

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number 21-318**

**CLINICAL PHARMACOLOGY and  
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology and Biopharmaceutics

*New Drug Application Filing and Review Form*

General Information About the Submission			
	Information		Information
NDA Number	21-318	Brand Name	Forteo™
OCPB Division (I, II, III)	DPE 2	Generic Name	Teriparatide (rDNA origin)
Medical Division	HFD-510	Drug Class	Bone metabolism
OCPB Reviewers	Sang M. Chung, Jim Wei	Indication(s)	Osteoporosis
OCPB Team Leader	Hae-Young Ahn	Dosage Form	3 mL cartridge
		Dosing Regimen	20 µg/dose QD
Date of Submission	11-11-00	Route of Administration	SC
Estimated Due Date of OCPB Review	06-15-01	Sponsor	Eli Lilly and Company
PDUFA Due Date	09-11-01	Priority Classification	1 S
Division Due Date	06-15-01		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	1	1	
multiple dose:				
Patients-				
single dose:	X	1	1	
multiple dose:	X	1	1	
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	5	5	
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X	1	1	
pediatrics:				
geriatrics:	X	1	1	
renal impairment:	X	1	1	
hepatic impairment:	X	1	1	
PD:				
Phase 2:				
Phase 3:	X	1	1	
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1	1	

<b>Population Analyses -</b>				
Data rich:	X			
Data sparse:				
<b>II. Biopharmaceutics</b>				
Absolute bioavailability:	X	1	1	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
<b>III. Other CPB Studies</b>				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
<b>Total Number of Studies</b>		16	16	
<b>QBR questions (key issues to be considered)</b>	Is the pharmacokinetics of teriparatide linear? What is the absolute bioavailability of teriparatide? What are the basic pharmacokinetic parameters?			

CC: NDA 21-318, HFD-850 (P. Lee), HFD-510 (Hedin), HFD-870 (Ahn, Chung, Wei, Haidar, Malinowski), CDR

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were increased by 73% and 77%, respectively in comparison with healthy subjects. CL/F was decreased by 32%. The age did not show significant impact on teriparatide disposition.

**Pharmacokinetics/pharmacodynamics relationship:** Despite the pharmacokinetic differences between gender or between sites of injection (thigh and abdominal), there were no significant differences with respect to safety, tolerability, or lumbar spine bone mineral density (BMD) responses to the peptide.

**RECOMMENDATION:**

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 21-318 (Teriparatide (rDNA origin) for subcutaneous injection 3 mL cartridge / Forteo™) submitted on November 11, 2000. The overall Human Pharmacokinetic Section is acceptable to OCPB. This recommendation, general comments (page 17) and labeling comments (page 17) should be sent to the sponsor as appropriate.

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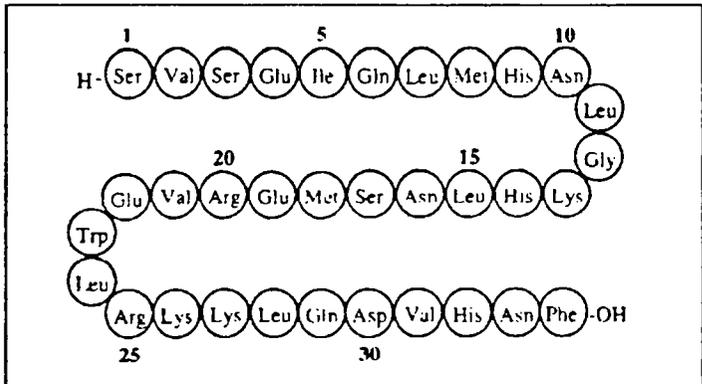
Study #	Title	Page
B3D-LC-GHBI	Absolute bioavailability of LY333334 administration via subcutaneous injection	35
B3D-LC-GHAB	LY333334: Single –dose dose range study: pharmacokinetic and pharmacodynamic properties	38
B3D-LC-GHAW	Pharmacokinetics and pharmacodynamics of LY333334 when administered alone and furosemide in stable chronic renal insufficiency.	40

B3D-MC-GHAC	Population pharmacokinetic/pharmacodynamic analyses of GHAC: effect of LY333334 in the treatment of postmenopausal women with osteoporosis.	44
B3D-MC-GHAJ	Population pharmacokinetic/pharmacodynamic analyses of GHAJ: effects of LY333334 in the treatment of men with osteoporosis.	48
PPD ANALYSES OF GHAC &GHAJ	Population pharmacodynamic analyses of GHAC AND GHAJ: Effect of LY333334 in the treatment of osteoporosis in postmenopausal women and in men.	51
B3D-LC-GHBR	Randomized, single-blind, crossover interaction study of LY333334 and digoxin pharmacodynamics in healthy volunteers	54

**BACKGROUND:**

What is the mechanism of drug action of teriparatide?

Teriparatide [Forteo™, LY333334, human parathyroid hormone (1-34), rhPTH (1-34)] is a recombinant DNA originated 34 amino acids of N-terminal parathyroid hormone (PTH). Endogenous 84-amino-acid parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. The biological actions of PTH are mediated through binding to PTH-specific cell-surface receptors. Teriparatide binds to these receptors and has the same actions in bone and kidney as PTH. Teriparatide is the first of a new class of bone formation agents based on a novel strategy to treat osteoporosis. Once-daily administration of teriparatide stimulates osteoblasts to synthesize new bone. The molecular formula of teriparatide is C 181 H 291 N 55 O 51 S 2 with molecular weight 4117.8 Dalton. A representation of the primary structure of teriparatide is shown in the following figure.



**BIOPHARMACEUTICS**

**Drug Formulation**

Are the clinical trial formulations the same as the to-be-marketed (TBM) formulation?

Two formulations were used in the development of this drug product. A \_\_\_\_\_ containing \_\_\_\_\_ was used for early Phase I and Phase II clinical trials. The lyophilized contents were reconstituted with either normal saline or with a supplied preserved diluent solution for clinical use. A preserved solution-filled cartridge formulation was used for some clinical pharmacology studies and for Phase III clinical trials. It was developed for commercial use. Its formulation is summarized in the following table.

**Table 1: Composition of preserved solution-filled cartridge formulation**

Ingredient	250 µg/mL
rhPTH(1-34)	250 µg
Glacial Acetic Acid	0.41 mg
Sodium Acetate	0.10 mg
Mannitol	45.4 mg
Metacresol	3.00 mg
Water for Injection	q.s. to 1 mL

**Reviewer's Comment:**

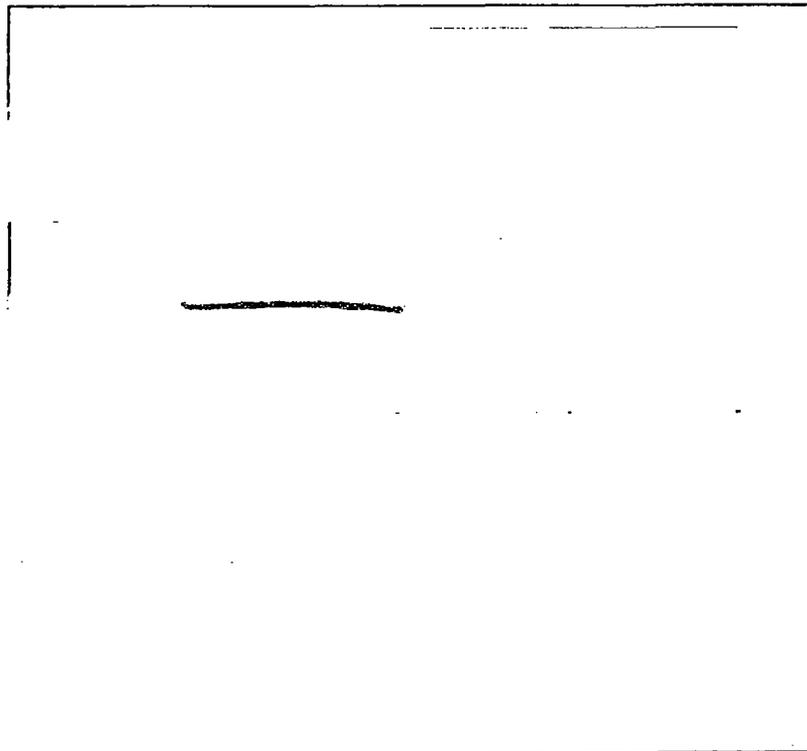
There are no bioequivalence studies in this submission. Although there were two formulations used in the drug development, the formulation used in pivotal Phase 3 clinical trials is the same as the commercial formulation. Therefore, BE studies may not be necessary.

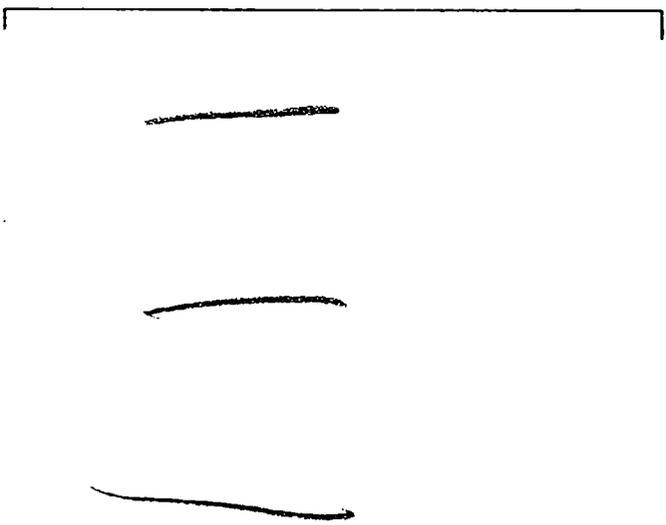
**Analytical Methodology**

There are no analytical methodology studies in this submission.

\_\_\_\_\_

standards is depicted in the following figure.





## CLINICAL PHARMACOLOGY

### I. PHARMACOKINETICS (PK):

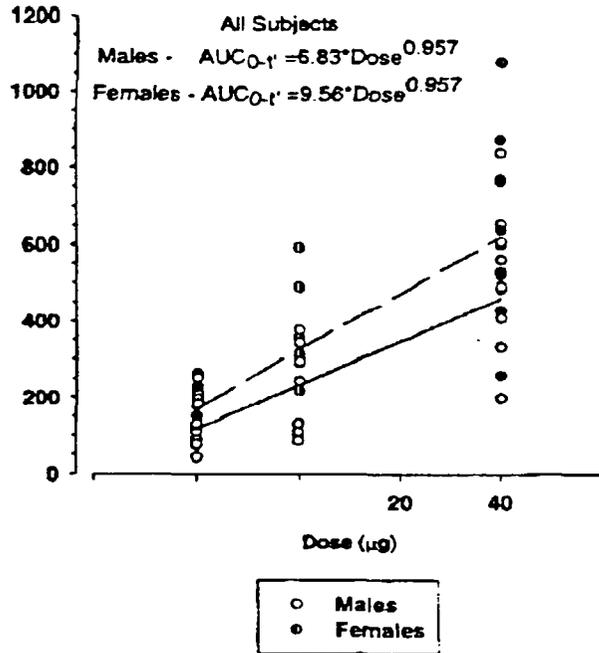
Is the pharmacokinetics of teriparatide linear?  
What is the absolute bioavailability (**F**) of teriparatide?  
What are the basic pharmacokinetic parameters?

#### *Dose proportionality study:*

In Study B3D-LC-GHBI and Amendment, the sponsor conducted a single-dose, single-blind, partially randomized, placebo-controlled, five-period crossover study in 11 healthy men and 11 healthy women aged from 50 to 84 years. The study determined the basic pharmacokinetic parameters including absolute bioavailability and dose proportionality following administrations of 20, 40 and 80 µg of teriparatide by subcutaneous injection and 17.5 µg by ———. The pharmacokinetic parameters are summarized in the following table.

SC Dose (µg)	N	CL/F (L/hr)	AUC <sub>0-t</sub> (pg hr/ml)	C <sub>max</sub> (pg/ml)
20	22	152.3 ± 91.2	165 ± 67.6	151.0±56.9
40	16	124.3 ± 65.8	393 ± 161	256.2±117.5
80	22	104.4 ± 27.9	816 ± 202.2	552.8±183.6

Clearance (CL/F) appeared to be decreased with doses increased. The reviewers communicated with the sponsor about this matter. The sponsor analyzed their data by transforming into log scale and



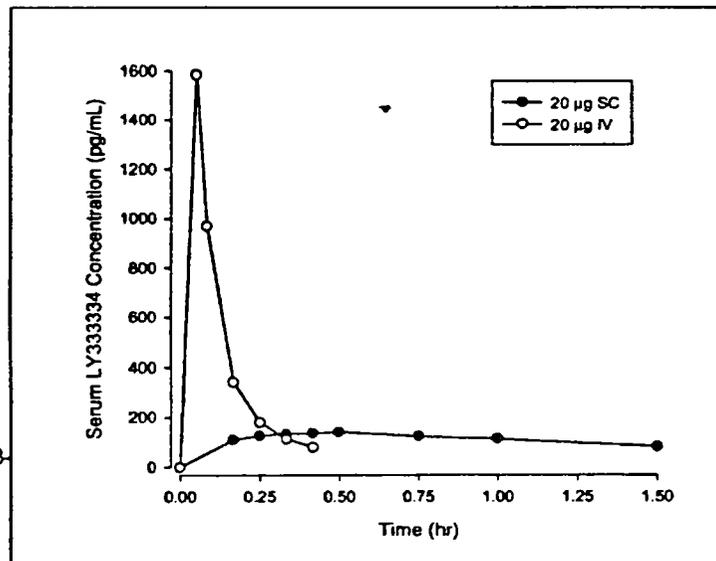
stated that teriparatide has linear dose proportionality in the dose range from 20 to 80 µg based on their power model [ $AUC_{0-t} = \alpha \times (dose)^{\beta}$ ]. Their analysis is shown in the figure above (95% of confidence interval of the slope included the value of 1 for the combined data or when separated by gender).

**Reviewer's Comment:**

The apparent clearance is regarded as a standard parameter to measure linearity of pharmacokinetic characteristics. There is a clear trend that apparent clearance CL/F decreased with dose increased. Furthermore, the data should not have been transformed into log scale for analysis of dose proportionality because the data and variations would become smaller under log scale. Therefore, the sponsor's conclusion is not acceptable.

**Absorption:**

In the same study, the rate and extent of absorption and absolute bioavailability were also determined. The following figure showed the serum concentration time profiles of 17.5-µg teriparatide by S.C. injection and I.V. infusion.



The results showed the overall disposition of the peptide after S.C. injection was determined by absorption rate (absorption half-life of 90 minutes), which was much slower than elimination rate (half-life of 8.5 minutes). The following table is the summary of pharmacokinetic parameters.

	N	T <sub>1/2</sub> (min)	K <sub>terminal</sub> (1/min)	T <sub>max</sub> (min)
SC, 20 µg	22	90.2 ± 107	0.0124 ± 0.0073	32.4 ± 14.5
SC, 40 µg	16	63 ± 19.2	0.012 ± 0.0036	28.8 ± 12.4
SC, 80 µg	22	52.2 ± 22.6	0.0159 ± 0.0075	34.0 ± 15.7
IV, 17.54 µg	22	8.53 ± 2.80	0.0886 ± 0.0265	3.49 ± 1.14

The bioavailability was estimated by both noncompartmental and population approaches (Study GHBI). The absolute bioavailability of 75% and 95% were determined by the noncompartmental and population approaches, respectively. The details of results are summarized in the following table.

Dose (µg)		Noncompartmental Approach				Population Approach	
		AUC <sub>0-last</sub> (pg hr/ml)	F (%)	AUC <sub>0-inf</sub> (pg hr/ml)	F (%)	AUC <sub>0-inf</sub> (pg hr/ml)	F (%)
SC							
20	All	165.3 ± 67.6	75.4 ± 30.0	322.0 ± 132.9	152 ± 89.5		95
	Male	143.2 ± 66.6	72.9 ± 24.3	339.3 ± 182.5	119 ± 23.8	229	96.5 ± 19.2
	Female	187.4 ± 64.0	77.6 ± 35.5	304.7 ± 59.38	181 ± 116	281	93.5 ± 13.2
IV							
17.5	All	192.3 ± 48.0		205.2 ± 49.34			
	Male	164.3 ± 31.7		176.5 ± 33.11		214	
	Female	223.1 ± 44.6		236.6 ± 45.72		253	

The comparison between conventional noncompartmental and population pharmacokinetic analyses is summarized in the following table:

	Noncompartmental approach	Population approach
K <sub>e</sub> (1/min)	0.0124	0.0099
T <sub>1/2</sub> (min)	8.53	5
CL <sub>e</sub> (L/hr)	90.34	77.1
V (L)	18.2	9.6
F (%)	75	95

**Reviewer's comments:**

Absolute bioavailability of 95% was claimed based on population approach. However, the value was significantly higher than the estimated F (75%) based on noncompartmental method using AUC<sub>0-last</sub>. It was found by the reviewer and concurred by the pharmacometrics reviewer that the population approach was too sensitive for boundary conditions to reproduce the sponsor's results. In addition, the results of F estimation using population approach were requested for 40 and 80-µg SC administration in order to compare the boundary conditions to those of 20-µg SC but the sponsor has not submitted the results. Also, F (152%) calculated using the AUC<sub>0-inf</sub> was significantly overestimated because of errors in the extrapolation of AUC after SC administration. Therefore, we concluded that conventional approach (75%) based on AUC from time zero to last sampling was the only acceptable estimation of absolute bioavailability. The above issue was conveyed to the sponsor through the telephone conference (20-FEB-2001).

The effect of administration sites on absorption was investigated in the single-dose dose-ranging study (Study LC-GHAB). The results showed that AUC<sub>0-t</sub> values were 14% higher for the thigh than for the abdomen at the 60-µg dose and 21% higher for the thigh than for the abdomen at 75-µg dose. However, the magnitude of difference was not statistically significant and the sponsor claimed it was also not

clinically relevant for safety and effectiveness of teriparatide in the pivotal Phase III studies. The pharmacokinetic parameters are summarized in the following table.

Dose (µg)	Route of Administration	N	AUC <sub>0-t</sub> (pg hr/ml)	C <sub>max</sub> (pg/ml)
30	Abdominal wall	8	741	381
	Thigh	9	766	402
60	Abdominal wall	9	1541	744
	Thigh	6	1785	772
75	Abdominal wall	8	1698	777
	Thigh	7	2451	905

**Reviewer's comments:**

At an internal meeting, the medical safety reviewer confirmed that the difference in plasma levels due to the site administration was not clinically relevant for safety and effectiveness of teriparatide in the pivotal Phase III studies.

**Distribution:**

The sponsor claimed the volume of distribution (Vd) of teriparatide as an average of 1.7 L/kg.

There was no accumulation with daily administration of teriparatide according to an open-labeled, partially randomized, outpatient healthy postmenopausal women study with 40-µg teriparatide once-daily SC administration (Study B3D-LC-GHAD). Mean pharmacokinetic parameters are summarized in the following table.

Dose (40 µg)	N <sup>a</sup>	C <sub>max</sub> (pg/ml.)	T <sub>max</sub> (min)	AUC <sub>0-2.5</sub> <sup>b</sup> (pg*hr/ml.)
1	18	479 (204 - 875)	54 (40 - 90)	802 (354 - 1140)
14	16	438 (146 - 697)	62 (40 - 91)	767 <sup>c</sup> (290 - 1143)
Overall	34	460 (146 - 875)	58 (40 - 91)	773 <sup>c</sup> (290 - 1143)
p-Value		0.733	0.816	0.167

a Represents the number of subjects sampled following the 1st and 14th doses. Subjects 2111 and 2114 did not receive the 14th dose.

b AUC 0-2.5 = area under the curve to 2.5 hours.

c Subject 1996 is not included in the AUC summary for dose 14 (n=15) and the AUC overall (n=33).

No serum or plasma protein binding studies have been performed with teriparatide.

**Reviewer's comments:**

The proposed Vd value (1.7 L/kg) was significantly overestimated compared to the values in Phase I studies (referring to the following table). The overestimation is apparent by the reflection of Vd of 0.24 ± 0.078 L/kg after IV and Vd of 0.32 L/kg after 20 µg SC. There appears to be errors in the application of the method to calculate Vd (Vd=CL<sub>s.c.</sub> /k) mainly because of using k<sub>a</sub> (0.0124 ± 0.0073 min<sup>-1</sup>) instead of k (0.0886 ± 0.0265 min<sup>-1</sup>) after SC.

	Vd/F L	
	Phase I (LC-GHBI)	Phase III
Dose ( $\mu\text{g}$ )	20	20 or 40
Female	9.1	94.4
Male	10.1	133

**Metabolism and Elimination:**

No metabolism or excretion studies have been done with teriparatide. However, the elimination mechanisms have been studied and published in literature. Teriparatide is reported to be fragmented in the hepatic Kupper cells and then excreted into urine.

Elimination from systemic circulation was rapid with 8.5 minutes serum elimination half-life and serum systemic clearance of 90.34 L/hr (Study B3D-LC-GHBI).

**II. Special Populations:**

Do special populations and disease state patients (renal, hepatic) require adjustment in their dosage regimens?  
 Is the pharmacokinetic profile of teriparatide in elderly population different from that in young population?

**Renal:**

In the Study LC-GHAW, the effect of chronic impaired renal function on teriparatide was assessed in a phase I, multi-center, single-blind, randomized, crossover study in healthy subjects and patients with mild to severe renal insufficiency. The study design had two treatments: treatment A: teriparatide 40  $\mu\text{g}$  SC + placebo, total 25 (male 14, female 11) and treatment B: teriparatide 40  $\mu\text{g}$  SC + furosemide 20-100 mg IV, total 26 (male 15, female 11) with three different groups under each treatment arm: Group 1: healthy subjects with age and gender generally matched for the chronic renal insufficiency (CRI) groups (CrCl  $\geq 90$  mL/min); Study Group 2: Stable mild to moderate CRI subjects (CrCl of 31-75 mL/min); and Study Group 3: stable severe CRI subjects (CrCl  $< 30$  mL/min).

There were no significant differences in any pharmacokinetic parameters in mild to moderate renal insufficiency (creatinine clearance of 31-75 ml/min, N=10) compared to healthy subjects (N=8). Although there was no statistically significant difference in  $C_{max}$ ,  $AUC_{0-1}$  and T1/2 between subjects with severe renal insufficient (N=10) and healthy subjects, the T1/2 and  $AUC_{0-1}$  was increased 77% and 73%, respectively (see the following table).

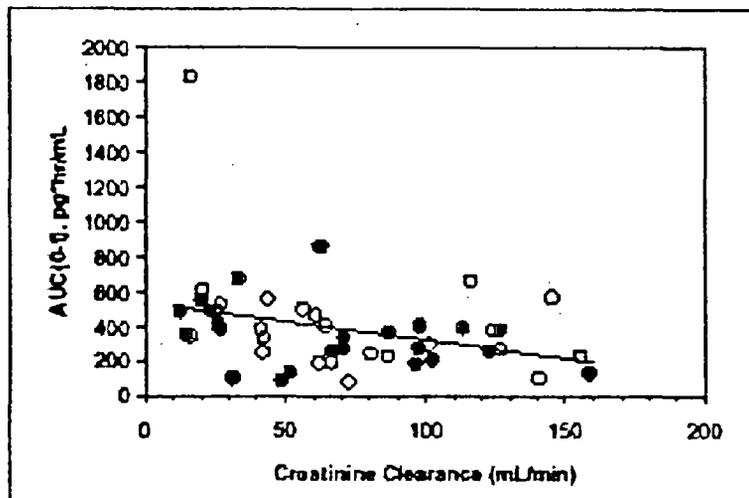
**Table GHAW.11.4. Mean Ratios of LY333334 Pharmacokinetic Parameters of Patients with Severe Renal Impairment Relative to Normal volunteers B3D-LC-GHAW**

Pharmacokinetic Parameter*	Least-Squares Mean		Percent Mean Ratio	Significance p-Value
	Normal	Severe Impairment		
$C_{max}$ (ng/mL)	222.8	227.7	102.2%	0.99
$AUC_{0-1}$ (ng·hr/mL)	317.0	456.2	143.7%	0.38
$AUC_{0-\infty}$ (ng·hr/mL)	321.7	453.8	141.2%	0.12
$AUC_{0-24}$ (ng·hr/mL)	438.8	627.4	142.9%	0.02 (0.16)
$t_{1/2}$ (min)	68.4	121.3	177.3%	0.06 (0.06)
CLT (L/hr)	95.2	65.9	69.3%	0.59 (0.16)
V/F (L)	163.4	154.5	94.6%	0.97

\*Abbreviations:  $C_{max}$  - maximum serum concentration;  $AUC_{0-1}$  - area under the curve from time 0 to 1 hours;  $AUC_{0-\infty}$  - area under the curve from time 0 to time of last concentration above BQL;  $AUC_{0-24}$  - area under the curve from time 0 to 24 hours;  $t_{1/2}$  - half life; CLT - apparent systemic clearance; V/F - apparent volume of distribution.  
 \* p-values for the log-transformed variables.

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There was a correlation between  $AUC_{0-1}$  and creatinine clearance. As depicted in the following figure,  $AUC_{0-1}$  increased as creatinine clearance decreased ( $p=0.027$ , open circles = Treatment A, closed circles = Treatment B). However, the sponsor concluded that there was no need to consider special dosing consideration for renal insufficiency.



**Reviewer's comments:**

In severely renal impaired patients, the  $AUC_{0-1}$  and  $T_{1/2}$  of teriparatide were increased by 73% and 77%, respectively ( $\alpha=0.12$  and  $0.06$ ).  $CL/F$  was decreased by 32%.

**Hepatic:**

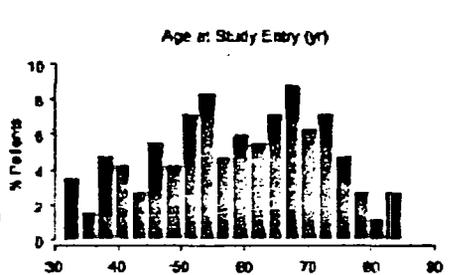
A specifically designed study of the effect of impaired hepatic function on teriparatide has not been performed. However, the impact of hepatic function was evaluated in the pivotal Phase III studies (LC-GHAC: Population PK/PD and GHAJ: Population PK) within the range of parameters included in the analysis, which were serum bilirubin, alanine transaminase, aspartate transaminase and gamma glutamyl transferase concentrations. The sponsor concluded that there was no significant association between teriparatide disposition and these hepatic function tests.

**Reviewer's comments:**

Based on the study report, patients with severe hepatic dysfunction were excluded from the study. Therefore, it is not known what the effect of the impaired hepatic function has on teriparatide disposition. The hepatic tests (measurement of serum bilirubin, alanine transaminase, aspartate transaminase or gamma glutamyl transferase concentrations) in these patients with osteoporosis may not be adequate enough to define the association between hepatic function and disposition of teriparatide because the majority of patients were within normal ranges. Therefore, the study can not be accepted.

**Age:**

The effect of age on teriparatide pharmacokinetics was explored in Study GHAJ as a covariate in the population pharmacokinetic analysis. The spectrum of patients' age is depicted in the following figure. It was concluded that there was no association between teriparatide clearance and age.



**Ethnic:**

In Study GHAC, the influence of ethnic origin on teriparatide disposition was examined. The populations were predominantly Caucasian with less than 1.5% representing Asian or other origins. Due to the limited ethnic diversity, the influence of race cannot be conclusively determined.

**Gender:**

In women, AUC<sub>0-t</sub> values were higher than in men for IV dose of 17.5 µg (Study LC-GHBI). The difference in systemic exposure was 26% at the dose.

**Brief summary of Study LC-GHBI related to gender**

Dose (µg)	Sex	AUC <sub>0-last</sub> (pg hr/ml)	F (%)
SC 20	Male	143.2 ± 66.6	72.9 ± 24.3
	Female	187.4 ± 64.0	77.6 ± 35.5
IV 17.5	Male	164.3 ± 31.7	
	Female	223.1 ± 44.6	

**Reviewer's comments:**

The difference in these pharmacokinetic parameters between men and women was not corrected by the body weight. The population pharmacokinetic analysis indicated that body weight had impact on pharmacokinetic parameters. However, in Phase III clinical trials, it was concluded that there were no gender differences with respect to response to the teriparatide (referring to Pop PK/PD review in Appendix).

**Pediatric:** No pediatric study was conducted.

**III. DRUG INTERACTIONS**

Do furosemide and hydrochlorothiazide interact with teriparatide in chronically renal impaired patients ?  
Is there any significant effect of teriparatide on diroxin therapeutic effect ?

**Furosemide:**

In the Study LC-GHAW, the serum pharmacokinetics of teriparatide was evaluated following single doses of 40 µg teriparatide with placebo (Treatment A) and 40 µg teriparatide with intravenous furosemide (Treatment B). Serum concentrations of teriparatide were assessed in blood samples collected for up to 24 hours for Treatment A and up to 3 hours for Treatment B.

The pharmacokinetic changes are summarized in the following table.

Table GHAW.11.2. Statistical Summary of Serum LY333334 Pharmacokinetic Parameters: Treatment B Versus Treatment A B3D-LC-GHAW				
Least-Squares Mean				
Pharmacokinetic Parameter*	Treatment A	Treatment B	Percent Mean Ratio	Significance p-Value
C <sub>max</sub> (pg/mL)	236.9	215 *	91.1	0.450
AUC <sub>0-3</sub> (pg · hr/mL)	369.6	337 *	91.4	0.399
AUC <sub>0-t</sub> (pg · hr/mL)	464.9	337 *	72.7	0.058
AUC <sub>0-∞</sub> (pg · hr/mL)	575.7	584 "	101.5	0.929 (0.287) <sup>a</sup>
t <sub>1/2</sub> (min)	69.7	103 *	149.0	0.033 (0.025) <sup>a</sup>
CL/F (L/hr)	96.9	81.5	84.1	0.035 (0.287) <sup>a</sup>
V/F (L)	137.9	177 †	128.6	0.063

Abbreviations: C<sub>max</sub> = maximum serum concentration; AUC<sub>0-3</sub> = area under the curve from time 0 to 3 hours; AUC<sub>0-t</sub> = area under the curve from time 0 to time of last concentration above BQL; AUC<sub>0-∞</sub> = area under the serum concentration versus time curve to infinity; t<sub>1/2</sub> = half-life; CL/F = apparent systemic clearance; V/F = apparent volume of distribution.  
\* p-values for the log-transformed variables.

The pharmacodynamic interactions regarding calcium was also determined. The changes in the serum and urine calcium levels are summarized in the following tables.

**Table GHAW.11.6. Serum Ionized Calcium AUC<sub>0-24</sub>: Comparison of LY333334 40 µg Administered with Intravenous Furosemide and LY333334 40 µg Administered with Placebo B3D-LC-GHAW**

Treatment	AUC <sub>0-24</sub> (LS Mean, mM·hr)	Pairwise Comparison	Percent Mean Ratio	P-Value
A: 40 µg LY333334	29.17	—	—	—
B: 40 µg LY333334 with Furosemide	29.06	B vs A	99.65	0.592
<b>Group</b>				
1: Normal	30.16	—	—	—
2: Mild/Moderate	28.82	2 vs 1	95.57	0.022
3: Severe	28.37	3 vs 1	94.08	0.025

Abbreviations: AUC<sub>0-24</sub> = area under the curve from time 0 to 24 hours; vs = versus.

**Table GHAW.11.7. Urine Calcium Excreted in 24 Hours: Comparison of LY333334 40 µg Administered with Intravenous Furosemide and LY333334 40 µg Administered with Placebo B3D-LC-GHAW**

Treatment	Urine Calcium (mmol) Excreted in 24 Hours	Pairwise Comparison	Percent Mean Ratio	P-Value for Ratio
A: 40 µg LY333334 with Placebo	2.280	—	—	—
B: 40 µg LY333334 with Furosemide	3.120	B vs A	136.8	0.00051
<b>Group</b>				
1: Normal	4.632	—	—	—
2: Mild/Moderate	1.846	2 vs 1	39.85	0.002
3: Severe	1.624	3 vs 1	35.06	0.004

Abbreviations: vs = versus.

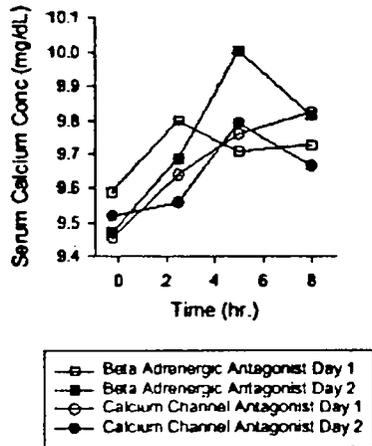
The sponsor concluded that there were no statistically significant treatment differences in the primary pharmacokinetic parameters except the terminal elimination half-life (49% higher) and CL/F (16% lower) following teriparatide with furosemide (Treatment B) than with placebo (Treatment A).

**Reviewer's comments:**

The study design, results, and conclusions are acceptable. The effect of furosemide on teriparatide PK parameters is very limited.

**Atenolol and Calcium Channel blockers**

In Study B3D-LC-GHAE, the effect of oral antihypertensive drugs on teriparatide was assessed in an open-label, nonrandomized, outpatient investigation. Drugs were atenolol (25-50 mg), diltiazem (240-300 mg), nifedipine (30 mg), felodipine (10 mg), and nisoldipine (10 mg). Drug interaction was evaluated only through pharmacodynamic measure, which was serum calcium level. Mean serum total calcium concentration versus time profiles is depicted in the following figure.



The sponsor concluded that when administered as a once-a-day treatment for hypertension, neither calcium channel antagonists nor atenolol potentate the early period blood pressure response associated with teriparatide.

**Reviewer's comments:**

According to the safety reviewer, the serum calcium level is reasonable and reproducible surrogate marker for serum levels of teriparatide. The major concern is number of subjects in each drug interaction studies (referring to the following table). The results should not be generalized based on number of subject(s) but could be presented with subject(s) in the study. The results should not be included for diltiazem and felodipine and nisoldipine because there were only 1 – 2 subjects.

	Drug	Dose (mg)	N
$\beta$ -adrenergic Receptor Antagonist	atenolol	25-50	6
Calcium Channel Antagonist	Cardizem <sup>®</sup> (diltiazem)	CD 240-300	2
	Procardia <sup>®</sup> (nifedipine)	XL 30	5
	Plendil <sup>®</sup> (felodipine)	10	1
	Sular <sup>®</sup> (nisoldipine)	10	1

**Hydrochlorothiazide (HCTZ):**

The effect of oral HCTZ on teriparatide was assessed in a single-blind, partially randomized, placebo-controlled study. Number of subjects was total 21 (male 10, female 11) but one woman did not complete the study. HCTZ 25 mg was given as a single oral dose on study days 4 through 11 and it was

administered with placebo (Treatment D) and teriparatide 40 ig (Treatment E). Drug interaction was evaluated with serum or urine calcium response. The co-administration of HCTZ 25 mg orally did not have a clinically significant effect on either serum or urine calcium response by SC administration of teriparatide 40 µg. Neither the magnitude nor the time course of the serum calcium response was different as a result of the co-administration of HCTZ with teriparatide. The results are shown in the following table.

Treatment	AUC 0-24 (LS Mean, mM*hr)	Pairwise Comparison	Percent Difference	P-Value for difference
C: Forteo 40µg	53.00	—	—	—
E: Forteo 40µg + HCTZ	55.93	E vs C	5.5%	0.434

**Reviewer's comment:**

The study design, results, and conclusions are acceptable. The interaction between HCTZ and teriparatide is limited and may not be clinically significant.

**Raloxifene:**

The interaction between raloxifene and teriparatide was assessed in a phase 1, multicenter, double-blind study. Twenty-six of postmenopausal women with osteoporosis were enrolled in the study. It was part of a 3-month safety study designed to evaluate the renal effects of teriparatide administered alone or in combination with raloxifene HCl or hormone replacement therapy. The sponsor concluded that raloxifene did not alter the effects of teriparatide based on safety data.

**Reviewer's comment:**

The safety reviewer agreed with the conclusion drawn by the sponsor because serum calcium level was remaining unchanged and there was no obvious adverse reaction after the co-administration of raloxifene and teriparatide.

**Digoxin:**

The Study B3D-LC-GHBR was to determine whether there was a clinically significant pharmacodynamic interaction between the transient calcemic effects of teriparatide and the therapeutic effects of digoxin. This report was submitted in June 26, 2001 as amendment to the original NDA.

The interaction was assessed with a phase I, randomized, single-blind, crossover study in healthy male (N=2) and female (N=13). The Interaction was evaluated through pharmacodynamic (PD) measurements of calcium-mediated markers and a noncalcium-mediated marker. The measured parameters were QS<sub>2C</sub> (refer the definition in the following table), two STIs (left ventricular ejection time (LVET) and pre ejection period (PEP)), total serum calcium concentration, and heart rate. The parameters were measured within 60 minutes before dosing and at approximately 0.5, 2, 4, and 6 hours after receiving dose.

	Definition
QS <sub>2C</sub>	QS <sub>2</sub> corrected for heart rate
QS <sub>2</sub>	The time interval in milliseconds (msec) from the Q wave on electrocardiogram to the closure of the aortic valve when recorded simultaneously by Doppler echocardiogram
LVET	The time interval from the opening to the closing of the aortic valve based on digitized doppler echocardiogram data
PEP	The time interval from the origin of the Q wave on ECG to the opening of the aortic valve.

The sponsor proposed STI evaluation as a useful pharmacodynamic measure to evaluate a digoxin-calcium interaction because 1) the measure has been shown to correlate with tissue digoxin levels, 2) STIs have been used in interaction studies, and 3) the mode of digoxin action is mediated by calcium and elevated serum calcium is shown to shorten STIs. The results showed that for STI measurements, There was significant mean difference (23-25 msec) between teriparatide alone (treatment A) and digoxin treatment after steady state. However, there was no significant difference between digoxin plus placebo and digoxin plus teriparatide. Summary of QS<sub>2c</sub>, LVET<sub>c</sub>, and PEP are depicted in the following figure and those statistical results are summarized in the following table.

Parameter	Treatment	Mean	Comparison	Difference	P-Value*
QS <sub>2c</sub> (msec)	A	372.8	B vs A	-23.0	<0.001
	B	349.8	C vs A	-24.7	<0.001
	C	348.1	C vs B	-1.7	0.784
LVET <sub>c</sub> (msec)	A	294.1	B vs A	-16.0	<0.001
	B	278.1	C vs A	-15.7	<0.001
	C	278.5	C vs B	0.3	0.993
PEP <sub>c</sub> (msec)	A	80.8	B vs A	-7.9	<0.001
	B	72.9	C vs A	-8.9	<0.001
	C	71.9	C vs B	-1.0	0.829

Abbreviations: A = LY333334 Alone; B = Digoxin plus Placebo; C = Digoxin plus LY333334;  
vs = versus.

\* Statistical significance at p<0.05.

For the heart rate, digoxin lowered the HR compared to teriparatide alone (A vs. B) and digoxin plus 20 µg SC teriparatide increased 3 bpm right after the administration compared to digoxin plus placebo (B vs. C). The results are shown in the following figure and table.

Parameter	Treatment	Mean	Comparison	Difference	P-Value*
HR (bpm)	A	72.6	B vs A	-6.2	0.009
	B	66.4	C vs A	-4.6	0.062
	C	68.0	C vs B	1.6	0.695

Abbreviations: A = LY333334 Alone; B = Digoxin plus Placebo; C = Digoxin plus LY333334  
vs = versus.

\* Statistical significance at p<0.05.

For serum calcium concentrations over time, There was no exacerbation or reduction of the effect of teriparatide on total serum calcium by dosing to steady state with digoxin.

Measurement Time (hr)	Treatment Mean Change (mmol/L)			P-Value		
	A	B	C	B vs A	C vs A	C vs B
0.5	0.018	0.017	0.017	0.929	0.929	1.000
2	0.050 <sup>†</sup>	0.000	0.028	0.009	0.249	0.133
4	0.025	-0.027	0.025	0.007	1.000	0.007
6	0.030 <sup>†</sup>	-0.033 <sup>†</sup>	0.030 <sup>†</sup>	0.001	1.000	0.001

Abbreviations: A = LY333334 Alone; B = Digoxin plus Placebo; C = Digoxin plus LY333334  
vs = versus.

\* Statistical significance for change from pretreatment baseline at p<0.05.

#### Reviewer's Comment:

The sponsor assessed the effect of teriparatide on digoxin through pharmacodynamic evaluation. There are three comments on the study:

1) It is known that digoxin PD change has about 1 week lag time compared to the digoxin plasma concentration change. Therefore, the information should be provided with digoxin plasma profile or PD evaluation after at least 7 days co-administration of teriparatide and digoxin.

2) The sensitivity to the change of serum calcium and the response to digoxin may be different in patients compared to healthy subjects. Therefore, the results of changes in serum calcium levels and pharmacodynamics in healthy subjects may be difficult to translate into patients under digoxin therapy.

#### IV. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS

Do the patient factors such as gender, age affect on the response of teriparatide?

The sponsor conducted population pharmacodynamic analyses on data from two studies GHAC and GHAJ. The objectives of the pharmacodynamic analyses were to describe the time course of lumbar spine BMD and biochemical marker responses to teriparatide treatment in men and postmenopausal women with osteoporosis, to evaluate the effect of gender on the pharmacodynamic responses and to identify patient factors that influence response to teriparatide treatment.

##### ***Comments from the pharmacometrics group of DPE 2/IOCPB:***

The sponsor has performed a thorough analysis in evaluating the population PK and dose-response relationship in men and women. It is unfortunate that the study in male patients was terminated prematurely. An exposure-response relationship was demonstrated for the 20 µg and 40 µg doses. This relationship did not differ between women and men with osteoporosis. A gender-related effect on PK was observed; however, it does not appear that this difference resulted in a gender-related difference in response. Gender-related differences in the effect of covariates on BMD response was shown. For example, older women showed greater response. In men, baseline BMD values were the important predictor for response. Dose adjustment based on gender or other covariates evaluated does not appear necessary (see Appendix 1).

##### **GENERAL COMMENTS (TO BE SENT TO THE SPONSOR):**

(1) There were inconsistent values of essential pharmacokinetics parameters between noncompartmental and population approaches in Study LC-GHBI (Phase I). The pharmacokinetic parameters derived from conventional noncompartmental approach are more reliable than those from the population approach when their results are conflict. In addition, extrapolated AUC from time zero to infinity showed significant overestimation after SC administration and thus parameters such as apparent clearance and volume of distribution derived from extrapolated AUC are not acceptable in noncompartmental method.

(2) For the hepatic special population study, the sponsor did not conduct the effect of impaired hepatic function on teriparatide according to the Agency's guidance. The impact of hepatic function was evaluated in the pivotal Phase III studies (LC-GHAC: Population PK/PD and GHAJ: Population PK). Based on the study report, patients with severe hepatic dysfunction were excluded from the study. The hepatic tests (the measurement of serum bilirubin, alanine transaminase, aspartate transaminase or gamma glutamyl transferase concentrations) in these patients with osteoporosis may not be adequate enough to define the association between hepatic function and disposition of teriparatide because the



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Sam Haidar, R. Ph., Ph.D. (Pharmacometrics Consultant)

Division of Pharmaceutical Evaluation II  
Office of Clinical Pharmacology and Biopharmaceutics

RD/ FT initialed by Hae-Young Ahn, Ph.D., Team Leader

CPB Briefing: 06-13-01

Attendees: Malinowski, John Hunt, Shiew-Mei Huang, John Lazor, Ray Baweja, Hae-Young Ahn, Wei Qiu, Steve B. Johnson, Sang Chung, Xiaoxiong"Jim" Wei.

CC: NDA 21-318 (orig.,1 copy), HFD-510 (Hedin), HFD-850 (Huang), HFD-870 (Chung, Wei, Ahn, Malinowski), CDR.

Code: AP

ATTACHEMNTS:

- A. APPENDIX 1:PHARMACOMETRICS REVIEW
- B. APPENDIX 2:INDIVIDUAL STUDY SYNOPSIS

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## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

### Division of Pharmaceutical Evaluation II

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<b>NDA:</b>	<b>21-318</b>
<b>Brand<sup>®</sup> Name</b>	<b>FORTÉO™</b>
<b>Generic</b>	<b>Teriparatide Injection (rDNA)</b>
<b>Submission Date:</b>	<b>November 29, 2000</b>
<b>Sponsor:</b>	<b>Elli Lilly and Company</b>
<b>Consult:</b>	<b>Population PK, PK-PD</b>
<b>Pharmacometrics Scientist:</b>	<b>Sam H. Haidar, R.Ph., Ph.D.</b>

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### Background

NDA 21-318 for teriparatide (FORTÉO™) injection was submitted by Elli Lilly and Company on November 29, 2000. Teriparatide injection (rDNA origin) [recombinant human parathyroid hormone (1-34), rhPTH(1-34)] is the first in a new class of bone formation agents. The proposed indication for teriparatide is the

The recommended dose is 20 µg every day, administered by subcutaneous injection into the thigh or abdomen.

Teriparatide is a polypeptide that is identical in sequence to the 34 N-terminal of the natural human parathyroid hormone (PTH). Endogenous PTH has a sequence of 84-amino acids, and it is the primary regulator of calcium and phosphate metabolism in bone and kidney. It stimulates bone formation by acting on osteoblasts (bone-forming cells), increasing the renal tubular reabsorption of calcium and excretion of phosphate, and increasing intestinal absorption of calcium.

This pharmacometric consult evaluated population PK and PD studies that provided answers to important questions about teriparatide properties. These are listed below.

- Was an exposure/response relationship observed for teriparatide in male and female osteoporosis patients?
- What are the PK and PD properties of teriparatide?
- Were there gender-related differences in PK and/or PD?
- What covariates/demographic factors had a significant effect on the PK and PD of teriparatide in the patient population? Is dose adjustment needed?

Answers to above are questions are detailed in the studies reviewed below and in the Reviewer Comments section at the end.

Study B3D-MC-GHAJ evaluated the population pharmacokinetics and PK-PD relationship of teriparatide in men with osteoporosis. Similarly, Study B3D-MC-GHAC evaluated the above in women with osteoporosis.

Details of the studies are given below.

## Study B3D-MC-GHAJ

**Title:** Population pharmacokinetic analysis of GHAJ: Effects of LY333334 in the treatment of men with osteoporosis

### **Methods:**

This was a multi-center, double-blind, calcium- and vitamin D-controlled, parallel, randomized, Phase 3 trial. A total of 437 men with primary osteoporosis were enrolled. Subjects were randomly assigned to three treatment groups: 40 µg daily dose, 20 µg daily dose, or placebo. Additionally, all subjects in the study were given calcium and vitamin D.

### *Sampling:*

Single blood samples were obtained following 1, 3, 6, and 12 months of treatment.

### *Pharmacokinetics:*

Pharmacokinetic analysis was performed using nonlinear mixed effect modeling and first order maximum likelihood in NONMEM. A one-compartment model with first order absorption and elimination, which was developed in previous studies, served as the base structural model for the disposition of LY333334 (teriparatide) following subcutaneous administration. Two estimation methods were used: first order conditional (FOCE) and first order conditional with interaction. Three interpatient variability models were tested: 1)  $\eta$  on Cl/F, 2)  $\eta$  on Cl/F and V/F, and  $\eta$  on Cl/F and V/F with covariance (omega block). Three residual error models were tested: additive, proportional, and a combination of the two. Covariates evaluated for significance included the following: treatment, site of injection, age, race, weight, body mass index, blood chemistries (including AST, ALT, alkaline phosphatase, GGT, BUN, bilirubin and serum creatinine) and baseline free testosterone.

### *Pharmacodynamics:*

A separate PD analysis was not performed for Study B3D-MC-GHAJ; however, data from this study was pooled and evaluated with Study B3D-MC-GHAC. More details are provided under B3D-MC-GHAC.

### **Results:**

A 1-compartment model, with first order absorption and first order elimination provided the best fit. PK parameters of the final model are listed in Table I. Weight appeared to have a significant effect on the volume of distribution. Patient body weight in this study ranged from 48.2 kg to 129.5 kg. Table II shows the effect of the full range of body weight on the predicted volume of distribution. In addition to weight, the site of injection was also found to affect the volume of distribution. Patients injecting teriparatide in the thigh had a 30% larger volume of distribution compared to those injecting in the abdomen. This resulted in lower  $C_{max}$  compared to the abdomen.

Teriparatide CL/F was found to correlate with creatinine clearance. Creatinine clearance (CLcr) values measured for patients in Study B3D-MC-GHAJ ranged from 40.9 to 310.1 mL/min. It was estimated that a 67% decrease in CLcr resulted in 31% decrease in teriparatide CL/F.

Figure 1 illustrates the effect of the above covariates on the predicted plasma profiles of teriparatide.

Table I. Population PK parameters following subcutaneous administration of teriparatide in men with osteoporosis.

Parameter Description	Population Estimate (% SEE)	Inter-Patient Variability (% SEE)
<b>Rate of Absorption</b>		
Parameter for Ka (hr <sup>-1</sup> )	16.4 (13.2)	--
<b>Clearance</b>		
Parameter for CL/F (L/hr)	94.3 (3.11)	31.8% (22.1)
Effect of creatinine clearance on CL/F <sup>a</sup>	0.336 (31.3)	
<b>Volume of Distribution</b>		
Parameter for V/F (L)	133 (3.86)	24.7% (24.3)
Effect of body weight on V/F <sup>b</sup> (kg <sup>-1</sup> )	0.0147 (16.0)	--
Relative increase in V/F for thigh injection	0.298 (25.7)	--
<b>Inter-Patient Variability</b>		0.0689 (23.5)
<b>Interaction Term (CL/F and V/F)</b>		
<b>Residual Error (proportional)</b>		38.6% (6.78)

Abbreviations: SEE = standard error of the estimate; Ka = absorption rate constant; CL/F = apparent clearance; V/F = apparent volume of distribution.

<sup>a</sup>CL/F = 94.3\*((creatinine clearance/124.9)\*\*0.336 )

<sup>b</sup>V/F = 133\*EXP((weight - 75.1)\*0.0147 )

Table II. Effect of body weight on volume of distribution estimates.

Body Weight (kg)	Population Estimate of Volume of Distribution <sup>a</sup> (L)
48.2 (population minimum)	90
59.5 (5 <sup>th</sup> percentile)	106
74.0 (median)	131
94.8 (95 <sup>th</sup> percentile)	178
129.5 (population maximum)	296

<sup>a</sup> For a patient injecting study drug into the abdomen.

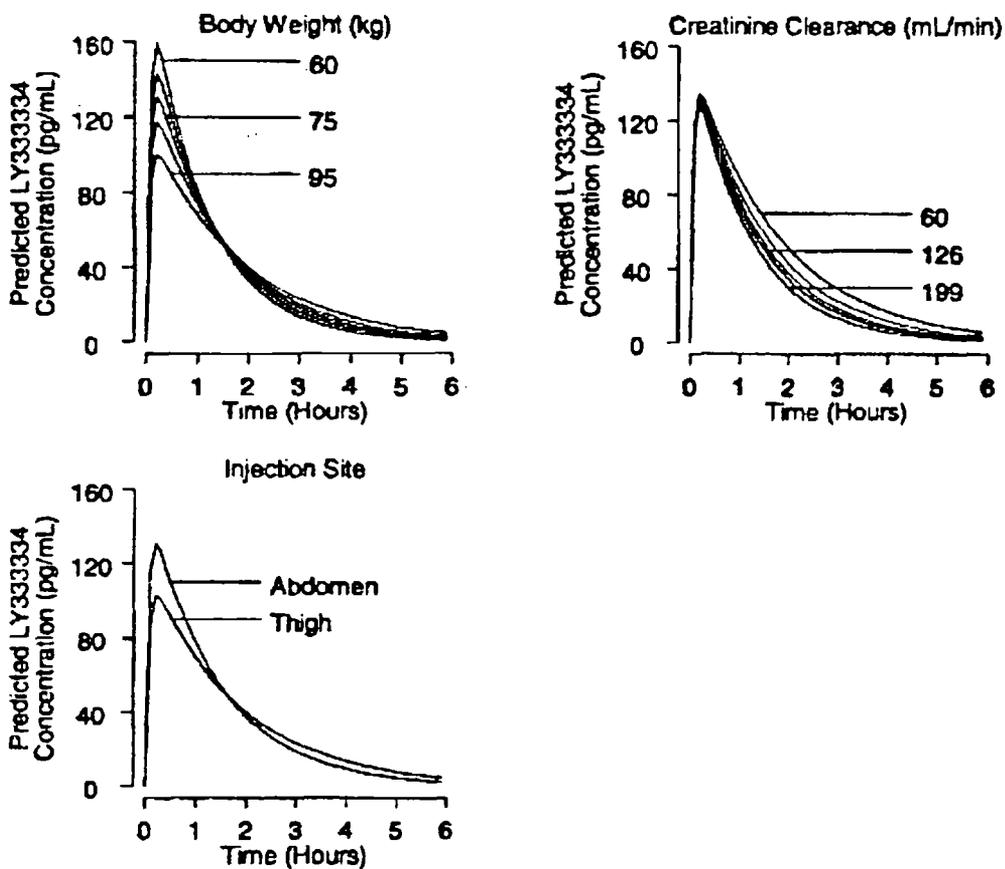


Figure 1.

**Final population pharmacokinetic model: Predicted effect of covariates on LY333334 concentrations.**

Selected covariate values represent the mean, 5th, 25th, 75th, and 95th percentile values (designations are listed for the 5th, mean, and 95th values) from the patient population. Except where noted, patient is in 20- $\mu$ g group with abdominal injection, body of weight of 75 kg, and creatinine clearance of 126 mL/min.

### Study B3D-MC-GHAC

Title: Population pharmacokinetic/Pharmacodynamic analyses of GHAC: Effects of LY333334 in the treatment of postmenopausal women with osteoporosis

**Methods:**

This was a multi-center, double-blind, calcium- and vitamin D-controlled, parallel, randomized, Phase 3 trial. A total of 1637 women with primary osteoporosis were enrolled. Subjects were randomly assigned to three treatment groups: 40 µg daily dose, 20 µg daily dose, or placebo. Additionally, all subjects in the study were given calcium and vitamin D.

*Sampling:*

Single blood samples were obtained following 1, 3, 6, 12 and 18 months of treatment.

*Pharmacokinetics:*

Pharmacokinetic analysis was performed using nonlinear mixed effect modeling and first order maximum likelihood in NONMEM. A one-compartment model with first order absorption and elimination, which was developed in previous studies, served as the base structural model for the disposition of LY333334 (teriparatide) following subcutaneous administration. Two estimation methods were used: first order conditional (FOCE) and first order conditional with interaction. Three interpatient variability models were tested: 1)  $\eta$  on C1/F, 2)  $\eta$  on C1/F and V/F, and  $\eta$  on C1/F and V/F with covariance (omega block). Three residual error models were tested: additive, proportional, and a combination of the two. Covariates evaluated for significance included the following: treatment, site of injection, age, years postmenopausal, ethnic origin, weight, body mass index, total body water, alcohol use, smoking status, blood chemistries (including AST, ALT, alkaline phosphatase, GGT, BUN, bilirubin) and creatinine clearance (calculated from 24 hour urine collection).

*Pharmacodynamics:*

PD models were developed for total lumbar spine BMD (bone mineral density), femoral neck BMD, and several biochemical markers of bone formation and resorption. Covariates evaluated in the PD modeling are listed in Table III. Three placebo-response models were evaluated:

Linear Model	$BMD = BMD_0 + \Theta \cdot Time$
Proportional Model	$BMD = BMD_0 \cdot (1 + \Theta \cdot Time)$
Exponential Model	$BMD = BMD_0 \cdot e^{(\Theta \cdot Time)}$

where  $BMD_0$  is the individual's baseline measurement. Those may be viewed as disease progression models, with the caveat that the effect of Vitamin D and calcium supplementation provided during the trial should be taken into account.

A back-propagation neural network analysis was performed to evaluate different biochemical markers as predictors of bone mineral density response to teriparatide treatment. According to the sponsor, the relationship between changes in biochemical markers and effect on spine BMD is complex and the appropriate model is unknown. Neural network analysis was chosen to avoid *a priori* assumption of the model form.

Table III. Patient covariates evaluated in the population PD analysis.

LY333334 treatment group	Bone-Specific Alkaline Phosphatase <sup>a</sup>
Injection site (abdomen or thigh)	Urinary Free Deoxypyridinoline/Creatinine ratio <sup>a</sup>
Age	Urinary N-telopeptide/Creatinine ratio <sup>a</sup>
Years postmenopausal	Thyroid-stimulating Hormone at screening
Ethnic origin	Endogenous PTH (1-84) at screening
Body weight	Procollagen I Carboxy-Terminal Propeptide <sup>a</sup>
Body Mass Index	Number of vertebral fractures <sup>a</sup>
Alcohol use	Number of nonvertebral fractures <sup>a</sup>
Smoking status	Total lumbar spine bone mineral density <sup>a</sup>
25-hydroxyvitamin D at screening	Femoral neck bone mineral density <sup>a</sup>
1,25-dihydroxyvitamin D <sup>a</sup>	

<sup>a</sup> Only baseline value used in pharmacodynamic covariate analyses.

### Results:

#### *Pharmacokinetics-*

A 1-compartment model, with first order absorption and first order elimination provided the best fit. PK parameters of the final model are listed in Table IV. The three covariates retained in the final model included dose, weight, and site of injection. Dose appeared to have a significant effect on bioavailability. The bioavailability of the 40 µg dose was predicted to be 80% relative to the 20 µg dose. Body weight and site of injection appeared to have a significant effect on the volume of distribution. Patient body weight in this study ranged from 39.5 kg to 120 kg. Table V shows the effect of the full range of body weight on the predicted volume of distribution. The site of injection was also found to affect the volume of distribution. Patients injecting teriparatide in the thigh had a 21% larger volume of distribution compared to those injecting in the abdomen. This resulted in lower  $C_{max}$  compared to the abdomen. The effect of the above covariates on the predicted plasma levels of teriparatide is illustrated in Figure 2.

#### *Pharmacodynamics-*

##### *(Combined male and female patients: Studies GHAI + GHAC)-*

The median observation period was 21 months in women and 11 months in men. To eliminate the effect of differences in duration of treatment, the effect of gender was evaluated at equal time intervals (0 to 12 months for both groups) and with all data included (18 and 24 months for women). Population PD analysis indicated no statistically significant gender differences in lumbar spine BMD response. It should be noted, however, that interpatient variability was high. Additionally, some patient factors affecting response did differ between men and women. For example, a greater BMD response was observed in older women or those with relatively high levels of endogenous PTH. In men, an important determining factor for response was baseline lumbar spine BMD. Those with a higher baseline were more likely to show a greater increase in BMD. Bone status at baseline, as reflected by biochemical markers, was a significant predictor of response in both men and women. Patients with high bone turnover at the start of treatment had a predicted increase in BMD that was 60% greater than patients with low bone turnover rate.

The placebo model, which included vitamin D and calcium supplementation, predicted that a typical patient would have a slight increase in total spine BMD (Figure 3). Age was an important factor affecting response in women: a typical 80 year-old patient had about a 3% increase in BMD at 24 months, while a typical 56 year-old patient had no change in BMD. In men, on the other hand, baseline BMD was the significant patient factor. Those with a high baseline spine BMD had a predicted 2.3% increase in BMD while those with a low BMD baseline had a predicted 2.2% decrease in BMD (Figure 4).

The time course of the rate of BMD increase in response to therapy appears to be greatest during the first year of treatment. A dose-response relationship was observed. The exposure-response model predicted a 7.4% and 10.9% increase in lumbar spine BMD following 12 months of treatment with 20 µg and 40 µg teriparatide, respectively (Figure 5).

Table IV. Population PK parameters following subcutaneous administration of teriparatide in post-menopausal women with osteoporosis.

Parameter Description	Population Estimate (%SEE)	Inter-Patient Variability (%SEE)
<b>Bioavailability</b>		
Bioavailability of 40 µg relative to 20 µg	0.803 (5.26)	--
<b>Rate of Absorption</b>		
Parameter for Ka (hr <sup>-1</sup> )	10.4 (10.1)	--
<b>Clearance</b>		
Parameter for CL/F (L/hr)	62.2 (3.65)	49.2% (17.4)
<b>Volume of Distribution</b>		
Parameter for V/F (L)	94.4 (4.92)	40.1% (23.9)
Effect of body weight on V/F <sup>a</sup> (kg <sup>-1</sup> )	0.0136 (20.0)	--
Relative increase in V/F for thigh injection	0.211 (35.4)	--
<b>Inter-Patient Variability</b>		0.125 (21.0)
<b>Interaction Term (CL/F and V/F)</b>		
<b>Residual Error (additive) (pg/mL)<sup>2</sup></b>	109 (33.9)	
<b>Residual Error (proportional)</b>	45.5% (7.54)	

Abbreviations: SEE = standard errors of estimation; Ka = absorption rate constant; CL/F = apparent clearance; V/F = apparent volume of distribution.

<sup>a</sup> V/F = 94.4 \* EXP((weight - 65.1) \* 0.0136)

Table V. Effect of body weight on predicted volume of distribution.

Body Weight (kg)	Population Estimate of Volume of Distribution <sup>a</sup> (L)
39.5 (population minimum)	66.6
65.6 (population average)	95.0
120 (population maximum)	199

<sup>a</sup> For a patient injecting study drug into the abdomen.

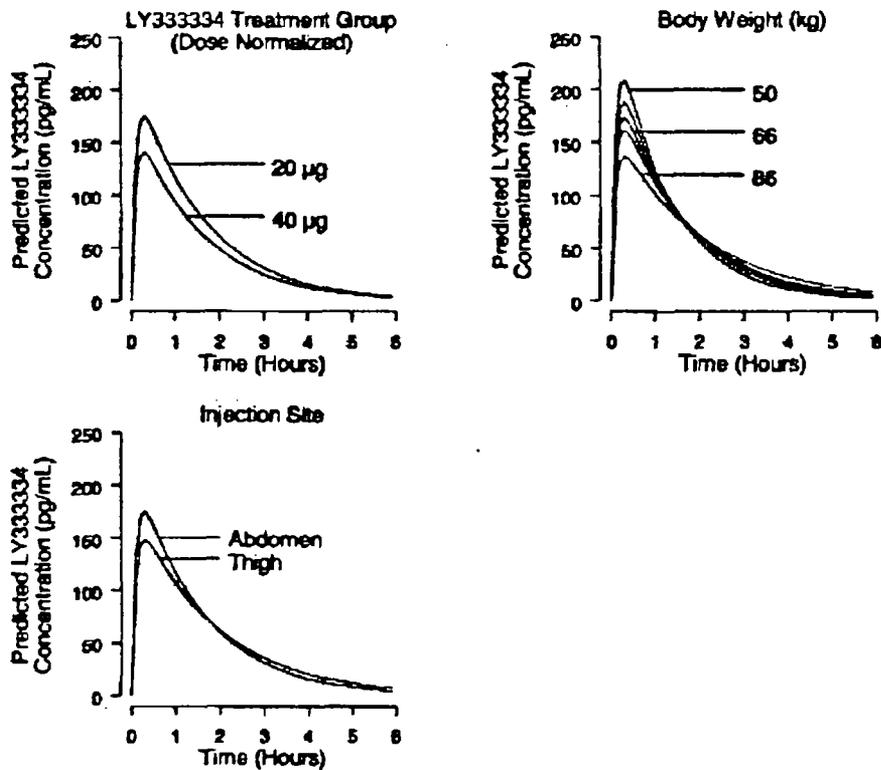


Figure 2

Final population pharmacokinetic model: Predicted effect of covariates on LY333334 concentrations.

Weights represent the mean, 5th, 25th, 75th, and 95th percentile values (designations are listed for the 5th, mean, and 95th values) from the patient population. Except where noted, patient is in 20-µg group with abdominal injection and a body of weight of 66 kg.

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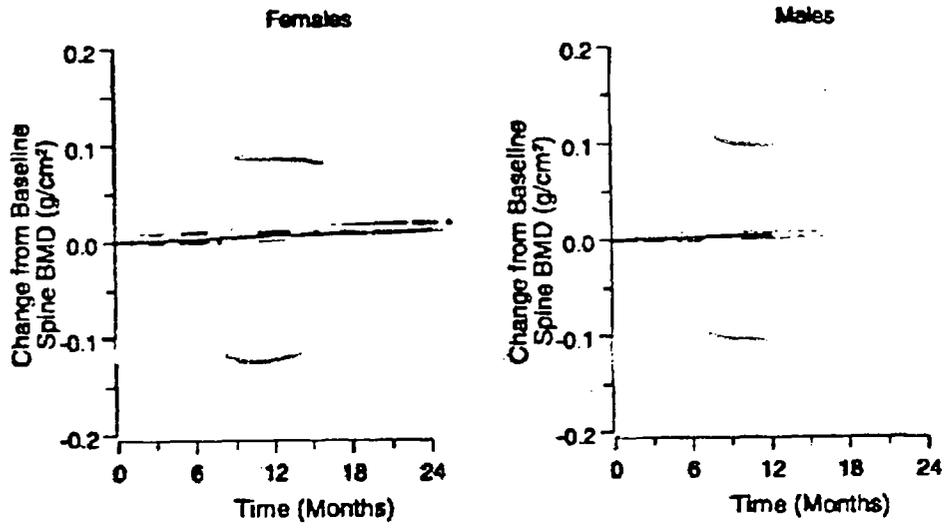


Figure 3

Final placebo-response model: Change in total lumbar spine bone mineral density over time.

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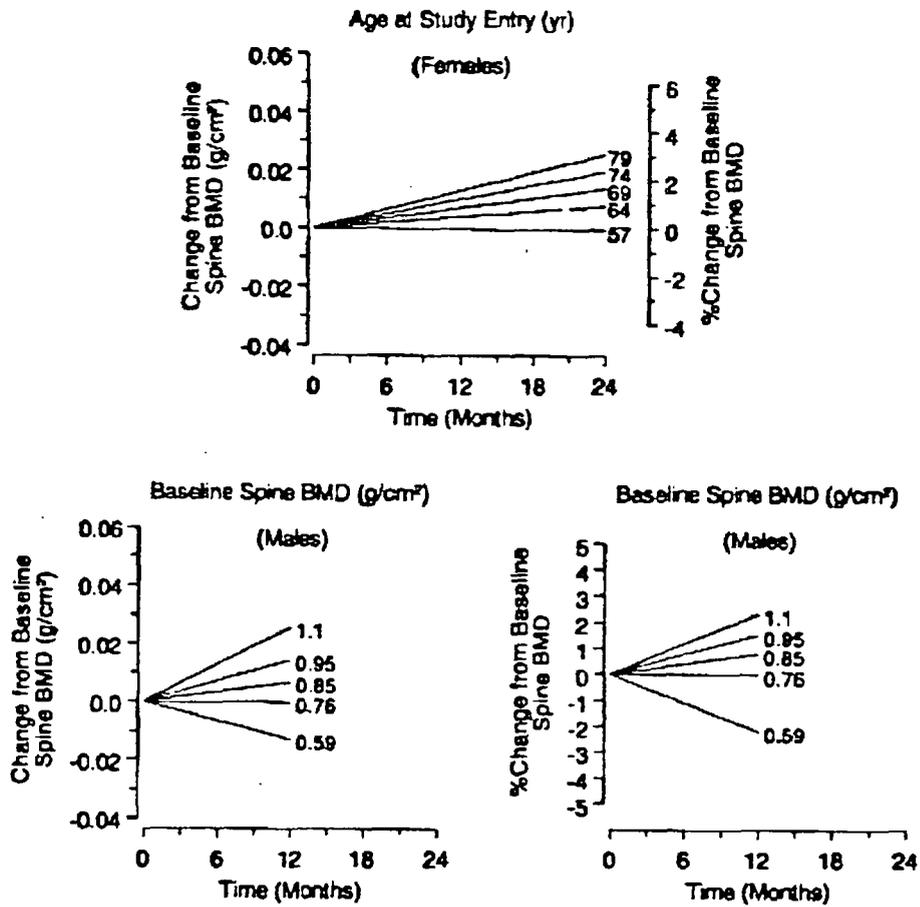
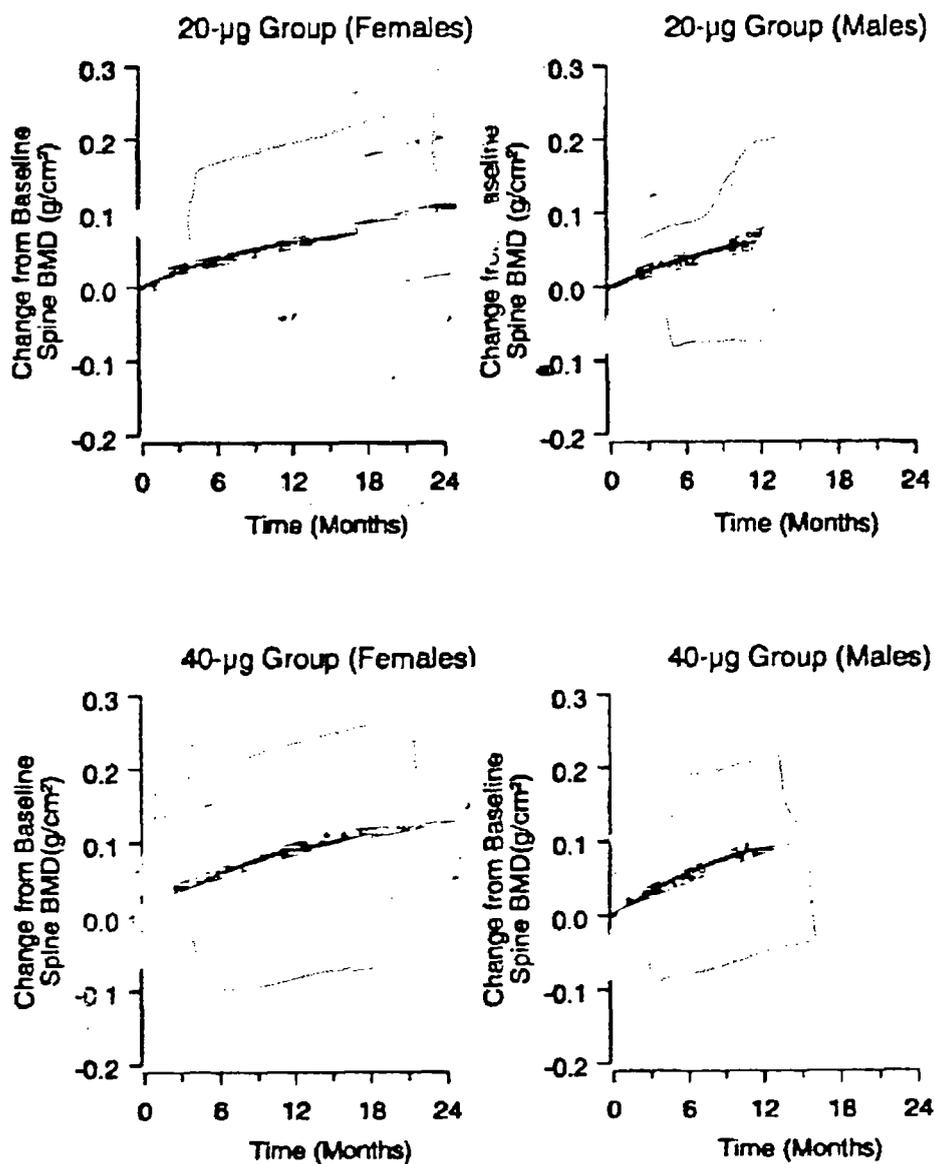


Figure 4

Final placebo-response model: Predicted effect of covariates on change in total lumbar spine bone mineral density.

Selected covariates represent the mean, 5th, 25th, 75th and 95th percentile values from the respective placebo patient populations.

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**Figure 5**

**Final treatment-response model: Change in total lumbar spine bone mineral density over time.**

Solid line represents the predicted change for the "typical" patient (mean values for each of the covariates in the final treatment-response model). Symbols represent the observed change for individual patients.

**Reviewer's Comments:**

The sponsor has performed a thorough analysis in evaluating the population PK and dose-response relationship in men and women. It is unfortunate that the study in male patients was terminated prematurely.

An exposure-response relationship was demonstrated for the 20 µg and 40 µg doses. This relationship did not differ between women and men with osteoporosis.

A small effect (increase in BMD) was observed in the placebo group, which also included vitamin D and calcium supplementation.

A gender-related effect on PK was observed; however, it does not appear that this difference resulted in a gender-related difference in response.

Gender-related differences in the effect of covariates on BMD response was shown. For example, older women showed greater response. In men, baseline BMD values were the important predictor for response.

Dose adjustment based on gender or other covariates evaluated does not appear necessary.

Absence of difference in response between the two sites of injection may need to be confirmed by the medical officer (HFD-510).

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Sam H. Haidar, R.Ph, Ph.D.  
Office of Clinical Pharmacology and Biopharmaceutics  
Division of Pharmaceutical Evaluation II

cc:

NDA 21-318

HFD-870 (Malinowski, Ahn, Chung, Wei, Haidar)

HFD-510 (Schneider, Hedin)

HFD-850 (Lee P.)

CDR

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Appendix 2. Study Synopsis

2. Synopsis

<u>Name of company:</u> Eli Lilly and Company	<u>Summary table referring to Part of the dossier.</u>	<u>(For National Authority use only)</u>
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<u>Name of active ingredient:</u> LY333334		

Clinical Study Synopsis: Study B3D-LC-GHBI

**Title:** Absolute Bioavailability of LY333334 Administered via Subcutaneous Injection

**Investigators:**

**Study Centers:** This was a single-center study.

**Dates of Study:** January 2000 through April 2000

**Clinical Phase:** Phase I

**Objectives:** Primary objective:  
- to determine the absolute bioavailability of LY333334 20-µg and 40-µg doses administered via subcutaneous injection.  
Secondary objectives  
- to evaluate the pharmacokinetics of LY333334 by gender  
- to evaluate the 24-hour time course of the serum and urinary calcium responses to LY333334  
- to evaluate the safety of LY333334.

**Methodology:** Single-dose, single-blind, partially randomized, placebo-controlled, five-period crossover study.

**Number of Subjects:** LY333334 and placebo Male 11, Female 11, Total 22

**Diagnosis and Inclusion Criteria:** Generally healthy men and women between the ages of 50 and 85 years, inclusive.

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LY333334 B3D-LC-GHBI

Main Report

**Dosage and Administration:** Test Product LY333334

Treatment B: 20 µg, given as a single subcutaneous injection  
CT16429.

Treatment C: 40 µg, given as a single subcutaneous injection  
CT16430.

Treatment D: 17.54 µg, given as a single 28-second intravenous  
infusion  
CT12510.

Treatment E: 40 µg, given as a single subcutaneous injection  
CT16429.

Reference Therapy

Treatment A: Placebo study material, given as a single  
subcutaneous injection  
CT16439.

Calcium 1000 mg/day and vitamin D 500 IU/day, given as two  
tablets twice daily (supplied by study site).

**Duration of Treatment:** For each subject, one parenteral dose/day, maximum of five  
doses. Minimum of 1 washout day between each of the first four  
treatments (Treatments A through D); minimum of 1 month  
between Treatments D and E.

**Criteria for Evaluation:** Safety—Vital signs, electrocardiogram (ECG), clinical laboratory  
parameters, and adverse events.

Pharmacokinetic—Serum concentrations of immunoreactive  
LY333334.

Pharmacodynamic—Serum total calcium and phosphorus. Urine  
excretion: calcium and phosphorus.

**Methods:** Bioanalytical—The concentration of immunoreactive LY333334  
in human serum samples was measured by a validated  
immunoradiometric assay (IRMA).

Pharmacokinetic—The pharmacokinetics of LY333334 were  
described by a one-compartment model. The model was  
parameterized in terms of clearance and volume of distribution  
with first-order rates of appearance and elimination.  
Subcutaneous and intravenous doses were simultaneously fit by  
population pharmacokinetic methods of analysis.

Statistical—A split-plot analysis of variance, based on maximum  
likelihood estimation, was the primary model applied to compare  
responses between genders and between treatments.

**Publications Based on the Study:** There are no publications based on this study.

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Summary and Conclusions:

The absolute bioavailability of LY333334 administered by subcutaneous injection averaged 95%. There are no clinically important gender differences in the pharmacokinetics, pharmacodynamics, safety, or tolerability of LY333334.

Total systemic exposure was approximately 23% higher in women than in men when administered by subcutaneous injection and approximately 18% higher when administered by rapid intravenous infusion. The magnitude was not considered clinically relevant.

LY333334 was rapidly removed from the systemic circulation with an elimination half-life of 5 minutes. The rate of systemic absorption from the subcutaneous tissue is 15 times slower than the rate of elimination. Therefore, the rate-limiting process that determines the overall disposition of the peptide was absorption. Following subcutaneous injection, the half-life of decline of peptide in the body (77 minutes) corresponds to the absorption half-life.

The serum calcium response following single-dose subcutaneous administration of LY333334 is not significantly different from the small fluctuations in serum calcium following administration of placebo in subjects who were equilibrated on supplemental calcium and vitamin D.

Changes in calcium excretion rate were consistent with the known effect of parathyroid hormone (PTH) on the kidney. However, the total amount of calcium excreted in 24 hours was not significantly different between subcutaneous injections of placebo and LY333334.

LY333334 was safe when administered at doses of 20 µg, 40 µg, and 80 µg in the subcutaneous tissue and at 20 µg administered by rapid intravenous infusion. Tolerability to the drug administered by the subcutaneous route was inversely related to the amount injected. There were no clinically important gender differences in the safety or tolerability of LY333334.

LY333334 administered by subcutaneous injection was associated with modest hemodynamic effects. The peptide tended to lower blood pressure and raise pulse rate by an amount that would not be clinically relevant. Rarely, patients experienced symptomatic orthostatic hypotension. The effect was self-limiting and more likely to occur at the 40-µg and 80-µg doses than at 20 µg.

LY333334 was not associated with clinically important changes in cardiac conduction or repolarization.

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## 2. Synopsis

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## Clinical Study Synopsis: Study B3D-LC-GHAB

**Title:** LY333334: Single-Dose Dose-Ranging Study: Pharmacokinetic and Pharmacodynamic Properties

**Investigators:** James R. Voelker, MD, Lilly Laboratory for Clinical Research

**Study Centers:** This was a single-center study.

**Dates of Study:** September 1995 through November 1995

**Clinical Phase:** Phase I

**Objectives:**

- Evaluate the safety of subcutaneous LY333334 (rhPTH 1-34) in healthy male and female subjects age 50 years and greater.
- Assess and compare pharmacokinetic properties of LY333334 administered as single-doses into the thigh and abdominal wall
- Assess acute pharmacodynamic properties of LY333334

**Methodology:** Open label, randomized, dose escalation.

**Number of Subjects:** Male 12, Female 12, Total 24.

**Diagnosis and Inclusion Criteria:** Healthy subjects.

**Dosage and Administration:** Test Product - LY333334, 200 µg powder in sterile vials, lot CT04792. Normal saline diluent, CT 94-548-DK.  
Part I: Single doses of 5, 15, 30, 60, 75, and 100 µg injected SC into the abdominal wall. Eight men and 8 women participated.  
Part II: Single doses of 30, 60, and 75 µg injected SC into the thigh. Four men and 4 women participated.

**Reference Therapy:** None.

**Comparator drug name:** None.

**Duration of Treatment:** For each subject: One dose/day, maximum of three doses, minimum of 3 days between consecutive doses.

**Criteria for Evaluation:** Safety-- Vital signs, serum laboratory tests - electrolytes, chemistries, CBC, differential counts.

PTH (LY333334) B3D-LC-GHAB

Main Report

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Pharmacokinetic-- Serum concentrations of immunoreactive LY333334

Pharmacodynamic-- Serum - Total and ionized calcium, phosphorus, and 1, 25-dihydroxyvitamin D<sub>3</sub> concentrations, bone-specific alkaline phosphatase activity. Urine excretion - Calcium, phosphorus, cAMP, N-telopeptide.

Methods:

Bioanalytical-- PTH(1-84) and rhPTH(1-34): separate

Pharmacokinetic-- Individual serum concentration-versus-time profiles were analyzed using noncompartmental modeling techniques

Statistical- Repeated measures were reduced to summary statistics for statistical analyses. Pretreatment determinations were averaged by subject to obtain subject-specific baselines, and the baseline was applied to generate adjusted responses with treatment. Comparison of treatments in separate groups of subjects was based on a split-plot analysis of variance. Statistical assessment of dose response was made through regression methods

Summary and Conclusions:

LY333334 demonstrates adequate safety in healthy older subjects when administered as a single dose ranging from 5 to 100 µg. LY333334 demonstrates modest and transient hemodynamic effects manifested by a slight lowering of blood pressure and raising of heart rate. Some subjects may be especially sensitive to the hemodynamic effect. LY333334 produces modest and transient calcemic and phosphatemic effects; responses that are consistent with the actions of endogenous PTH. A hypercalcemic dose was not identified in this study.

The pharmacokinetics of LY333334 are linear and predictable when administered by subcutaneous injection over the dosing range of 15 to 100 µg. Immunoreactive LY333334 serum concentrations peak approximately 47 minutes after subcutaneous injection and then decline in a monoexponential fashion with an apparent elimination half-life of 78 minutes. A rapid rise and decline in immunoreactive LY333334 concentrations provides the desirable pharmacokinetic profile that is believed to be associated with an anabolic bone response. LY333334 produces increases in serum 1,25-(OH)<sub>2</sub>D concentration and urinary cAMP excretion; renal responses that are consistent with the actions of endogenous PTH. A single dose of LY333334 does not acutely change serum BSAP or urine N-telopeptide, biochemical markers of bone turnover.

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## 2. Synopsis

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LY333334	

### Clinical Study Synopsis: Study B3D-LC-GHAW

**Title:** Pharmacokinetics and Acute Pharmacodynamics of LY333334 when Administered Alone and with Furosemide in Stable Chronic Renal Insufficiency

**Investigators:** \_\_\_\_\_

**Study Centers:** There were 2 study centers.

**Dates of Study:** June 1998 through June 2000

**Clinical Phase:** Phase I

**Objectives:** Primary objective:  
 -to evaluate the effect of stable chronic renal insufficiency (CR) on the serum and urinary calcium response to LY333334.  
 Secondary objectives:  
 -to determine if the acute calcemic and calciuretic effects of LY333334 are affected by furosemide administration  
 -to evaluate the influence of renal function on the pharmacokinetics of LY333334 with and without furosemide  
 -to evaluate the influence of renal function on the secondary endpoints of pharmacodynamic response [serum 1,25-(OH)<sub>2</sub>D and phosphorous] to LY333334.

**Methodology:** A multi-center, single-blind, randomized, crossover study in healthy subjects and patients with mild to moderate renal insufficiency.

LY333334 B3D-LC-GHAW

Main Report

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**Number of Subjects:** LY333334 + Furosemide: Male 15, Female 11, Total 26;  
LY333334 + Placebo: Male 14, Female 11, Total 25.

**Diagnosis and Inclusion Criteria:** Study Group 1: Healthy subjects with age and gender generally matched for the CrCl groups. CrCl in this healthy control group was  $\geq 90$  mL/min.  
Study Group 2: Stable mild to moderate CrI subjects. Mild-moderate CrI was defined as a CrCl of 31-75 mL/min.  
Study Group 3: Stable severe CrI subjects. Severe CrI was defined as a CrCl  $\leq 30$  mL/min.

**Dosage and Administration:** Test Product LY333334  
Treatment A: LY333334 500 µg/mL was administered subcutaneously as single doses of 40 µg.  
Treatment B: LY333334 500 µg/mL was administered subcutaneously as single doses of 40 µg.  
LY333334 lot numbers CT11171; CT16430.  
Reference Therapy  
Treatment A: Placebo for furosemide 10 mL of 0.9% normal saline was administered as a single intravenous injection infused over a 5-minute time period.  
Treatment B: Furosemide (20 to 100 mg) was administered as an intravenous injection containing 3 mL of solution infused over a 5-minute time period. The size of the furosemide dose varied among subjects, depending on the underlying CrCl.

**Duration of Treatment:** For each subject: one dose of Treatment A or Treatment B per test period. At least 60 hours separated the two LY333334 doses.

**Criteria for Evaluation:** Safety—vital signs, orthostatic blood pressure measurements, electrocardiogram (ECG), clinical laboratory parameters, and adverse events.  
Pharmacokinetic—Noncompartmental pharmacokinetic parameters of serum LY333334.  
Pharmacodynamic—Serum total and ionized calcium concentrations, serum phosphorus concentration, serum 1,25-(OH)<sub>2</sub> vitamin D, urinary calcium, phosphorus, and sodium excretion.

**Methods:** Bioanalytical— , of LY333334 was performed on serum samples obtained at 0.25, 0.5, 0.75, 1.0, 1.5, 2.25, 3.0, 3.75, 4.5, 5.25, and 24 hours after LY333334 + placebo dosing, and 0.25, 0.5, 0.75, 1.0, 2.25, and 3 hours after LY333334 + furosemide dosing.  
Pharmacokinetic—LY333334 pharmacokinetic parameters were obtained by analyzing the individual serum concentration-versus-time profiles

using noncompartmental methods of analysis.

Statistical—Pharmacodynamic, hemodynamic, and pharmacokinetic parameters were compared between CRI groups and between treatments via a split-plot mixed-effects model based on maximum likelihood estimation. The group of healthy subjects served as control. For the pharmacodynamic parameters, serum 1,25-(OH)<sub>2</sub>D was included as a covariate for serum calcium and furosemide excretion as a covariate for urine calcium. Regression methods were applied to model selected pharmacokinetic parameters as a function of creatinine clearance.

**Publications Based on the Study:**

There are no publications based on this study.

**Summary and Conclusions:**

- Compared to normal subjects, patients with mild, moderate, and severe renal impairment had approximately 60-65% lower calcium excretion in 24 hours following administration of 40 µg LY333334. Because the fractional excretion of calcium in the renal insufficiency groups was equivalent to or higher than in the healthy group, the difference in cumulative response is presumed to be due to differences in the number of functioning nephrons.
- The ionized serum calcium response to LY333334 was significantly reduced in patients with renal insufficiency compared to healthy subjects. Neither the renal insufficiency nor the healthy groups showed a response in serum total calcium. These results suggest that chronic renal insufficiency is associated with resistance to the calcemic effect of LY333334.
- Subjects with mild to severe renal impairment appeared to have diminished serum 1,25-(OH)<sub>2</sub>D and phosphaturic responses following administration of 40 µg LY333334.
- The amount of calcium excreted when LY333334 was coadministered with intravenous furosemide was 37% higher than the amount of calcium excreted following administration of LY333334 plus placebo (p<0.001). The magnitude of this effect is not considered clinically significant.
- Compared to the response during treatment with LY333334, the coadministration of furosemide with LY333334 was associated with a 2% (p<0.02) increase in serum total calcium AUC<sub>0-24</sub>. No differences occurred in the maximum concentration or in serum ionized calcium concentration. The small increase in calcium exposure is not considered clinically important.
- The pharmacokinetics of LY333334 in subjects with mild or moderate chronic stable renal insufficiency (creatinine clearance of 31-75 mL/min) did not differ significantly from normal subjects.

- Neither maximum serum concentrations nor total systemic exposure to LY333334 differed significantly between patients with moderate to severe renal insufficiency and normal subjects. Although total systemic exposure correlated with creatinine clearance (range, 13-161 mL/min), the magnitude of the effect was small and does not warrant special dosing considerations.
- A 40 µg dose of LY333334 was well tolerated in healthy subjects and in patients with stable mild to severe chronic renal insufficiency. The presence of renal insufficiency did not adversely alter the tolerability to LY333334.
- Concomitant acute intravenous administration of a large furosemide dose with LY333334 did not adversely effect the tolerability of the peptide in patients with severe renal insufficiency. Isolated cases of symptomatic orthostatic hypotension occurred in healthy volunteers and patients with mild to moderate renal insufficiency during coadministration. In all but one case the episode during combined treatment occurred during the initial exposure to LY333334. The data do not allow a determination to be made regarding the mechanism of the effect or the relative roles of LY333334 and furosemide.
- LY333334 was associated with a modest reduction in standing blood pressure in patients with mild or moderate renal insufficiency but not in patients with severe renal insufficiency. The data do not allow a determination to be made regarding the cause for the disparate effects, including the possible contributing role of comorbid conditions.
- When compared to the hemodynamic response associated with LY333334 given alone, the concomitant acute intravenous administration of a relatively large furosemide dose did not adversely affect blood pressure or pulse rate in healthy subjects or patients with mild to severe renal insufficiency.
- Based on the overall results of this study, it appears that LY333334 can be safely administered to patients with chronic renal insufficiency and to patients receiving furosemide.

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## 2. Synopsis

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### Clinical Study Synopsis: Study B3D-MC-GHAC

**Title:** Population Pharmacokinetic/Pharmacodynamic Analyses of GHAC: Effects of LY333334 in the Treatment of Postmenopausal Women with Osteoporosis

**Investigators:** This multicenter study included 99 principal investigators.

**Study Centers:** There were 99 study centers.

**Dates of Study:** 17 December 1996 (assigned to treatment) through 12 April 1999

**Clinical Phase:** Phase 3

**Objective:** Use population analyses to: 1) characterize the pharmacokinetics of LY333334 in postmenopausal women with osteoporosis; identify patient factors and laboratory parameters that may influence LY333334 disposition in this patient population; 2) describe the time course of total lumbar spine and femoral neck bone mineral density responses to placebo and LY333334 (supplemented with calcium and vitamin D) treatment; evaluate the effects of dose and systemic exposure to LY333334 on total lumbar spine and femoral neck bone mineral density; identify patient factors that may influence total lumbar spine and femoral neck bone mineral density responses to placebo and LY333334 treatment; 3) describe the time course of biochemical marker responses to LY333334 treatment; identify patient factors that may influence the response of biochemical markers of bone formation and resorption to LY333334 treatment; evaluate the potential for biochemical markers to be used as indicators of bone mineral density response to LY333334 treatment.

**Methodology:** Double-blind, calcium- and vitamin D-controlled, randomized study.

**Number of Subjects:** LY333334 20 µg day: Female (Total) 541 patients.  
LY333334 40 µg day: Female (Total) 552 patients.  
Placebo: Female (Total) 544 patients.

**Diagnosis and Inclusion** Women ages 30 to 85 years, postmenopausal for a minimum of

PTH (LY333334) B3D-MC-GHAC

Population Pharmacokinetics Report

<b>Criteria:</b>	5 years, with a minimum of one moderate or two mild atraumatic vertebral fractures.
<b>Dosage and Administration:</b>	<p><b>Test Product and Reference Therapy</b></p> <p>LY333334 20 µg/day or 40 µg/day given subcutaneously, or placebo study material for injection:  CT06412, CT06485, CT06501, CT06515, CT06522, CT06524, CT06531, CT06533, CT06565, CT06567, CT06574, CT06576, CT06607, CT06610, CT06622, CT06624, CT06664, CT06666, CT06689, CT06696, CT06698, CT06700, CT07306, CT07317, CT07336, CT07343, CT07350, CT07413, CT07420, CT07436, CT07449, CT07584, CT07594, CT07796, CT07808, CT07815, CT07822, CT08130, CT08137, CT08139, CT08148, CT08180, CT08202, CT08497, CT08504, CT08507, CT08514, CT08592, CT09153, CT09160, CT09182, CT09338, CT09342, CT09414, CT09457, CT09484, CT09514, CT09518, CT09618, CT09676, CT09796, CT09800, CT09804, CT09876, CT09880, CT09978, CT09984, CT10010, CT10021, CT10026, CT10031, CT10127, CT10173, CT10287, CT10291, CT10295, CT10299, CT10325, CT10353, CT10357, CT10361, CT10365, CT10369, CT10373, CT10472, CT10476, CT10480, CT10556, CT10567, CT10571, CT10575, CT10579, CT10583, CT10587, CT10591, CT10595, CT10599, CT10603, CT10607, CT10611, CT11267, CT11310, CT11316, CT11366, CT11597, CT11601, CT11774, CT13196.</p> <p>Calcium tablets, 500 mg (open-label): 1000 mg/day, given once daily:  2MK83M, 1MX91M, 1MF68M, 0MG60M, 0MP60M, 0MU63M, 0NE23M, 1MF68M, 1MP70M, 1MX91M, 2MF79M, 2MK83M, 2MM69M.</p> <p>Vitamin D tablets, 400 IU (open-label): 400 to 1200 IU/day, given once daily:  3803803, 3803804, 3803805, 3803806, 3858902, 3939505, 3939507, 4006002, 4052901, 4170A04.</p>
<b>Duration of Treatment:</b>	<p>LY333334: 1 to 751 days</p> <p>Placebo: 1 to 750 days</p>
<b>Criteria for Evaluation:</b>	<p>Single blood samples were obtained following 1, 3, 6, 12, and 18 months of treatment for population pharmacokinetic analysis. Serum biochemical markers (bone-specific alkaline phosphatase, procollagen I carboxy-terminal propeptide); urine biochemical markers (N-telopeptide, free deoxyypyridinoline); bone mineral density (total lumbar spine and femoral neck) were evaluated in the population pharmacodynamic analyses.</p>
<b>Pharmacokinetic Methods:</b>	<p>A population pharmacokinetic model was developed using all available data from the pharmacokinetic subset. A one-compartment model with first-order appearance and elimination was selected as the base structural model. Patient factors with clinical and demographic significance, which might influence the</p>

pharmacokinetics of LY333334, were identified *a priori*. The effect of these factors (such as age, body weight, dose, and creatinine clearance) was evaluated on the parameters of the pharmacokinetic model. Potentially significant patient factors were added to the base model in combination to develop a full model. Patient factors were then removed individually from the full model to evaluate their significance. A final pharmacokinetic model was developed which included all significant patient factors. The final pharmacokinetic model was validated using parameter sensitivity and leverage analysis.

**Pharmacodynamic Methods:** For total lumbar spine and femoral neck bone mineral density (BMD), a population pharmacodynamic model was first developed to describe bone formation or loss in patients randomly assigned to placebo (supplemented with calcium and vitamin D) treatment. Patient factors with clinical and demographic significance were identified *a priori* and evaluated in the pharmacodynamic model. A pharmacodynamic model describing the therapeutic response was then developed for patients randomly assigned to LY333334 treatment using the placebo-response model as a baseline function. Patient factors which influenced the response to LY333334 treatment were identified and a final pharmacodynamic model was developed which included all significant patient factors. The effect of LY333334 concentrations on change in BMD was evaluated using exposure estimates from the final pharmacokinetic model.

For each of the biochemical markers of bone formation and resorption, a population pharmacodynamic model was developed to describe the therapeutic response in patients randomly assigned to LY333334 (supplemented with calcium and vitamin D) treatment. Patient factors which influenced the response to LY333334 treatment were identified and a final pharmacodynamic model was developed which included all significant patient factors.

The final population pharmacodynamic models for total lumbar spine and femoral neck BMD were used to generate individual estimates of change in BMD at 21 months, the median observation period. Individual estimates of biochemical marker values at 1 month were calculated from the final models for the biochemical markers of bone formation and resorption. The individual BMD and biochemical marker estimates were combined for all patients completing at least 12 months of LY333334 treatment. Population models were developed for both total lumbar spine and femoral neck BMD to evaluate the biochemical marker values at 1 month and the associated changes from baseline as indicators of response to LY333334 treatment.

**Publications Based on the Study:**

There are no publications based on this study.

**Summary and Conclusions:**

LY333334 was rapidly absorbed and eliminated following subcutaneous administration. For the typical patient, LY333334 concentrations peaked within 30 minutes and declined to less than the limit of quantitation \_\_\_\_\_ by 3 hours after injection of a 20- $\mu$ g dose. The population pharmacokinetics demonstrated that subcutaneous injection into either the abdominal wall or thigh had no clinically significant effect on the systemic exposure to LY333334. Furthermore, high serum concentrations of LY333334 were not associated with drug-related serious adverse events or clinically relevant hypercalcemia or hypercalciuria. The peptide may be administered without regard to age, body weight, smoking habits, or alcohol consumption.

Pharmacodynamic analyses of changes in bone mineral density (BMD) demonstrated that age, body weight and bone turnover status at the initiation of treatment influenced the response to LY333334. Bone status at baseline, as reflected by total lumbar spine BMD or by urinary N-telopeptide (NTX), was a significant predictor of total lumbar spine BMD response to LY333334 treatment. Those patients having lower BMD and/or higher urinary excretion of NTX were shown to have a greater increase in total lumbar spine BMD. Older women also had greater improvement in total lumbar spine BMD in response to LY333334 treatment than younger women. Age, bone turnover status at study entry, and body weight were significant predictors of femoral neck BMD response to LY333334 treatment. The therapeutic effect of LY333334 was greatest in older patients with average body weight and high urinary NTX excretion, indicative of high bone turnover, at study entry.

The pharmacodynamics of biochemical response to LY333334 administration demonstrated that biochemical markers of bone formation (serum procollagen I carboxy-terminal propeptide [PICP] and serum bone-specific alkaline phosphatase [BSAP]) responded more rapidly to LY333334 treatment than did biochemical markers of bone resorption (urinary NTX and urinary free deoxypyridinoline). These changes are consistent with positive, or anabolic, effects of LY333334 on bone. Peak concentrations of PICP were observed after only 1 month of treatment with LY333334, followed by a maximal increase in BSAP within 8 months of treatment. Biochemical markers of bone resorption reached maximal responses after 8 to 12 months of treatment. A near dose-proportional effect on the magnitude of response was observed for all biochemical markers. In general, higher baseline concentrations of biochemical markers of bone formation (indicative of increased bone turnover) were associated with a greater response to LY333334 treatment for all biochemical markers. The magnitude of the change in PICP concentration at 1 month was shown to be a better predictor of the change in total lumbar spine or femoral neck BMD at 24 months than other biochemical markers.

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PTH (LY333334) B3D-MC-GHAC

Population Pharmacokinetics Report

## 2. Synopsis

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## Clinical Study Synopsis: Study B3D-MC-GHAJ

**Title:** Population Pharmacokinetic Analyses of GHAJ: Effects of LY333334 in the Treatment of Men with Osteoporosis

**Investigators:** This multicenter study included 36 principal investigators.

**Study Centers:** There were 37 study centers.

**Dates of Study:** July 1997 through March 1999

**Clinical Phase:** Phase 3

**Objective:** Use population analyses to characterize the pharmacokinetics of LY333334 in men with primary osteoporosis and to identify patient factors and laboratory parameters that may influence LY333334 disposition in this patient population.

**Methodology:** Study B3D-MC-GHAJ was a global, Phase 3, multicenter, double-blind, calcium and vitamin D-controlled, parallel, randomized study. Four hundred thirty-seven men with primary osteoporosis were enrolled in the study. Approximately one-third of the patients were randomly assigned to LY333334 40-µg/day plus calcium and vitamin D, one-third of the patients were randomly assigned to LY333334 20-µg/day plus calcium and vitamin D, and one-third of the patients were randomly assigned to placebo plus calcium and vitamin D.

**Number of Subjects:** Male 437, Female 0, Total 437;  
 LY333334 20 µg/day: Male (Total) 151 patients  
 LY333334 40 µg/day: Male (Total) 139 patients  
 Placebo: Male (Total) 147 patients.

**Diagnosis and Inclusion Criteria:** The study patients were men with primary osteoporosis, aged 30 to 85 years, inclusive. L 2 to L-4 vertebrae must have been intact without artifacts, crush fractures, or other abnormalities which would have interfered with the analysis of the posterior-anterior lumbar spine bone mineral density (BMD) measurement which must have been at least 2.0 SD below that of young, healthy men.

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Dosage and Administration: Test Product and Reference Therapy

LY333334: 20 µg/day, given once daily; 40 µg/day, given once daily; Placebo, given once daily.

CT08419 CT08474 CT11100 CT08468 CT09988 CT09607 CT10897 CT13077 CT09328 CT11585 CT10889 CT08426 CT09587 CT09960 CT10877 CT13065 CT09583 CT09955 CT12531 CT09992 CT10901 CT11951 CT09611 CT08475 CT09595 CT08110 CT13061 CT09969 CT08461 CT09603 CT10881 CT12998 CT10893 CT11898 CT09964 CT09599 CT09973 CT10377 CT10865 CT08433 CT09591 CT10859 CT11894

Calcium tablets 1000 mg/day, given once daily:

CT: 1MF68M 1MP70M 1MX91M 1MF79M 2MK83M 2M1M69M

Vitamin D tablets 400 IU, given once daily:

CT: 3939505 3939507 4006002 41770A04

Mean Duration of Treatment: LY333334:

20-µg group: 297.5 days

40-µg group: 282.68 days

Placebo: 312.92 days

Criteria for Evaluation:

Single blood samples were obtained following 1, 3, 6, and 12 months of treatment for population pharmacokinetic analysis.

Pharmacokinetic Methods:

A population pharmacokinetic model was developed using all available data. A one-compartment model with first-order appearance and elimination was selected as the base structural model. Patient factors with clinical and demographic significance, which might influence the pharmacokinetics of LY333334, were identified *a priori*. The effect of these factors (such as age, body weight, dose, and creatinine clearance) was evaluated on the parameters of the pharmacokinetic model. Potentially significant patient factors were added to the base model in combination to develop a full model. Patient factors were then removed individually from the full model to evaluate their significance. A final pharmacokinetic model was developed which included all significant patient factors. The final pharmacokinetic model was validated using parameter sensitivity and leverage analysis.

Publications Based on the Study:

There are no publications based on this study.

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Summary and Conclusions:

LY333334 was rapidly absorbed and eliminated following subcutaneous administration. For the typical patient, LY333334 concentrations peaked within 30 minutes and declined to less than the limit of quantitation (LLOQ) by 2 hours after injection of a 20- $\mu$ g dose. The population pharmacokinetics demonstrated that subcutaneous injection into either the abdominal wall or thigh had no clinically significant effect on the systemic exposure to LY333334. Furthermore, high serum concentrations of LY333334 were not associated with drug-related serious adverse events or clinically relevant hypercalcemia or hypercalciuria. LY333334 may be administered without regard to age, body weight, smoking habits, or alcohol consumption.

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**1. Title Page**

**Population Pharmacodynamic Analyses  
of GHAC and GHAJ: Effects of LY333334 in the  
Treatment of Osteoporosis in Postmenopausal Women  
and in Men**

LY333334  
Clinical Pharmacokinetics/Pharmacodynamics

Eli Lilly and Company  
Protocol B3D-MC-GHAC and  
Protocol B3D-MC-GHAJ  
Date report approved by Lilly Medical: 19 September 2000

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This study was performed in compliance with the principles of good clinical practice (GCP). The information contained in this report is confidential and the information contained within it may not be reproduced or otherwise disseminated without the approval of Eli Lilly and Company or its subsidiaries.

## 2. Summary

Population pharmacodynamic analyses were performed on combined datasets from two pivotal Phase 3 studies, B3D-MC-GHAC and B3D-MC-GHAJ, in order to provide an overall evaluation of the patient population response and identify patient factors that influence response to LY333334 treatment. The evaluation of the pharmacodynamics of lumbar spine bone mineral density (BMD) and biochemical markers of bone formation and resorption after chronic administration of LY333334 are the subject of this report.

The objectives of the lumbar spine BMD pharmacodynamic analyses were to:

1) describe the time course of lumbar spine BMD responses to placebo and LY333334 (supplemented with calcium and vitamin D) treatment in postmenopausal women and in men with osteoporosis; 2) evaluate the effect of gender on lumbar spine BMD response to placebo and LY333334 treatment; 3) identify patient factors that may influence lumbar spine BMD response to placebo and LY333334 treatment.

The objectives of the biochemical marker pharmacodynamic analyses were to:

1) describe the time course of biochemical marker responses to LY333334 treatment in postmenopausal women and in men with osteoporosis; 2) evaluate the effect of gender on biochemical response to LY333334 treatment; 3) identify patient factors that may influence the response of biochemical markers of bone formation and resorption to LY333334 treatment; 4) evaluate the relationship between early changes in biochemical markers, in response to LY333334 treatment, and subsequent gains in lumbar spine bone mineral density.

### Methods:

A population pharmacodynamic model for lumbar spine BMD was first developed to describe bone formation or loss in patients randomly assigned to placebo (supplemented with calcium and vitamin D) treatment. Patient factors with clinical and demographic significance were identified a priori and evaluated in the pharmacodynamic model. A pharmacodynamic model describing the therapeutic response was then developed for patients randomly assigned to LY333334 treatment using the placebo-response model as a baseline function. Patient factors that influenced the response to LY333334 treatment were identified and a final pharmacodynamic model was developed which included all significant patient factors.

For each of the biochemical markers of bone formation and resorption, a population pharmacodynamic model was developed to describe the therapeutic response in patients randomly assigned to LY333334 (supplemented with calcium and vitamin D) treatment. Since biochemical markers did not significantly change as a function of time in the placebo population, placebo-response models were not developed. Patient factors that influenced the response to LY333334 treatment were identified and a final pharmacodynamic model was developed which included all significant patient factors.

The final treatment-response model for lumbar spine was used to calculate BMD values at 12 months of treatment for each patient, based on the individual's parameter estimates (empirical Bayesian estimate). These predicted BMD measurements were merged with the observed biochemical marker values, at baseline, 1 month, and 3 months of treatment, for patients who completed the 12-month visit. A neural network was developed to characterize the relationship between biochemical marker values at 1 month and 3 months, and response to treatment, as measured by change in total lumbar spine BMD.

#### Summary and Conclusions:

Population pharmacodynamic analyses confirmed that there were no statistically significant gender differences in lumbar spine BMD response. However, patient factors that influenced response differed between women and men. Older women, and women with low endogenous PTH(1-84) concentrations at baseline, were more likely to have a greater change in BMD than young women or those with endogenous PTH concentrations near the upper limit of normal (65 pg/mL). Men with higher baseline lumbar spine BMD values were more likely to have a greater change in BMD. Bone status at baseline, as reflected by serum bone-specific alkaline phosphatase (BSAP) and urinary N-telopeptide/creatinine (NTX), was a significant predictor of lumbar spine BMD response in both women and men. Patients beginning treatment while in an existing state of high bone turnover were predicted to have an increase in lumbar spine BMD that was approximately 60% higher than patients with low bone turnover status.

The pharmacodynamics of biochemical response to LY333334 administration demonstrated that markers of bone formation respond more rapidly to LY333334 treatment than do markers of bone resorption. These responses reflect the anabolic effects of LY333334 on bone. Maximum increases in serum BSAP, urinary NTX, and urinary free deoxypyridinoline were 25% to 50% lower in men compared with women. It is possible that the 30% lower systemic exposure to LY333334 observed in men was responsible for their smaller biochemical marker responses compared with women. In general, patients beginning treatment in an existing state of increased bone turnover were more likely to have a greater biochemical marker response to LY333334.

The magnitude of change in biochemical markers during the first 3 months of LY333334 treatment was shown to provide an early indication of the subsequent increase in bone mass in response to LY333334 treatment. Increases in PICP concentration, from baseline to 1 month after initiation of treatment, were highly correlated with improvements in total lumbar spine BMD at 12 months. This relationship was more pronounced in women than in men. The results of these analyses provide insight into the complex relationships between the influence of patient-specific factors and biochemical responses on the subsequent change in lumbar spine BMD in patients treated with LY333334.

## 2. Synopsis

<u>Name of company:</u>	<u>Summary table referring</u> (For National Authority use to Part _____ of the _____ dossier. only)
<u>Name of finished product:</u>	<u>Volume</u> <u>Page:</u> •
<u>Name of active ingredient:</u>	

### Clinical Study Synopsis: Study B3D-LC-GHBR

**Title:** Randomized, Single-Blind, Crossover, Interaction Study of LY333334 and Digoxin Pharmacodynamics in Healthy Volunteers

**Investigators:** \_\_\_\_\_

**Study Centers:** This was a single-site study.

**Dates of Study:** January 2001 through March 2001

**Clinical Phase:** Phase I

**Objectives:** The primary objective was to assess whether LY333334 administration results in a clinically significant change in the calcium-mediated pharmacodynamic effect (systolic time interval or (ST<sub>2</sub>) of digoxin. The secondary objective was to assess whether LY333334 administration results in a clinically significant change in the noncalcium-mediated pharmacodynamic effects of digoxin using heart rate (HR).

**Number of Subjects:** Up to 18 subjects were planned for recruitment to ensure that at least 10 subjects completed the study. Fifteen subjects completed the study.  
Male = 2, Female = 13, Total = 15

**Diagnosis and Inclusion Criteria:** Overly healthy males or females as determined by medical history and physical examination; between the ages of 18 and 60 years, inclusive; body mass index between 18 and 30, inclusive; no clinically significant abnormal laboratory tests. Women were infertile by virtue of surgery or menopause, or were using a medically acceptable form of birth control during the study.

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Teriparatide B3D-LC-GHBR

Main Report

**Dosage and Administration:** Test Product

**Treatment A:** LY333334 supplied from CT17127 250 µg/ml.

**Treatment B:** Oral digoxin was obtained from a commercial source in 0.25 mg strengths. (Manufacturer's Lot No.: OZP1676) and LY333334 placebo sc (CT17131 placebo).

**Treatment C:** Digoxin plus LY333334 20 µg sc as in the preceding text.

**Duration of Treatment:** LY333334 (20 µg sc) was given alone on Day 1. Digoxin up to 0.5 mg per day was dosed to steady state from Day 2 to 14. Day 15 and 16 treatments were oral digoxin and sc placebo or oral digoxin and LY333334 20 µg sc administered in a randomized crossover fashion on consecutive days.

**Criteria for Evaluation:** Safety—Records of observations made at specific times, unexpected signs, symptoms and/or concomitant medications were recorded, in the appropriate forms, throughout the study. Routine medical assessments took place during each clinical research unit (CRU) visit and at other times as needed. The subjects were additionally screened for signs and symptoms of digoxin toxicity. Oral temperature, blood pressure, and pulse rate (supine and sitting) were measured, and continuous electrocardiogram rhythm telemetry was used during the 3 study days. A Lilly clinical pharmacologist/investigator was responsible for monitoring the safety of study participants throughout the course of the study and for taking appropriate action concerning any event that seemed unusual, even if this event was considered to be an unanticipated benefit to the study participant.

Pharmacokinetic—There are no pharmacokinetic evaluations intended for this study.

Pharmacodynamic—Systolic time intervals (STIs), pulse rate (HR), and total serum calcium concentrations were measured within 60 minutes before dosing and at approximately 0.5, 2, 4, and 6 hours after receiving dose.

The primary endpoint was  $QS_2$  ( $QS_2$  corrected for heart rate)  $QS_2$  defined as the time interval in milliseconds (msec)

from the Q wave on electrocardiogram (ECG) to the closure of the aortic valve when recorded simultaneously by Doppler echocardiogram.

Secondary endpoints were HR, total serum calcium concentrations, and two other STIs: 1) LVET (Left Ventricular Ejection Time) as defined as the time interval from the opening to the closing of the aortic valve based on digitized doppler echocardiogram data. 2) PEP (pre ejection period) as defined as the time interval from the origin of the Q wave on ECG to the opening of the aortic valve. Holter monitor data was analyzed for ventricular tachycardia, AV junctional rhythms, 2<sup>nd</sup> or 3<sup>rd</sup> degree AV block, or ventricular fibrillation.

Methods:

Bioanalytical—Not applicable

Pharmacokinetic—There are no pharmacokinetics evaluations intended for this study.

Statistical—An analysis of variance was conducted which included treatment, time, and interaction as fixed effects, and subject as a random effect. Pairwise comparisons between treatments were made by time.

Publications based on this study As of 1 June 2001, there are no publications based on this study.

Summary and Conclusions:

Systolic time intervals measurements were analyzed with overall ANOVA (omnibus), at each time point (BY Time), and within day statistical testing. These examinations demonstrated that for the primary endpoint,  $QS_{2c}$ , there existed a mean 23 to 25 msec reduction after the subject was dosed to steady state with digoxin. This reduction was statistically significant in all cases. However, there was no difference between treating with digoxin plus placebo sc versus digoxin plus LY333334 20  $\mu$ g sc.

Secondary endpoints ( $LVET_c$ ,  $PEP_c$ , and HR) supported, in general, the above conclusions of statistical differences after treating with digoxin, but no differences between treating with digoxin plus placebo sc versus digoxin plus LY333334 20  $\mu$ g sc. However, secondary to higher levels of variability in these measures, the results were not statistically significant in all cases.

The study was adequately powered to find a difference in  $QS_{2c}$  of 6 msec if one were to have existed ( $\alpha = 0.05$ ,  $\beta = 0.2$ ). This supports the conclusion that there is no interaction between digoxin dosed to steady state and LY333334 20  $\mu$ g sc on central calcium-mediated (STIs) and noncalcium-mediated (HR) pharmacodynamic markers of digoxin activity. LY333334 20  $\mu$ g sc does not increase cardiac sensitivity to digoxin.

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Hae-Young Ahn  
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