse effects detected following withdrawal of teriparatide. There was no evidence of adverse effects that might be attributed to long-term suppression of endogenous PTH secretion.

## 8. Benefit/Risk Assessment

In patients with osteoporosis, teriparatide provides substantial vertebral and nonvertebral antifracture benefits within a relatively short duration of treatment. Essentially all men and postmenopausal women respond to teriparatide as measured by BMD. Teriparatide is safe and well tolerated, and there were no serious adverse effects associated with teriparatide therapy. Considered together, teriparatide is a valuable intervention therapy for postmenopausal women and for men with osteoporosis. This section of the document describes:

- teriparatide as a true bone formation agent that provides a new approach to the treatment of osteoporosis
- the demonstrated benefits of teriparatide on vertebral and nonvertebral fracture risk, and on bone mass in patients with osteoporosis
- the risks identified during clinical studies of teriparatide, including adverse effects and laboratory findings related to the known physiologic effects of PTH
- the benefit-risk rationale for selection of the recommended 20- $\mu$ g/day dose of teriparatide.

### 8.1. Rationale for Teriparatide as a Therapeutic Agent

Once daily administration of teriparatide directly stimulates osteoblasts to synthesize bone on trabecular, endocortical, and periosteal surfaces resulting in enhancement of architectural and biomechanical properties. Histomorphometric and biomechanical studies demonstrate that the effect of teriparatide on bone is distinct from currently available osteoporosis therapies (*Marcus 2000*). The mechanism by which teriparatide acts is fundamentally different from that of resorption inhibitors (that is, bisphosphonates, estrogens, SERMs, and calcitonin), which reduce osteoclast-mediated bone resorption, secondarily reduce the rate of bone formation (because formation and resorption are coupled processes in vivo), and overall decrease the rate of bone turnover. Importantly, despite the availability of antiresorptive therapies, a significant unmet medical need remains for osteoporosis treatments that quickly and safely reduce the risk of fracture and the associated morbidity. The results presented in the NDA for teriparatide confirm hypotheses initially posed in the 1920s regarding the beneficial effects of daily administration of PTH on bone (*Bauer et al. 1929; Selye 1932*). The clinical study results summarized in this briefing document demonstrate an excellent benefit-to-risk profile for teriparatide in the treatment of osteoporosis in postmenopausal women and in men.

The potential for a causal relationship between teriparatide treatment and reported adverse events and treatment-emergent abnormal findings was assessed by review of data from 24 clinical studies which enrolled over 2800 women and men. The maximum exposure duration to teriparatide was 2 years. The primary Phase 3 safety database

consisted of 1637 postmenopausal women treated for up to 2 years in Study GHAC. The safety experience for teriparatide also includes approximately 1800 patient-years of observation after treatment withdrawal from the first and second visits of an ongoing 5-year, observational, follow-up study, Study GHBJ. Additionally, results from this study will allow continued assessment of patients after teriparatide treatment has been withdrawn. In the completed studies, teriparatide was safe and well tolerated when administered daily for up to 2 years. No serious safety concerns were identified during the Phase 3 clinical studies or during the 18 months of follow-up in Study GHBJ.

## **8.2. Summary of Demonstrated Benefits**

### **Teriparatide Therapy Reduces the Risk of Vertebral Fractures in Women With Postmenopausal Osteoporosis**

- Study GHAC clearly established that, compared with placebo, teriparatide doses of 20 and 40 µg given for up to 2 years were effective in reducing the risk of new vertebral fractures and of vertebral fractures classified as moderate or severe. The two doses were comparable with respect to fracture risk reduction.

### **Teriparatide Therapy Improves Clinical Correlates of New Vertebral Fractures**

- Clinical studies of marketed antiresorptive drugs have failed to demonstrate treatment-related reductions in episodes of back pain, a clinically important symptom of vertebral fracture (*Nevitt et al. 2000*). In contrast, teriparatide significantly reduced the incidence of new or worsened back pain collected as an adverse event. There was a significant 26% reduction in the spontaneous reports of new or worsened back pain in the 20-µg group and a 30% reduction in the 40-µg group.

### **Teriparatide Therapy Reduces the Risk of Nonvertebral Fractures in Women With Postmenopausal Osteoporosis**

- In Study GHAC, each dose of teriparatide given for up to 2 years resulted in significant reductions in the risk of nonvertebral fractures, and in the risk of nonvertebral fragility fractures, defined as those fractures caused by trauma that probably would not have fractured a nonosteoporotic bone.
- An analysis of time-to-first-nonvertebral-fracture demonstrated that teriparatide treatment did not result in increased skeletal fragility at any time, and there is evidence for separation of the incidence curves at less than 1 year of treatment.

### **Teriparatide Therapy Increases BMD in Postmenopausal Women and in Men**

- In postmenopausal women, treatment with teriparatide 20 or 40 µg/day for up to 2 years caused statistically significant, dose-related increases in lumbar spine and hip BMD (Study GHAC). Only 3 months of treatment were needed to demonstrate significant increases in BMD. The increase in lumbar spine BMD at endpoint was approximately 10% and 14% for the 20- and 40-µg groups, respectively. Statistically

significant increases in BMD compared with placebo were also observed at the hip and hip subregions. Total body BMD and BMC were increased, confirming that the increases in bone mass of the spine and hip did not occur at the expense of other skeletal sites.

- In men, treatment with teriparatide resulted in statistically significant, dose-related increases in lumbar spine BMD, which increased approximately 1% in the placebo group, 6% in the 20- $\mu$ g group, and 9% in the 40- $\mu$ g group. The responses were similar for men with either idiopathic or hypogonadal osteoporosis. At the femoral neck, significant BMD gains were observed in the teriparatide 20- and 40- $\mu$ g groups, respectively, but BMD in the placebo group was unchanged from baseline.
- Pharmacodynamic analyses showed no significant differences in lumbar spine BMD responses between the men in Study GHAJ and the postmenopausal women in Study GHAC.

### **Teriparatide Therapy Reduces the Incidence of Vertebral Fractures in Men with Osteoporosis**

- The proportion of men with new vertebral fractures with up to 14 months of teriparatide treatment and 18 months of observational follow-up was decreased by 50%, compared with placebo, which established a positive trend ( $p < 0.10$ ) for vertebral fracture reduction. Teriparatide also significantly reduced the incidence of moderate or severe vertebral fractures.
- While guidelines for the treatment of osteoporosis in men are not available, there is precedent for considering fracture efficacy in postmenopausal women as supportive for compounds that have been shown to increase BMD in men. Therefore, the BMD results and the encouraging, but limited, vertebral fracture data in men, along with the fracture efficacy demonstrated in women, support the position that teriparatide is indicated for the treatment of osteoporosis in postmenopausal women and in men.

### **Skeletal Efficacy is Durable Following Cessation of Teriparatide Therapy**

- While longer-term data are being accrued in Study GHBJ, findings from this observational study thus far demonstrate that significant reductions in vertebral and nonvertebral fracture risk, preservation of height, and BMD responses to teriparatide are maintained for at least the first 18 months after treatment is withdrawn. For women who were treated with teriparatide in Study GHAC and then followed for an additional 18 months, the risk reduction for one or more new, posttreatment, vertebral fractures was 40% and 45% for the 20- and 40- $\mu$ g groups.

### **Teriparatide Stimulates Formation of Normal Bone**

- Histomorphometric findings from iliac crest biopsies of women with osteoporosis treated with teriparatide demonstrated that teriparatide stimulates new bone formation

through direct effects on osteoblasts, confirming results from previous clinical and nonclinical studies (Reeve et al. 1980; *Hodsman and Steer 1993*; *Jerome et al. 2001*).

### 8.3. Summary of Demonstrated Clinical Risks

Overall, treatment with teriparatide was well tolerated. There was no significant difference among treatment groups in mortality or in the number of patients reporting a serious adverse event.

Based on a review of the primary, Phase 3, safety database (Study GHAC) and clinical pharmacology studies as well as consideration of the known effects of PTH, the following adverse effects were considered to be associated with teriparatide therapy:

#### **Leg cramps, Nausea, and Headache**

- Leg cramps (at the 20- $\mu$ g dose), nausea (at the 40- $\mu$ g dose), and headache (at the 40- $\mu$ g dose) appeared to be related to teriparatide administration. All of the adverse events were relatively mild, and nausea at the 40- $\mu$ g dose was the only adverse event to cause significant discontinuation from the Phase 3 studies. A similar safety profile was observed in men receiving treatment with teriparatide (Study GHAJ) for nausea and headaches, although there was no increased incidence of leg cramps.

#### **Orthostatic Hypotension**

- While orthostatic hypotension was not a clinically significant finding in the Phase 3 studies, it is considered a treatment-related effect based on the known pharmacology of PTH, and observations in the clinical pharmacology studies.

#### **Transient Increases in Serum and Urine Calcium**

- Treatment with teriparatide was associated with small, statistically significant increases in the 4- to 6-hour (peak) postdose serum calcium concentrations in postmenopausal women and in men consistent with the known physiologic effects of PTH. The 24-hour postdose serum calcium was not different between placebo- and teriparatide-treated groups, confirming that the increase in serum calcium concentrations was transient.
- In Study GHAC, 1.5% of patients in the placebo group, 11% of patients in the teriparatide 20- $\mu$ g group, and 28% of patients in the teriparatide 40- $\mu$ g group had at least one serum calcium concentration that exceeded the ULN (2.64 mmol/L, [10.6 mg/dL]), but in about two thirds of these patients, the serum calcium was normal on repeat testing. In greater than 99% of patients in the 20- $\mu$ g group, the peak serum calcium concentrations were below 2.76 mmol/L (11 mg/dL).
- In men treated with teriparatide (Study GHAJ) the peak postdose serum calcium concentrations were elevated above normal at least once in 0%, 6%, and 16% of

patients in the placebo, 20- and 40- $\mu$ g groups, respectively, but were not elevated in most patients upon repeat testing.

- There were small increases in urinary calcium excretion associated with teriparatide treatment in postmenopausal women and in men consistent with the known physiologic effects of PTH. There was no difference among the placebo, 20 and 40- $\mu$ g groups in the percent of patients who had at least one 24-hour urine calcium excretion that exceeded the ULN (300 mg/day). Urolithiasis was not increased in patients treated with teriparatide.

#### **Increases in Serum Uric Acid**

- In women and men treated with teriparatide 20  $\mu$ g, there were asymptomatic but statistically significant, 13% to 20% increases in median serum uric acid levels. The increases presumably reflected the known physiologic action of PTH on the kidney.

#### **Antibodies to Teriparatide**

- Some women developed antibodies to teriparatide that did not appear to neutralize the biological activity of teriparatide or produce any adverse clinical outcomes. No men in Study GHAJ were found to have antibodies, perhaps because of their shorter duration of exposure compared with women in Study GHAC.

### **8.4 Potential Risk Based on Nonclinical Studies**

The sponsor and its Oncology Advisory Board have extensively reviewed the unexpected occurrence of osteosarcoma in the 2-year rat study. In man, osteosarcoma is a very rare primary malignant tumor of bone, with an annual incidence of osteosarcoma estimated at less than 1/200,000 based on data from large national and international cancer registries. No osteosarcomas or other primary bone tumors have been reported in patients treated with teriparatide, and the reports of any type of cancer in the Phase 3 studies demonstrate no increased overall risk resulting from treatment with teriparatide.

The sponsor has concluded that the increased incidence of osteosarcoma seen in rats is not likely to be predictive of an increased risk of osteosarcoma in patients with osteoporosis who are treated with teriparatide. Many factors, including those discussed in Section 3.6, were considered in reaching this conclusion.

1. There are important differences between the intended human clinical use and the exaggerated, skeletal effects in the 2-year rat experiment, which are attributed to:
  - near-lifetime (80% to 90% of life span), daily exposure to teriparatide in the rat study, compared with the relatively short duration of treatment (approximately 2% to 3% of life span) anticipated in humans
  - fundamental differences in bone physiology between rats and humans, including near-lifetime, skeletal growth and the lack of haversian remodeling in rats
  - near-lifetime stimulation of rat osteoblasts leads to an exaggerated pharmacologic effect on bone mass, and was associated with bone neoplasia. Prolonged stimulation of target cells in rats with hormones not related to PTH has been shown to lead to neoplasia which was not predictive of an increased risk in humans.
2. Teriparatide did not cause proliferative or preneoplastic changes in bones of cynomolgus monkeys administered teriparatide for 18 months at plasma level exposures approximately eight times greater than those which occur in humans, and more than two times greater than those in rats that developed osteosarcomas.
3. Extensive testing showed that teriparatide is not genotoxic, and it did not increase the incidence of bone neoplasia in rats treated for 1 year, or of neoplasms in soft tissues of rats treated for 2 years.
4. Hyperparathyroidism is associated with chronic stimulation of osteoblasts, but this disease is not associated with an increased risk of bone cancer.

## **8.5. Benefit-Risk Rationale for Dose Selection**

### **8.5.1. Pharmacokinetic/Pharmacodynamic Considerations**

Pharmacokinetic and pharmacodynamic analyses in Studies GHAC and GHAJ support the administration of teriparatide to postmenopausal women and to men without regard to gender, age, body weight, smoking status, alcohol use, decreased renal function, or site of injection (abdominal wall or thigh).

While systemic exposure to teriparatide is approximately 20% to 30% lower in men than in women given the same doses, there were no gender differences with respect to safety, tolerability, or lumbar spine BMD responses to teriparatide.

### **8.5.2. Dose-Response: Benefits**

To determine the most appropriate dose for clinical use, the effects of teriparatide 20 and 40 µg on change in lumbar spine, femoral neck, and total body BMD and on fracture risk reductions in postmenopausal women were compared.

Treatment with teriparatide 40 µg increased lumbar spine, femoral neck, and total body BMD at endpoint significantly more than the 20-µg dose. However, both teriparatide doses were similarly effective in reducing the risk of vertebral fractures and the risk of multiple and severe vertebral fractures. Similar effectiveness was seen with teriparatide 20 and 40 µg in reducing the risk of any nonvertebral fragility fracture. There was no apparent difference between doses in the onset of the effect, nor was there an apparent difference in nonvertebral fragility fracture incidence in the first 6 months after treatment was withdrawn. Overall, 20 µg appears to provide as much benefit as 40 µg in terms of fracture prevention.

### 8.5.3. Dose-Response: Risks

The majority of exposure to teriparatide was at 20 and 40 µg because these doses were used in the largest studies, GHAC and GHAJ. Teriparatide doses ranged from 5 to 100 µg/day in short-term trials and 20 to 40 µg/day in the long-term trials. A total of 1943 of the patients studied received teriparatide, including 815 patients at 20 µg/day and 1107 patients at 40 µg/day.

Table 8.1 includes findings from Study GHAC relevant to dose selection.

**Table 8.1. Safety Findings Relevant to Dose Selection  
B3D-MC-GHAC**

Finding	Placebo	PTH20	PTH40
	(N=544) n (%)	(N=541) n (%)	(N=552) n (%)
≥1 High serum calcium	8 (1.5)	60 (11) <sup>c</sup>	153 (28) <sup>c</sup>
Confirmed high serum calcium	1 (0.2)	16 (3.0) <sup>c</sup>	53 (10) <sup>c</sup>
Nausea	41 (7.5)	51 (9.4)	98 (18) <sup>c</sup>
Headache	45 (8.3)	44 (8.1)	72 (13) <sup>a</sup>
Leg cramps	6 (1.1)	17 (3.1) <sup>a</sup>	13 (2.4)
Discontinuation due to adverse event	32 (5.9)	35 (6.5)	59 (11) <sup>b</sup>

Abbreviation: N = number of randomly assigned patients in treatment group(s); n = number of patients in each treatment group with the safety finding.

<sup>a</sup> p<0.05 versus placebo; <sup>b</sup> p<0.01 versus placebo; <sup>c</sup> p<0.001 versus placebo.

Based on review of these findings relevant to dose selection in Study GHAC, treatment with teriparatide 20-µg was less likely than teriparatide 40-µg to result in 1) a serum calcium level that exceeded the ULN, 2) headache or nausea, or 3) discontinuation due to an adverse event. This rationale for dose selection was also applicable to men treated with teriparatide.

### 8.5.4. Optimally Effective Dose for Treatment of Osteoporosis

The optimally effective dose of teriparatide is the one that provides the most favorable benefit-risk balance in the broadest population of therapy recipients. The lowest of more than one effective dose is preferred for chronic use in disease treatment and prevention.

Teriparatide 20 and 40 µg were equally effective in reducing new vertebral fracture and nonvertebral fracture risk to a statistically significant and clinically substantial extent in postmenopausal women. Both teriparatide 20 and 40 µg increased BMD in the lumbar spine, regions of the hip, and in the total body in postmenopausal women and in men. Both doses were effective in increasing markers of skeletal turnover, and neither was associated with any adverse skeletal effects.

Studies GHAC and GHAJ showed that while both doses of teriparatide were safe, daily administration of 20 µg of teriparatide was less likely than 40 µg of teriparatide to result in an abnormally high postdose serum calcium concentration, and was better tolerated in both men and women.

The sponsor has concluded that teriparatide 20 µg provides the optimum benefit-risk balance in a broad population of patients with osteoporosis. Therefore, the sponsor is seeking approval to market teriparatide 20 µg/day as the lowest effective dose for the treatment of osteoporosis in postmenopausal women and in men with osteoporosis.

## **8.6. Summary and Conclusions**

The benefits of teriparatide on the skeleton have been demonstrated by large-scale clinical studies conducted in postmenopausal women and in men. In postmenopausal women, teriparatide significantly reduced the risk of vertebral fractures and nonvertebral fractures. Teriparatide effectively increased lumbar spine, femoral neck, and total body BMD. The optimally effective dose of teriparatide for treatment of osteoporosis in postmenopausal women and in men is 20 µg once daily.

Risks associated with teriparatide were few. Leg cramps, nausea, and headaches were side effects associated with teriparatide therapy. While symptomatic orthostatic hypotension was observed in 1 patient receiving teriparatide in the clinical pharmacology studies, this was not a significant finding in the Phase 3 studies. Small increases in the serum uric acid were clinically unimportant. The small and transient nature of the calcemic effects of teriparatide and the lack of associated adverse clinical effects indicate that routine monitoring of serum calcium during treatment is not required.

The benefits of treatment with teriparatide injection are therefore substantial and the risks minimal. The achievement of the strong benefit on vertebral and nonvertebral fracture risk within a relatively short duration of treatment, represents a major advantage of this new approach to treat osteoporosis. Thus, teriparatide represents an important new option for osteoporosis treatment in postmenopausal women and in men.

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