CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020815

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OCT 23 1997

Clinical Pharmacology & Biopharmaceutics Review

NDA:	**20-815**
SUBMISSION DATE:	**June 8, 1997**
BRAND NAME:	**EVISTA™**
GENERIC NAME:	**Raloxifene hydrochloride tablets**
REVIEWER:	**Carolyn D. Jones, Ph.D.**
CONSULTANT:	**Robert Shore, Pharm.D.** **Raymond Miller, Ph.D.**
SPONSOR:	**Eli Lilly and Company** **Indianapolis, IN**
Type of Submission:	**Original NDA (NME)** **Code: 1P**

SYNOPSIS:

EVISTA™ (raloxifene hydrochloride), the methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride, is a selective estrogen receptor modulator (SERM) that belongs to the benzothiophene class of compounds. The SERM profile of EVISTA™ includes estrogen agonist effects on bone and lipid metabolism thereby reducing the elevated bone resorption observed in postmenopausal women, but no agonist effects in uterine or breast tissues. Thus, EVISTA™ is proposed for the prevention of osteoporosis in postmenopausal women and it is designed to provide an alternative to estrogen replacement therapy. The recommended dosage by the sponsor is one 60-mg EVISTA™ tablet daily which may be administered any time of day without regard to meals. Each EVISTA™ tablet contains 60 mg of raloxifene HCl, which is the molar equivalent of 55.71 mg of free base.

The disposition of raloxifene has been evaluated in 276 postmenopausal women in conventional clinical pharmacology studies and in more than 1300 postmenopausal women in selected raloxifene trials whose data points were used in the population pharmacokinetic and pharmacodynamic analyses. Raloxifene exhibits high within-subject variability (approximately 30%) of most pharmacokinetic parameters.

Raloxifene is absorbed rapidly after oral administration and presystemic glucuronide conjugation is extensive. Absolute bioavailability of raloxifene is about 2.0%. The time to reach average

maximum plasma concentration and bioavailability are functions of systemic interconversion and enterohepatic cycling of raloxifene and its glucuronide metabolites. Administration of raloxifene HCl with a standardized, high-fat meal increases the absorption of raloxifene

Following oral administration of single doses ranging from 30 to 150 mg of raloxifene HCl, the apparent volume of distribution is 2348 L/kg and is not dose dependent. Raloxifene and the monoglucuronide conjugates are highly bound to plasma proteins; serum albumin , and α 1-acid glycoprotein , but not to sex steroid binding globulin. *In vitro*, raloxifene did not interfere with the binding of warfarin, phenytoin, or tamoxifen to plasma proteins.

Biotransformation and disposition of raloxifene in humans have been determined following oral administration of ^{14}C-labeled raloxifene. Raloxifene undergoes extensive first-pass metabolism to the glucuronide conjugates: raloxifene-4'-glucuronide, raloxifene-6-glucuronide, and raloxifene-6, 4'-diglucuronide. No other metabolites have been detected. Unconjugated raloxifene comprises less than 1% of the total radiolabeled material in plasma. Raloxifene is primarily excreted in feces, and negligible amounts are excreted unchanged in urine. Less than 6% of the raloxifene dose is eliminated in urine as glucuronide conjugates.

Following intravenous administration, raloxifene is cleared at a rate approximating hepatic blood flow. Apparent oral clearance is 44.1 L/Kg-hr. Raloxifene and its glucuronide conjugates are interconverted by reversible systemic metabolism and enterohepatic cycling, thereby prolonging its plasma elimination half-life to 27.7 hours after oral dosing. Results from single oral doses of raloxifene predict multiple-dose pharmacokinetics. Following chronic dosing, clearance ranges from 40 to 60 L/Kg-hr. Increasing doses of raloxifene HCl (ranging from 30 to 150 mg) result in slightly less than a proportional increase in the area under the plasma time concentration curve (AUC).

Raloxifene was studied in cirrhotic patients. Plasma raloxifene concentrations were approximately 2.5 times higher in patients than in controls and correlated with bilirubin concentrations. No studies were conducted in the renally impaired population.

Drug-drug interactions were conducted. Antacids did not affect the systemic exposure of raloxifene and raloxifene had no effect on the pharmacokinetics of digoxin. However, a increase in AUC and a similar decrease in the volume of distribution was observed when warfarin and raloxifene were coadministered. The administration of ampicillin did not significantly impact the pharmacokinetics of raloxifene, although C_{max} was reduced 28%, AUC was not affected. A statistically and clinically significant effect was observed when cholestyramine and raloxifene were coadministered. The sponsor has recommended in the package insert that these drugs not be coadministered.

The sponsor conducted a population pharmacokinetic analysis and determined that the pharmacokinetics of raloxifene were independent of age in healthy postmenopausal women. The sponsor also stated that pharmacokinetic differences due to race

showed no discernible differences in raloxifene plasma concentrations among Caucasian, Hispanic, Black and Asian females. However, the sample size of the subpopulations were not sufficient to draw any conclusions.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 20-815 submitted on June 8, 1997. The Human Pharmacokinetics Section is acceptable. Please convey recommendation, general comments (p.49) and labeling comments (p.49) to sponsor as appropriate.

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(Appendices and Attachment available from DPE-II upon request)

BACKGROUND:

Marked decreases in estrogen availability, such as after oophorectomy or menopause, lead to marked increases in bone resorption. After menopause, bone is initially lost rapidly because the compensatory increase in bone formation is inadequate to offset resorptive losses. This imbalance between resorption and formation may be related to loss of estrogen, and estrogen replacement therapy reduces resorption of bone by inhibiting the formation and action of osteoclasts, thereby decreasing overall bone turnover. EVISTA™'s effects on bone are manifested as reductions in the serum and urine levels of bone turnover markers (serum alkaline phosphatase), histologic evidence of decreased bone resorption and formation, and increased bone mineral density (BMD). The effects of EVISTA™ on bone turnover in postmenopausal women parallel those of estrogen.

Raloxifene hydrochloride (HCl) has the empirical formula $C_{28}H_{27}NO_4S$ HCl, which corresponds to a molecular weight of 510.05. The drug is an off-white to pale-yellow solid that is very slightly soluble in water.

EVISTA™ is supplied in a tablet dosage form for oral administration.

The initial evaluation of the clinical pharmacology of raloxifene as an agent for the therapy of breast cancer began in 1982 and was terminated in 1984. These studies included: single dose and dose advancement up to 200 mg, multiple dose (200 mg for 2 weeks), ^{14}C-drug metabolism studies, dose ranging as an oral solution, and interaction with ethinyl estradiol (in males). Phase II studies for prevention and treatment of osteoporosis began in 1992 using a different formulation of raloxifene than that used previously. Phase I studies were not repeated. Since 1992, 20 clinical pharmacology studies have been conducted. Of the 351 subjects for whom pharmacokinetic results are available, 276 were postmenopausal women. Population pharmacokinetic analyses were also performed on data from more than 1300 patients, enrolled in three Phase III osteoporosis prevention studies and three Phase II support studies. The three large randomized, placebo-controlled, double-blind osteoporosis prevention trials were: (1) a North American trial of 544 women; (2) a European trial of 601 women; and (3) an international trial of 619 women who had undergone hysterectomy.

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DRUG FORMULATION:

During the evaluation of raloxifene hydrochloride (HCl) in human clinical studies, the progression of drug product formulations can be classified into three main categories:

Table 1 : Clinical Drug Product Ingredient 30-mg, 60-mg and 150-mg Strengths and 60 mg To-be-marketed formulation

Ingredients	Clinical Trial	To-be-marketed
Raloxifene HCl		
Polysorbate 80		
Anhydrous Lactose		
Lactose Monohydrate		
Crospovidone		
Magnesium Stearate		

The drug product

The drug substance is manufactured at Eli Lilly and Company, Shadeland, Indiana. The majority

The drug product manufacturing process used

Differences between the were:

None of these changes were significant according to SUPAC. Batch sizes for most of the pharmacokinetic and clinical studies were However, the batches used for the dose proportionality studies excluding the 60 mg batch were

Bioequivalence studies have shown that the commercial tablets manufactured at production scale were bioequivalent to the clinical trial tablets.

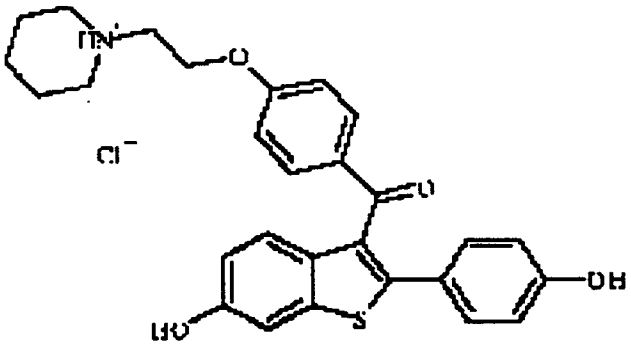

FIGURE 1: The chemical structure of raloxifene hydrochloride (EVISTA™)

DISSOLUTION:

The sponsor submitted *in vitro* dissolution profiles that contained mean and range data for 60 mg raloxifene hydrochloride clinical trial tablets. In addition, the clinical trial tablet and the commercial tablet lots used in the bioequivalence study were also evaluated for dissolution at the time of their release and near the time the bioequivalence study was conducted. Individual data dissolution were observed in the clinical trial formulation over this time period.

Similarity in dissolution was assessed by

The If the factor
are considered similar.

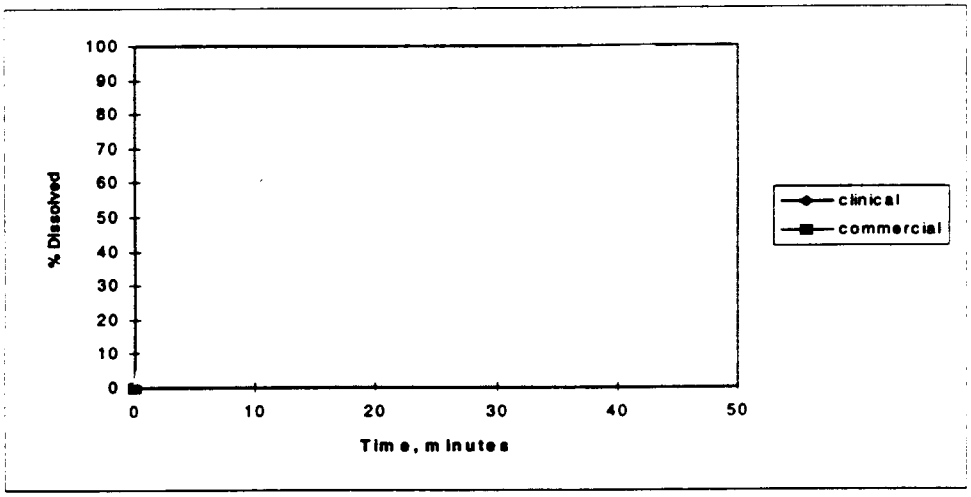

FIGURE 2: Dissolution characteristics of raloxifene clinical and commercial tablets used in the bioequivalence study

Several media were investigated for dissolution

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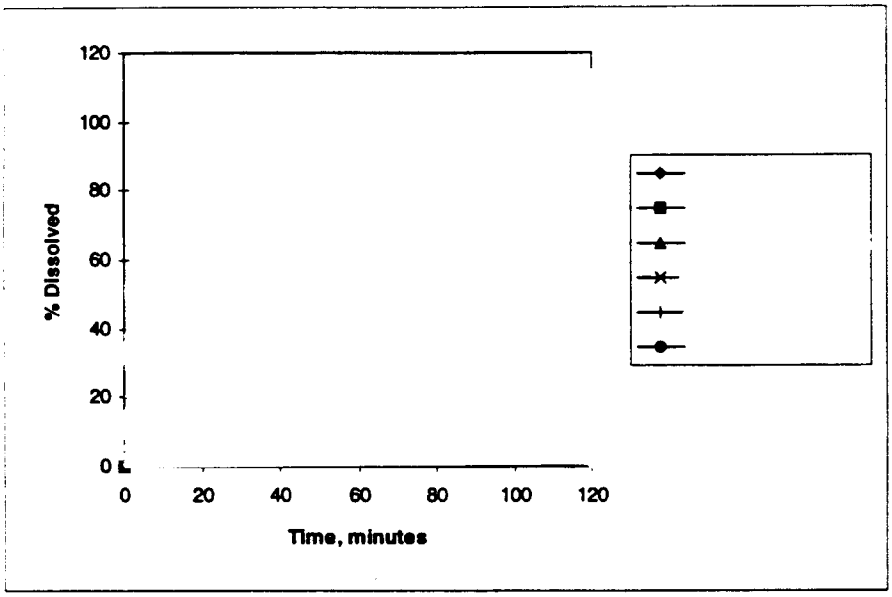

FIGURE 3: Dissolution characteristics of raloxifene hydrochloride evaluated in

The above profiles (Figure 3) show

Table 2. The Solubility of Raloxifene Hydrochloride		
Solvent	mg/mL (25°C)	mg/mL (37°C)

ANALYTICAL METHODOLOGY:

Throughout the development of raloxifene, several different methods had been used to quantitate the compound in biological fluids. In addition, the glucuronide conjugates of raloxifene had been quantitated, both directly and indirectly, as total raloxifene in hydrolyzed plasma (TRHP). Total raloxifene in hydrolyzed plasma is a sum of unconjugated raloxifene and all of its glucuronide conjugates that are hydrolyzed by β-glucuronidase. During the early development of raloxifene (prior to 1990's), the compound had been quantitated in plasma and urine When raloxifene was re-evaluated in the 1990's, newer analytical techniques were available.

Initially the assays for both raloxifene and TRHP were but further development led to the use of that could be used to quantitate raloxifene at concentrations and TRHP at concentrations A The assay proved to be more sensitive and specific so LC/MS/MS was used for the pharmacokinetic samples collected during the clinical studies and during the clinical pharmacology studies.

The assay for raloxifene, or a modification, was validated at three different laboratories: Eli Lilly in Indianapolis, Lilly Laboratory for Bioanalytical Research (LLBR) in Toronto At all three laboratories, at three or more concentrations were analyzed with each analysis batch to determine acceptability of the data from the batch.

The assay was validated at both Eli Lilly in Indianapolis and at

Table 3. Analytical Methods Used in the Analysis of Raloxifene in Plasma and Urine Samples	
Limit of quantitation (LOQ) -	
Linearity -	
Specificity -	
Precision -(intra- and interday)	
Accuracy -(intra- & interday)	
Stability -	

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES

I. Bioavailability/Bioequivalence

A. *Absolute Bioavailability*

Ten healthy postmenopausal female subjects, between the inclusive, participated in this study. In Part I of the study, 2 subjects received only a single IV dose of 0.5 mg raloxifene HCl. In Part II, 8 subjects received doses of 1.0 mg raloxifene HCl intravenously and then received 120 mg orally (2 x 60-mg raloxifene HCl tablets). The following conclusions were drawn from this study:

1. Presystemic glucuronidation is extensive.

3. Intravenously administered raloxifene distributes extensively in the body and is cleared by glucuronidation approximating hepatic blood flow.
4. Raloxifene interconverts with its glucuronide conjugates both by reversible systemic metabolism and enterohepatic cycling, thereby prolonging its plasma elimination half-life after oral dosing

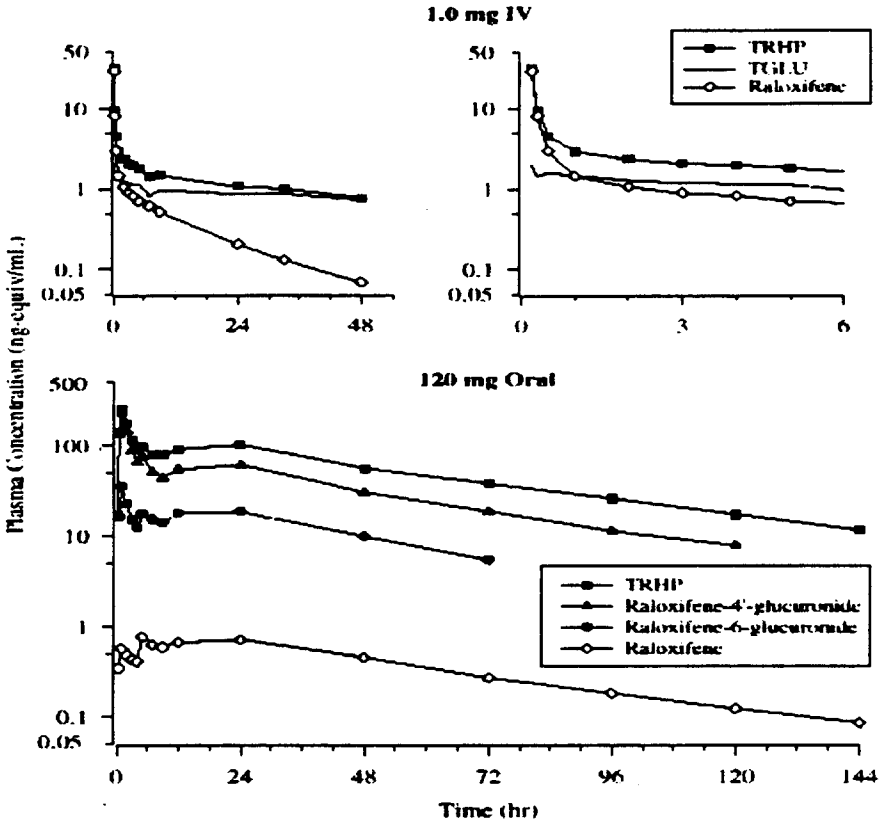

Figure 4: Mean (N=8) Plasma Concentration versus Time Plots (Semilogarithmic) for IV Infusion (upper panels) and Oral Dosing (lower panel). TRHP---total raloxifene in hydrolyzed plasma

Table 4. Mean (%CV) Raloxifene Pharmacokinetic Parameters Following IV Infusion of 1.0 mg Raloxifene HCl and Oral Administration of 2 x 60 mg Raloxifene HCl Tablets

	Arithmetic Mean (CV as %) by Dose Route [a]	
Parameter	IV	Oral
C_{max} (ng/mL)	26.9 (30)	0.915 (34)
T_{max} (hr)	[0.2] [b]	6.0 [c]
$AUC_{0-\infty}$ (ng•hr/mL)	22.1 (19)	52.7 (36)
$t_{1/2}$ (hr)	12.1 [d]	33.0 [d]
MRT (hr)	11.6 (13)	60.6 (35)
CL_p or CL_p/F (L/hr/kg)	0.647 (18)	36.3 (43)
V_{ss} or V_{ss}/F (L/kg)	7.52 (22)	2236 (60)
F (%)	[100]	2.0 (32)
Raloxifene / TRHP $AUC_{0-\infty}$ ratio (%)	22.0 (34)	0.69 (33)

[a] n = 8 subjects of protocol Part II.
[b] End of infusion.
[c] Median (range).
[d] Harmonic mean (range).

B. Bioequivalence

The pivotal 60 mg clinical trial formulation and the to-be-marketed formulation were evaluated for bioequivalence in thirty-nine healthy postmenopausal female subjects,

Thirty-seven females actually completed the single-blind, three-period, replicate design, crossover study. Raloxifene pharmacokinetics were determined after three temporally isolated single doses. There was a washout of 14 days between each drug.

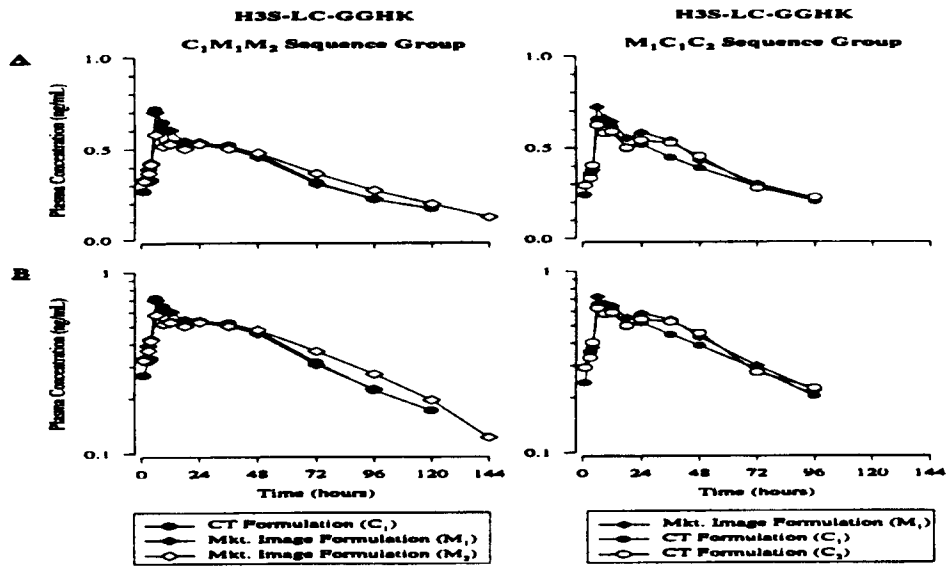

Figure 5: Mean Raloxifene Plasma-Concentration Time Plots (linear and log scales) 60 mg tablets

The mean raloxifene pharmacokinetic parameters are summarized in Table 5. The two formulations were bioequivalent with no sequence or carryover effects.

Table 5: Mean (CV as %) Raloxifene Pharmacokinetic Parameters By Treatment and Sequence Following Administration of 2 x 60-mg Raloxifene HCl Tablets

Parameter	Market-Image Tablet By Sequence			Clinical Trial Tablet By Sequence		
	$C_1M_1M_2$ M_1 (n=18)	$C_1M_1M_2$ M_2 (n=17)	$M_1C_1C_2$ M_1 (n=20)	$C_1M_1M_2$ C_1 (n=18)	$M_1C_1C_2$ C_1 (n=20)	$M_1C_1C_2$ C_2 (n=20)
C_{max} (ng/mL)	0.876 (49.5)	0.728 (40.7)	0.868 (39.5)	0.931 (46.8)	0.786 (33.9)	0.754 (35.3)
T_{max} (hr)	6.0 [a]	12.0 [a]	10.7 [a]	10.7 [a]	9.0 [a]	12.0 [a]
AUC_{0-t} (ng,hr/mL)	45.0 (39.2)	48.7 (39.7)	45.1 (37.3)	47.2 (35.6)	41.3 (32.8)	42.6 (48.7)
$AUC_{0-\infty}$ (ng,hr/mL)	51.6 (42.0)	54.5 (37.8)	50.9 (38.8)	51.9 [b] (33.3)	44.5 [c] (37.9)	47.8 (48.7)

[a] median (range) values given. Arithmetic means (CV as %) are 16.5 (117), 21.1 (82.7), 20.7 (87.5), 25.0 (105), 17.1 (101), and 20.3 (82.0) in order from left to right.

[b] n = 17 observations, terminal phase could not be estimated for Subject 0005.

[c] n = 18 observations, terminal phase could not be estimated for Subjects 0004 and 0025.

The purpose of this particular study design was to determine if any added value was achieved using a replicate design of both the clinical trial and to-be-marketed formulations. No significant narrowing of the confidence intervals occurred as a result of using this replicate design. This same approach was used for all of the bioequivalence studies.

Table 6: Principal Bioequivalence Evaluation of Raloxifene Pharmacokinetic Parameters Following Administration of 2 x 60-mg Market-Image and Clinical Trial Tablets[a]

	Least-Squares Means		Ratio of	90% Confidence
Parameter	Market-Image	Clinical Trial	Means	Interval
C_{max}	0.761	0.785	0.97	0.89 to 1.06
AUC_{0-t}	42.4	41.4	1.02	0.96 to 1.09
$AUC_{0-\infty}$	47.8	46.2	1.03	0.97 to 1.11

[a]Log-Transformed data

A second bioequivalence study using 41 healthy postmenopausal females was conducted comparing the 60 mg clinical trial formulation and the 60 mg to-be-marketed formulation that was manufactured The market-image 60-mg raloxifene HCl tablet was bioequivalent to the 60-mg raloxifene HCl tablet used in pivotal efficacy and safety trials. No differences in study design nor outcome between the European manufactured tablets and the U.S. manufactured tablets were observed.

Additional bioequivalence studies were conducted using 30 mg and 150 mg tablet strengths that were used in various clinical efficacy trials. However, these two dosages will not be marketed in the United States. Bioequivalence of 30-mg market image raloxifene HCl tablets (treatment M) and 30-mg Phase III clinical trial raloxifene HCl tablets (treatment C) in 36 postmenopausal women was assessed using a dual-sequence crossover design. One 30 mg tablet was expected to yield raloxifene plasma concentrations that would be too low to fully assess the single dose plasma concentration-time profile. Therefore, the 30 mg study was conducted by giving four 30 mg tablets for adequate assessment.

Table 7: Principal Bioequivalence Evaluation of Raloxifene Pharmacokinetic Parameters Following Administration of 4 x 30-mg Market-Image and Clinical Trial Tablets[a]

	Least-Squares Means		Ratio of	90% Confidence
Parameter	Market-Image	Clinical Trial	Means	Interval
Cmax	0.864	0.702	1.23	1.10 to 1.37
AUC0-t	39.68	33.59	1.18	1.10 to 1.27
AUC0-∞	45.35	38.42	1.18	1.09 to 1.27

[a]Log-Transformed Data

The statistical evaluation indicates that the 30 mg market-image and clinical trial tablets were not bioequivalent.

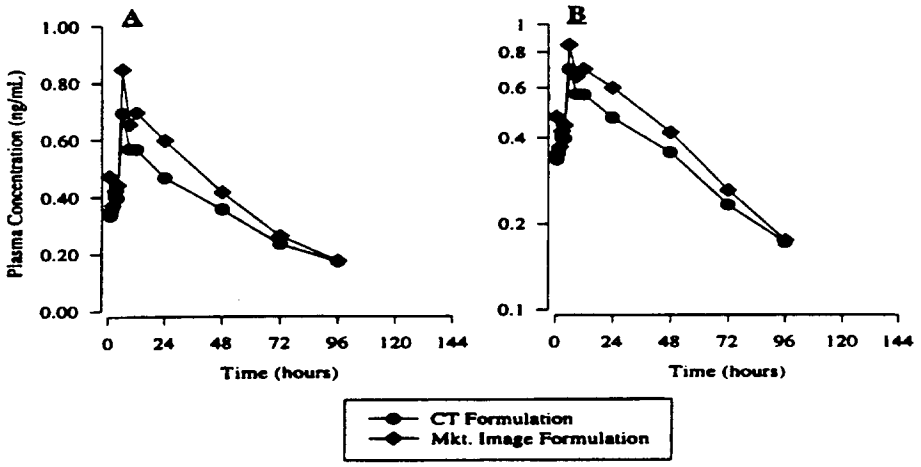

Figure 6: Overall Mean Plasma Raloxifene Concentration-Time Profiles 4 x 30 mg tablets (linear and log scales)

Bioequivalence of 150-mg market image raloxifene HCl tablets (1 x 150 mg) and 150-mg Phase III clinical trial raloxifene HCl tablets in 37 postmenopausal women was assessed using a dual-sequence crossover design. The two tablets were bioequivalent.

Table 8: Principal Bioequivalence Evaluation of Raloxifene Pharmacokinetic Parameters Following Administration of 1 x 150-mg Market-Image and Clinical Trial Tablets[a]

Parameter	Least-Squares Means		Ratio of Means	90% Confidence Interval
	Market-Image	Clinical Trial		
C_{max}	0.758	0.751	1.01	0.92 to 1.11
AUC_{0-t}	43.50	43.30	1.00	0.93 to 1.08
$AUC_{0-\infty}$	48.94	48.61	1.01	0.93 to 1.09

[a]Log-Transformed Data

The following conclusions were drawn from this study:

1. The 60 mg clinical trial and to-be-marketed formulations are bioequivalent.
2. The 60 mg to-be-marketed tablet formulation manufactured ' is bioequivalent to the clinical trial formulation.
3. The 30 mg tablet clinical trial and market-image formulations are bioinequivalent. However, the 150 mg tablets were bioequivalent. These two dosages will not be marketed in the United States.

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II. Pharmacokinetics

The estimated steady-state volume of distribution for raloxifene following oral administration (Vss/F) averaged 601 L/kg (35.8% CV), reflecting a small value of F due to extensive first-pass metabolism. Assuming the systemic bioavailability is approximately the value of Vss calculated at 6 L/kg would still be much greater than total body water, 0.7 L/kg. This suggested extensive distribution of raloxifene, in addition to, high first-pass metabolism.

A. Single vs. Multiple Dose Administration

Eleven healthy postmenopausal female subjects received a single oral dose of one 150-mg raloxifene HCl tablet. Following a 7-day washout period, subjects were administered one 150-mg tablet of raloxifene HCl daily for 28 days. The objectives of this study were to examine the pharmacokinetics of 150-mg raloxifene tablets in postmenopausal females following a single and multiple doses of raloxifene HCl. The similarity of single- and multiple-dose values for individual subjects, indicated that raloxifene pharmacokinetics are linear with respect to time during a 4-week dosing regimen (see Tables 9 and 10).

Table 9: Mean (CV as %) Single-Dose (Dose 1) and Steady-State (Dose 29) Raloxifene Pharmacokinetic Parameters Following Once Daily Administration of 1 x 150-mg Raloxifene HCl Tablet

	Arithmetic Mean (CV as %) By Dose	
Parameter	**Dose 1**	**Dose 29**
$AUC_{0-\infty}$ or AUC_{τ} (ng•hr/mL)	57.1 (40)	54.0 (36)
$t_{1/2}$ (hr)	32.3	32.5
CL/F (L/hr/kg)	46.3 (46)	47.4 (41)
V_z/F (L/kg)	2784 (50)	2853 (56)
λ_z (hr^{-1})	0.0215	0.0213
MRT (hr)	59.3	61.6

[a] Harmonic mean (range).

Table 10: Linearity of Raloxifene Pharmacokinetics: Least Squares Means and 90% Confidence Intervals[a]

	Least Squares Mean		Difference in	90% Confidence
Parameter	**Dose 29**	**Dose 1**	**Means (%)[a]**	**Interval (%)[b]**
CL/F (L/hr)	47.4	46.3	2.4	-21.8 to 26.6
V_z/F (L/kg)	2853	2784	2.5	-29.4 to 34.3

[a]Nontransformed Data

[b]Differences in least-squares mean values are expressed as percentages of Dose 1 values. The point estimate of difference in equivalent means is 0.0 %.

The half-life for raloxifene was and the dosing interval was 24 hours. Raloxifene accumulated in the body as would be expected for any dosing interval shorter than the $t_{1/2}$ of the

drug substance. The actual accumulation factor, calculated as a ratio (AUC_{ss}/AUC_{0-24}) of mean values is 4.0. The metabolite accumulation ratios were all below those for raloxifene, indicating that the metabolites accumulate less than raloxifene.

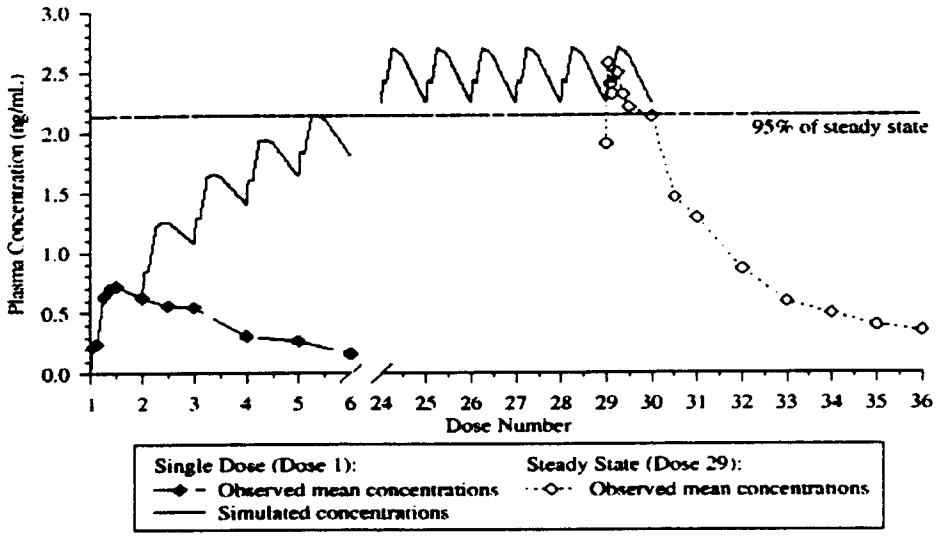

Figure 7: Simulation of Mean Steady-State Raloxifene Concentrations Based on Superposition of Single-Dose Concentrations

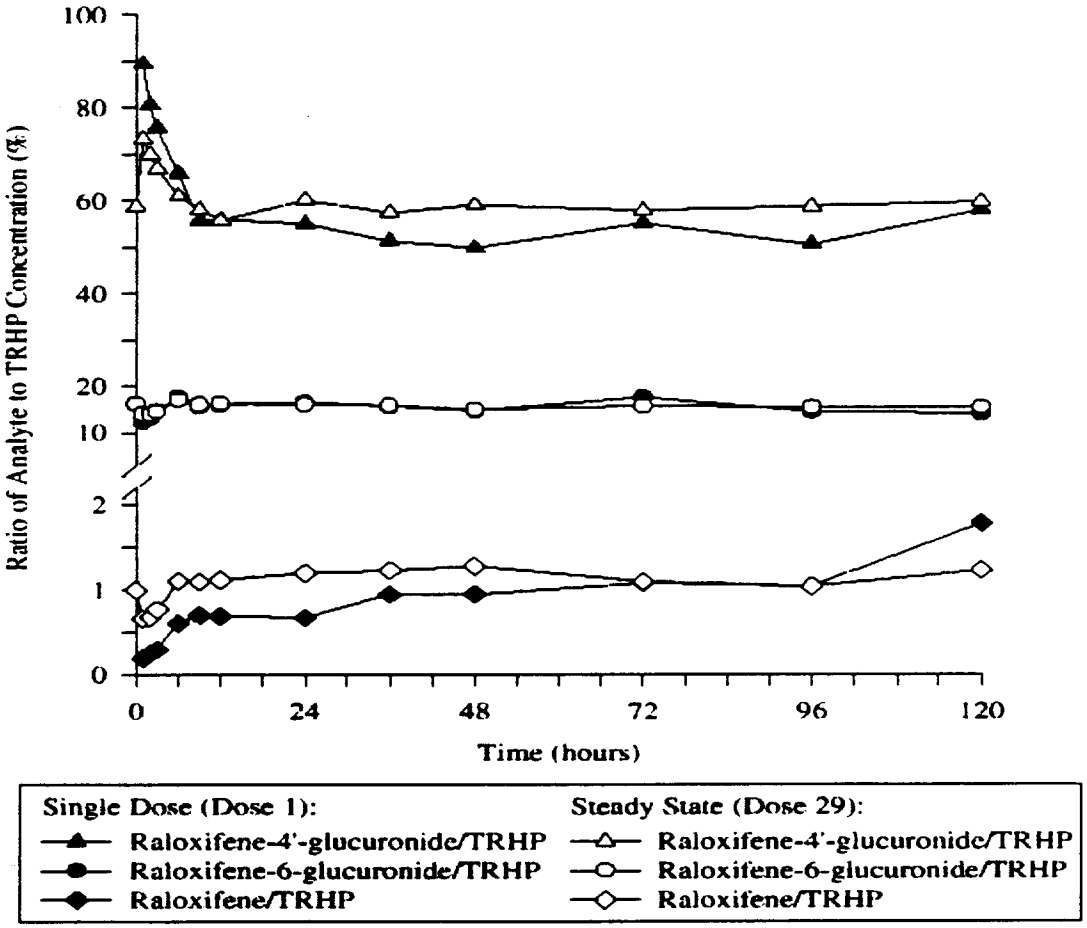

Figure 8: Mean Analyte/THRP Concentration Ratios versus Time

Raloxifene/TRHP (Total raloxifene hydrolyzed plasma) concentration ratios increased rapidly during the first 6 hours and thereafter approached steady-state ratios. Only raloxifene was available for absorption within an hour of the first dose and glucuronides appeared in plasma only after raloxifene was absorbed. Therefore, the concentration ratios, coupled with metabolite T_{max} values indicated that raloxifene was rapidly absorbed and almost completely conjugated during first-pass through the gut wall and liver.

The following conclusions were drawn from this study by the sponsor and the reviewer concurs:

1. Oral clearance, steady-state distribution volume, and elimination rate remain constant during a 4-week, 150-mg, once-daily dosing regimen and indicate that raloxifene pharmacokinetics are linear with respect to time.
2. Raloxifene accumulation is predictable from single-dose data, indicating linear pharmacokinetics
3. Raloxifene metabolites accumulate to a lesser degree than does raloxifene

C. Food Effects

The effect of food and the effect of ampicillin therapy on the pharmacokinetics of raloxifene HCl were determined. Single oral doses of raloxifene HCl (120 mg as 2 x 60-mg tablets) were administered during each of three treatment periods in a nonblinded, randomized, two-way crossover of fed and fasted conditions in fourteen healthy postmenopausal female subjects, ages 52 to 76 years. The first two periods evaluated the food effect using a standardized high fat diet and fasted conditions. In the third study period, the hypothesis that raloxifene undergoes enterohepatic cycling was tested by administering raloxifene HCl during concurrent antibiotic treatment. Ampicillin was administered for 1 day prior to raloxifene HCl dosing and continued for six days (4 capsules/day).

When raloxifene HCl was given with a standard breakfast, mean C_{peak1} for total raloxifene in hydrolyzed plasma (TRHP) increased approximately 64% (p=0.003). Smaller increases in AUC_{0-t} and $AUC_{0-\infty}$ of 16% to 18% were statistically significant (p=0.05) (Table 11). The effects of food on $C_{peak}1$, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for raloxifene were significantly different using the 90% confidence interval approach, although the increases in these parameters were of similar magnitude to those for TRHP.

Table 11: Food Effect: Least Squares Mean and Confidence Intervals using Log-transformed Data

Parameter [a]	Least Squares Mean		Ratio of means [b]	90% Confidence Interval	Significance p-value
	Fed	Fasted			
Raloxifene					
C_{peak1}	0.848	0.566	1.50	1.00 to 2.25	0.10
C_{max}	1.092	0.852	1.28	0.97 to 1.69	0.14
AUC_{0-t}	49.10	41.54	1.18	0.95 to 1.47	0.19
$AUC_{0-\infty}$	54.26	46.89	1.16	0.93 to 1.44	0.26
TRHP					
C_{peak1}	337	205	1.64	1.38 to 1.95	0.0003
C_{max}	338	228	1.48	1.25 to 1.75	0.001
AUC_{0-t}	9022	7693	1.17	1.03 to 1.33	0.05
$AUC_{0-\infty}$	10047	8378	1.20	1.04 to 1.39	0.05

[a] Units for parameters: C_{max}, and C_{peak1} ng/mL; AUC_{0-t} and $AUC_{0-\infty}$, ng•hr/mL.

[b] Analyses of C and AUC parameters are based on log-transformed data. Antilogs of transformed scale fed minus fasted differences and their 90% confidence limits supply a fed/fasted ratio estimate and corresponding 90% confidence interval. The point estimate of the ratio of equivalent means is 1.0.

The effect of food on CLp/F and Vss/F for raloxifene and λ_z for both raloxifene and TRHP were not statistically significant. Simulation of chronic dosing conditions suggested that administration of raloxifene HCl with food leads to changes in raloxifene concentrations (Css,av) which are (2.2 ng/mL fasted versus. 2.5 ng/mL fed).

The following conclusions can be drawn by this study:

1. Although statistically significant, these changes are clinically insignificant. Therefore, raloxifene HCl can be administered without regard to meals.

Table 12: Food Effect: Least Squares Mean and Confidence Intervals using Nontransformed Data

Parameter [a]	Least Squares Mean Fed	Least Squares Mean Fasted	Difference in means [b] (%)	90% Confidence Interval	Significance p-value
Raloxifene					
λ_z	0.025	0.022	15.4	-1.4 to 32.3	0.13
CL_p/F	35.07	39.59	-11.4	-33.2 to 10.3	0.36
V_{ss}/F	1743	2160	-19.3	-44.6 to 6.0	0.20
TRHP					
λ_z	0.031	0.032	-2.6	-18.6 to 13.4	0.77

[a] Units for parameters: λ_z, hr^{-1}; CL_p/F, L/hr/kg; V_{ss}/F, L/kg.

[b] Fed minus fasted differences in least-squares mean values are expressed as a percentage of the fasted reference value. The point estimate of the difference in equivalent means is 0.0%.

Ampicillin therapy altered $AUC_{0-\infty}$, C_{peak1}, T_{peak1}, terminal half-life, clearance, or volume of distribution of raloxifene. Ampicillin therapy did, however, result in lower raloxifene concentrations between 4 and 24 hours after dosing, including a 28% reduction in C_{max} (p=0.03) and lowered AUC by approximately 8%. Since this time period contained the first two meals administered after raloxifene HCl dosing, this result suggested that raloxifene undergoes enterohepatic cycling. However, multiple dose simulation suggested that administration of raloxifene HCl with ampicillin did not affect raloxifene plasma concentrations under chronic dosing conditions.

The following conclusions can be drawn from this study:

1. Ampicillin and raloxifene can be coadministered.

Table 13: Ampicillin Effect: Least Squares Mean and Confidence Intervals (Log Transformed Data)

Parameter [a]	Least Squares Mean Ampicillin	Least Squares Mean Fasted	Ratio of means [b]	90% Confidence Interval	Significance p-value
Raloxifene					
C_{peak1}	0.469	0.566	0.83	0.56 to 1.10	0.32
C_{max}	0.614	0.852	0.72	0.55 to 0.89	0.03
AUC_{0-t}	32.12	41.54	0.77	0.60 to 0.94	0.06
$AUC_{0-\infty}$	35.98	48.38	0.86	0.68 to 1.05	0.23
AUC_{0-t}	1.14	1.20	0.95	0.77 to 1.13	0.64
AUC_{0-24}	8.36	12.79	0.65	0.55 to 0.76	0.0004
TRHP					
C_{peak1}	231	205	1.13	0.94 to 1.31	0.47
C_{max}	240	228	1.05	0.91 to 1.20	0.51
AUC_{0-t}	7565	7693	0.98	0.84 to 1.13	0.84
$AUC_{0-\infty}$	7880	8372	1.01	0.80 to 1.21	0.96
AUC_{0-t}	590	572	1.03	0.89 to 1.17	0.69
AUC_{0-24}	2783	2958	0.94	0.81 to 1.08	0.47

[a] Units for parameters: C_{peak1} and C_{max}, ng/mL ; AUC_{0-t} and $AUC_{0-\infty}$, ng•hr/mL.

[b] Analyses of C and AUC parameters are based on log-transformed data. Antilogs of transformed scale ampicillin minus fasted differences and their 90% confidence limits supply a ampicillin/fasted ratio estimate and corresponding 90% confidence interval. The point estimate of the ratio of equivalent means is 1.0.

III. Metabolism

The metabolism of raloxifene was investigated in males *in vivo* using either a single oral dose of 200 mg ^{14} C-LY156758 raloxifene HCl

Radioactivity was monitored in blood, feces, urine, saliva, and breath following drug administration.

Raloxifene was 3 x better absorbed when given as a hydroalcoholic solution as compared to a capsule. Total recovery of radioactivity for the two studies. Ninety percent of the dose was excreted in the feces with only about excreted in the urine. Radioactivity was not excreted in the breath or saliva.

In a 2 week multiple dose study where 200 mg (4 x 50 mg capsules) of raloxifene was administered, maximum urinary excretion for both parent drug and metabolites occurred within 12 hours. Less than 1% of the administered dose was recovered as parent drug in the urine within 48 hours. The metabolism of raloxifene was extensive and mostly conjugated glucuronides were found in plasma and urine. Ninety-five percent of the circulating compound was in the conjugated form. The major urinary metabolites of raloxifene are raloxifene-4'-glucuronide and raloxifene-6,4'-diglucuronide. The diglucuronide conjugate accounted for

approximately of the radioactivity excreted in urine. Urinary recovery of conjugate was 2.7% after single dose administration and 6.3% after multiple dose administration. The metabolites of raloxifene found in human urine were the same as those found in human plasma.

Approximately of the raloxifene obtained after enzymatic hydrolysis of the plasma was accounted for by raloxifene-4'-glucuronide and raloxifene-6-glucuronide. Other possible metabolites that would liberate raloxifene after enzymatic hydrolysis that could be in plasma were the diglucuronide conjugate, raloxifene-6-monosulfate, raloxifene-4'-monosulfate, and the disulfate conjugate of raloxifene. The diglucuronide appeared to be present in the plasma samples, however, the sulfate conjugates were not. All of these pathways can be reversed by the enzyme β-glucuronidase, known to be present in most tissues and in very high concentrations in gastrointestinal flora. Therefore, the glucuronide conjugates of raloxifene may serve as prodrugs for raloxifene.

A single oral dose of raloxifene HCl was administered as a solution. Peak plasma concentrations (C_{max}) for all analytes were found at the first sampling time of 0.5 hours, indicating rapid absorption of raloxifene. Plasma concentrations of raloxifene-4'-glucuronide and raloxifene-6-glucuronide were approximately 167- and 20-fold higher, respectively, than those of raloxifene at all times following administration (including the earliest sample times), indicating extensive first-pass metabolism of the compound. The concentration ratios between raloxifene and the two metabolites were relatively stable from approximately 8 to 12 hours after administration, suggesting interconversion and equilibration between raloxifene and glucuronide metabolites.

The stability of the glucuronide and sulfate conjugates in feces was examined by spiking the glucuronide and sulfate conjugates into predose feces and then storing and processing the samples similarly to the study samples. A huge peak appeared in the chromatogram which was not found in the blank fecal sample and had the same retention time as raloxifene. Very small peaks appeared at the retention time for the 6-glucuronide, 4'-glucuronide, 6-monosulfate, and 4'-monosulfate. These data indicated that the glucuronide and sulfate conjugates of raloxifene were not stable in feces and that the conjugates were hydrolyzed to raloxifene in fecal samples. Therefore, any raloxifene found in the feces may have been excreted as the conjugates and then hydrolyzed in the gastrointestinal tract to raloxifene or it may be nonabsorbed drug.

Figure 9: Metabolic Pathways for Raloxifene and Its Metabolites

The following summary statements which the reviewer is in agreement with can be made regarding raloxifene metabolism:

1. The secondary peaks observed in the plasma concentration versus time curves suggest that enterohepatic circulation occurred for raloxifene.
2. Hydrolysis of the glucuronide conjugates to raloxifene, either by enterohepatic recycling or interconversion by tissues, could contribute to the long half-life observed for raloxifene.
3. Raloxifene was easily regenerated from the glucuronide metabolites by feces in vitro.

IV. Dose and Dosage Form Proportionality and Linearity

The primary objective of the study was to describe steady-state pharmacokinetics of raloxifene and TRHP as a function of dose. The study drug was administered in a nonblinded, randomized, crossover design with four treatment regimens in immediate succession without washout to sixteen healthy postmenopausal female subjects, between
14 of which completed this study. The regimens were: 1 x 30-mg; 1 x 60-mg; 2 x 60-mg, and 1 x 150-mg raloxifene HCl tablets, each administered once daily (QD) for 14 days.

Table 14: Mean (CV) Pharmacokinetic Parameters of TRHP Following 30-, 60-, 2x 60- and 150- mg Doses of Raloxifene HCl

Parameter	Arithmetic Mean (CV as %) [a]			
	30 mg	60 mg	2x60 mg [c]	150 mg
AUC_{ss} (ng•hr/mL)	2420.0 (48)	4373.9 (30)	6613.0 (36)	8518.6 (40)
Dose/Weight Normalized AUC_{ss} (ng•hr/mL)/(mg/kg)	5769.8 (39)	5293.0 (26)	3997.4 (32)	4171.5 (41)
$C_{ss,av}$ (ng/mL)	100.8 (48)	182.2 (30)	275.5 (36)	354.9 (40)
Dose/Weight Normalized $C_{ss,av}$ (ng/mL)/(mg/kg)	240.4 (39)	220.5 (26)	166.6 (32)	173.8 (41)
$\bar{C}_{ss,min}$ (ng/mL)	85.8 (64)	145.5 (42)	221.7 (37)	301.9 (45)
Dose/Weight Normalized $\bar{C}_{ss,min}$ (ng/mL)/(mg/kg)	204.7 (59)	175.7 (39)	133.6 (33)	147.1 (45)
$C_{ss,max}$ (ng/mL)	174.8 (41)	303.7 (27)	451.7 (38)	552.9 (36)
Dose/Weight Normalized $C_{ss,max}$ (ng/mL)/(mg/kg)	419.6 (34)	371.6 (28)	275.9 (38)	273.9 (40)
T_{max} [b] (hr)	1	1	1	2

[a] n = 14 unless otherwise noted.
[b] Median (range).
[c] n = 13 for 2x60 mg group.

A criterion for dose proportionality was that plasma concentration of drug and its metabolites at any given time all increase in direct proportion to dose. The results from this study indicated that over the raloxifene HCl daily dose range from 30 to 150 mg, AUC_{ss} and $C_{ss,min}$ for both raloxifene and TRHP increased linearly, but less than proportionally, with increasing dose (Table 14 & Figure 10). Double dose comparisons involving the same formulation (2 x 60 mg versus 1 x 60 mg) and different formulations (1 x 60 mg versus 1 x 30 mg) indicated that formulation did not affect the dose proportionality.

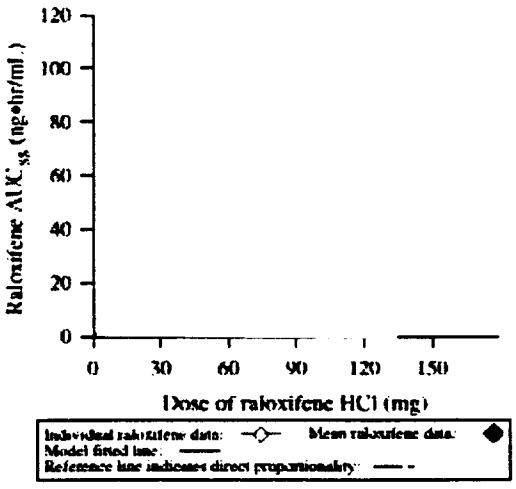

Figure 10: Mean and Individual AUC for Raloxifene as a Function of Raloxifene HCL

Although raloxifene concentrations increased less than 5:1 over the 30- to 150-mg dose range,

statistical analysis demonstrated that a linear model best described the concentration-dose relationship over this dose range. From the linear model, it was estimated that as the daily dose was increased by 30 mg, the corresponding incremental increase in average plasma concentration was approximately 0.39 ng/mL for raloxifene. When the daily dose was increased from 30 mg to 60 mg of raloxifene HCl, the predicted average raloxifene plasma concentration ($C_{ss,av}$) should increase from 0.64 ng/mL to 1.03 ng/mL.

A statistically significant increase in raloxifene oral plasma clearance (CL_p/F) was observed with increasing dose (Table 15). This could suggest either increased systemic clearance (CL) or decreased F (fraction of dose reaching the systemic circulation) with increasing dose. Raloxifene clearance (CL) following intravenous administration was 76 L/hour and was attributable solely to metabolic clearance. This clearance value approximated hepatic blood flow. Since CL is limited by hepatic blood flow, it is unlikely that raloxifene clearance (CL) increases over the 30- to 150-mg dose range. Oral clearance values (CL_p/F) at steady state and following a single dose were essentially the same. The differences in oral clearance (CL_p/F) in this study, therefore, may be due to a decline in the fraction of dose reaching systemic circulation (F) over the dose range studied.

Table 15: Treatment Least-Squares Means and Confidence Intervals: Increase in Oral Plasma Clearance with Increasing Dose

Parameter	Contrast	Least-Squares Means		Difference in Means [a] (%)	90% Confidence Interval
		Test	Reference		
Raloxifene					
CL_p/F	60 vs 30	36.62	33.09	10.6	-4.7 to 26.0
	2x60 vs 30	48.03	33.09	45.1	27.6 to 62.6
	150 vs 30	42.72	33.09	29.1	13.7 to 44.5

[a] Point estimates of percentage differences for equivalents means should approximate 0.0%. Analysis of CL_p/F estimates are based on untransformed data so differences in least-squares mean values are expressed as a percentage of reference value and a 90% confidence interval for this percentage are given.

The sponsor also conducted a pilot study to evaluate dosage form equivalence of the three tablet strengths (30, 60 and 150 mg). The primary goal of this study was to compare pharmacokinetics of these tablets which were used in clinical trials. It should be noted that the excipient to active ingredient ratios were not the same and the various tablets did not have proportional formulas (see Table 16).

The study was a randomized four-way crossover study in which subjects received temporally

isolated doses of raloxifene HCl ranging between 60 and 150 mg. The washout period between doses was 7 days. Treatments consisted of the following:

Treatment A. 60 mg of raloxifene HCl as one 60-mg tablet
Treatment B. 60 mg of raloxifene HCl as two 30-mg tablets
Treatment C. 150 mg of raloxifene HCl as one 150-mg tablet
Treatment D. 150 mg of raloxifene HCl as five 30-mg tablets

Individual and mean values for Treatments A (1 x 60-mg tablet) and B (2 x 30-mg tablets) were not bioequivalent and faster absorption was obtained in the 2 x 30 mg treatment. The same holds true for the 150 mg tablets; they were not bioequivalent.

Table 16: Treatment Least-Squares Means and Confidence Intervals: Relative Bioavailability of Formulations

Parameter	Contrast	Least Squares Means		Ratio of Means	90% Confidence Interval
		Test	Reference		
		Raloxifene			
Cmax	B vs A	0.423	0.308	1.38	0.96 to 1.97
	D vs C	0.983	0.615	1.60	1.12 to 2.29
Tmax	B vs A	5.4	9.1	-40%	NA
	D vs C	7.8	12.1	-36%	NA
AUC_{0-t}	B vs A	8.7	9.4	0.93	0.67 to 1.28
	D vs C	26.8	21.0	1.28	0.93 to 1.76
$AUC_{0-\infty}$	B vs A	18.1	14.1	1.28	0.82 to 1.99
	D vs C	29.4	28.7	1.02	0.66 to 1.59
		TRHP			
Cpeak1	B vs A	143	134	1.07	0.85 to 1.33
	D vs C	288	182	1.58	1.27 to 1.98
Tpeak1	B vs A	0.96	1.13	-15%	NA
	D vs C	1.31	1.69	-22%	NA
AUC_{0-t}	B vs A	3098	3110	1.00	0.76 to 1.31
	D vs C	7854	6832	1.15	0.88 to 1.51
$AUC_{0-\infty}$	B vs A	3864	3941	0.98	0.76 to 1.26
	D vs C	8180	7600	1.08	0.82 to 1.41

Treatments: A = 60-mg, B = 2 x 30-mg, C = 150-mg , and D = 5 x 30-mg tablets
Abbreviations: TRHP = total raloxifene hydrolyzed plasma; Cmax = maximum plasma concentration (ng/mL); Cpeak1= maximum concentration of first peak (ng/mL); Tmax = time of Cmax (hr); Tpeak1 = time of Cpeak1 (hr); AUC = area under the curve (ng·hr/mL); NA = not applicable.

The following conclusions can be drawn from this study:

1. Raloxifene pharmacokinetics are linear, but less than proportional with increasing dose.
2. The dosage forms of raloxifene are not bioequivalent. Multiple tablets demonstrated increased absorption rate.

Treatment emergent adverse events did increase with increasing dosage. The most common events were headache and pain.

V. Special Populations

A. Renal

Renal impairment was not evaluated.

B. Hepatic Impairment

Eight healthy subjects (5 females and 3 males) and 9 cirrhotic subjects (5 females and 4 males), following an overnight fast, received a single oral dose of one 60-mg raloxifene HCl tablet. Each subject received a body weight-adjusted bolus of intravenous lidocaine followed by measurement of the blood levels of the primary metabolite of lidocaine n-dealkylation, monoethylglycinexylidide (MEGX) as an assessment of liver function. The objective of this cohort study was to identify differences in the pharmacokinetics of a single oral dose of raloxifene in subjects with stable cirrhosis compared to healthy volunteers of the same age, ethnicity, and gender.

Plasma concentrations of raloxifene, raloxifene-4'-glucuronide, and raloxifene-6-glucuronide in subjects with cirrhosis were higher than concentrations in healthy cohorts. There was a 2.5-fold difference between subject groups in $AUC_{0-\infty}$ values, indicating substantially greater systemic exposure in the group with cirrhosis. Raloxifene oral clearance (CL_p/F) and apparent steady-state distribution volume (V_{ss}/F) were approximately one-half the values of those in healthy subjects. However, there were negligible (6%) differences between groups with respect to elimination rate parameters (λ_z, $t_{1/2}$ or MRT) suggesting either no change in systemic clearance (Cl_p) or a decrease in proportion to a decrease in distribution volume (V_{ss}). Subjects with cirrhosis eliminated raloxifene, raloxifene-4'-glucuronide, raloxifene-6-glucuronide, at rates comparable to those for healthy individuals.

Table 17: Comparison of LBW-Adjusted Pharmacokineitc Parameters for Cirrhotic and Healthy Subjects: Treatment Least-Squares Means and Confidence Intervals

Parameter [a]	Least-Squares Mean		Ratio or Difference(%) in Means [b]	90% Confidence Interval	Significance p-value
	Cirrhotic	Healthy			
Raloxifene					
C_{max}	0.540	0.257	2.10	1.09 to 4.04	0.07
$AUC_{0-\infty}$	28.19	11.29	2.50	1.39 to 4.49	0.02
λ_z	0.026	0.025	6%	-28% to 39%	0.77
CL_p/F	31	69	-54%	-88% to -24%	0.01
V_z/F	1405	3699	-65%	-99% to -25%	0.01
$AUC_{0-\infty}$ ratio Raloxifene/ TRHP	0.51	0.54	-5%	-42% to 33%	0.82
Raloxifene-4'-glucuronide					
C_{max}	200	88	2.28	1.26 to 4.15	0.03
$AUC_{0-\infty}$	3872	1067	3.63	1.94 to 6.80	0.003
λ_z	0.045	0.055	-18%	-77% to 40%	0.58
Raloxifene-6-glucuronide [c]					
TRHP					
C_{max}	229	119	1.93	1.16 to 3.23	0.04
$AUC_{0-\infty}$	5881	2448	2.40	1.48 to 3.90	0.007
λ_z	0.044	0.041	6%	-39% to 51%	0.82

[a] Units for parameters: C_{max}, ng/mL; $AUC_{0-\infty}$, ng•hr/mL; λ_z, hr^{-1}; CL_p/F, L/hr/kg; V_z/F, L/kg; $AUC_{0-\infty}$ ratio Raloxifene/TRHP, %.

[b] Analyses of C_{max} and AUC parameters are based on log-transformed data. Antilogs of transformed scale differences and their 90% confidence limits supply a cirrhotic/healthy ratio estimate and corresponding 90% confidence interval. The point estimate of the ratio of equivalent means is 1.0. Analyses of the other parameters are based on untransformed data; the point estimate of the percent difference in equivalent means approximates 0.0%.

[c] Raloxifene-6-glucuronide data were too limited for statistical evaluation.

The primary pharmacokinetic effect of cirrhosis also appeared with the glucuronide metabolites as well. The pattern of pharmacokinetic differences for raloxifene and its metabolites suggested that the effective distribution volume of the monoglucuronides and/or diglucuronide was relatively low in the cirrhotic liver. Change in either clearance alone or distribution volume alone would have an impact on terminal half-life and no effect was observed.

No clear association between serum MEGX concentration and pharmacokinetic parameters was found. Several reasons inherent in the design and conduct of the study exist for the lack of association. One reason is that for many subjects the serum sample collection times deviated from nominal by 15 minutes. Also, MEGX values below the assay quantification limit provided no differentiation between healthy and cirrhotic subjects. The study used only Child-Pugh Class A diseased individuals which represents a mild degree of liver dysfunction. Thus, the usefulness of MEGX testing to gauge the relationship between severity of liver disease and raloxifene pharmacokinetics although found negligible, really could not be adequately assessed.

A significant association ($p<0.001$; $r=0.90$) was observed between raloxifene-4'-glucuronide $AUC_{0-\infty}$ values and total serum bilirubin concentration (Figure 11). The associations for raloxifene ($p=0.030$; $r=0.55$) and TRHP ($p<0.0001$; $r=0.82$) were also significant. This association suggested that individuals with a serum bilirubin above the upper limit of normal (1.0 mg/dL) may experience higher systemic exposure to raloxifene and TRHP as did the cirrhotic subjects in this study. Therefore, serum bilirubin appeared to identify the subset of subjects who have hepatic dysfunction of such magnitude as to produce significant changes in raloxifene

pharmacokinetics. If serum bilirubin exceeds 1.0 mg/dL, then reduction in dose frequency may be a consideration. The reviewer is in agreement with this comment.

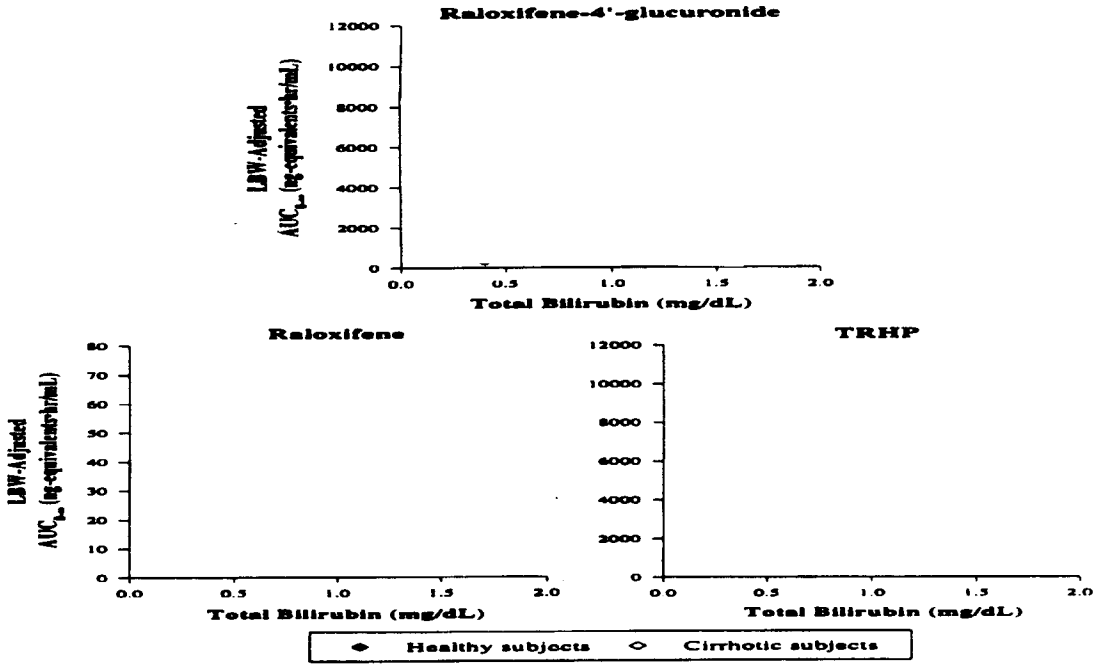

Figure 11: Relationship Between Systemic Drug Exposure (LBW-Adjusted $AUC_{0-\infty}$ Values) and Hepatic Function (Bilurubin Concentration)

As further evidenced, the sponsor simulated administration of raloxifene HCl. The graph indicated that every other day dosing of raloxifene in cirrhotics can yield concentrations similar to those for once-daily dosing of healthy individuals.

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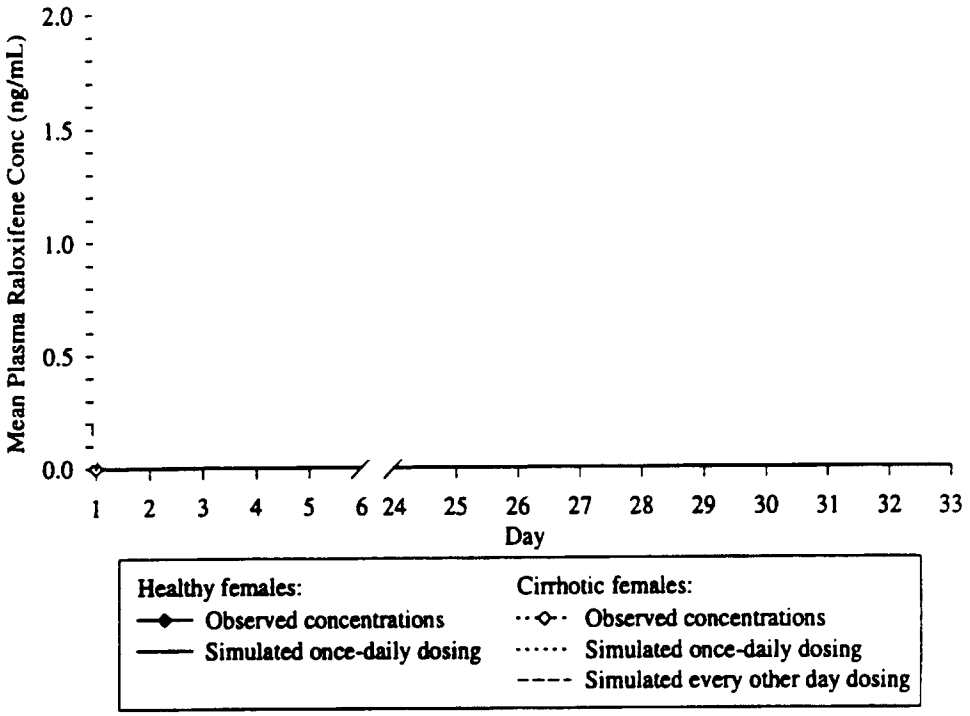

Figure 12: Simulation of Steady-State Raloxifene Concentrations for Healthy and Cirrhotic Female Subjects Based on Repeated Administration of 60 mg Raloxifene HCl.

The following conclusions can be drawn:

1. A 2.5 fold increase in pharmacokinetic values occurs when raloxifene is administered in cirrhotic patients.
2. A good correlation exists between serum bilirubin and metabolite AUC.
3. Raloxifene dosage adjustments such as every other day dosing may be required if bilirubin exceeds 1.0 mg/dL.

C. Gender

Fourteen healthy male subjects, between the ages of 45 and 64 years received a single oral dose and 14 healthy female subjects, between the ages of 45 and 63 received two temporally isolated oral doses of 120 mg raloxifene HCl administered as 2 x 60-mg tablets. Washout time between doses for the female subjects was 21 days.

The primary goals of this study were to evaluate the effect of gender differences on raloxifene pharmacokinetics and to obtain estimates of within- and between-subject variability for raloxifene and metabolites in postmenopausal females. The pharmacokinetics of raloxifene and raloxifene metabolites [raloxifene-4'-glucuronide, raloxifene-6-glucuronide, and TRHP following oral administration of raloxifene were characterized.

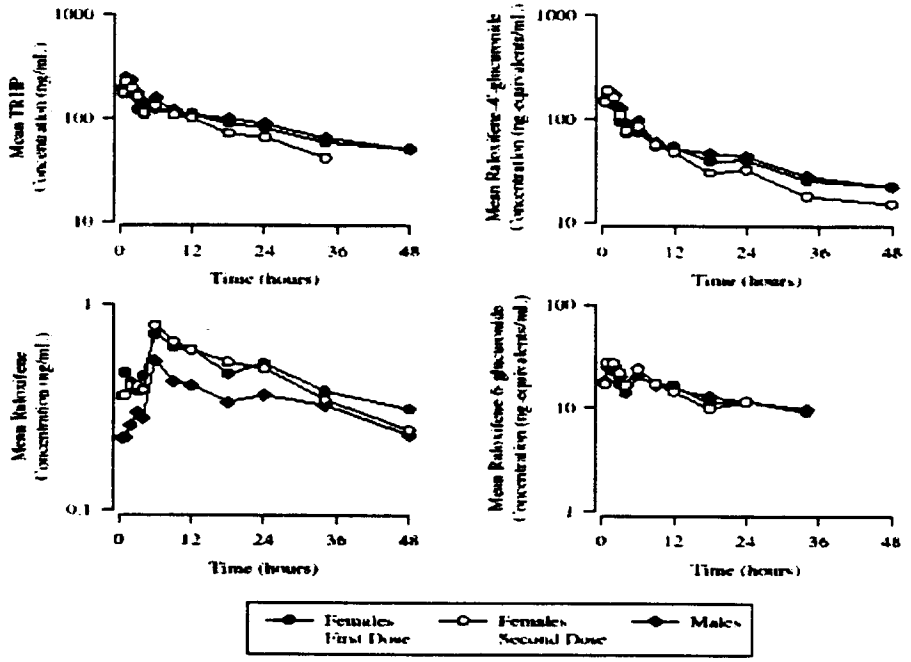

Figure 13: Plasma Concentration vs Time Curves for Raloxifene and Its Metabolites in Male and Female Subjects

Following oral administration of a 120-mg dose, the multiple peaks present in plasma concentration-time profiles of raloxifene and raloxifene metabolites in all subjects again suggested enterohepatic circulation of the compound. The decline of all analytes appeared parallel and the the ratios of raloxifene- and the two metabolites-to-TRHP are relatively stable 12 hours after the dose. These phenomena are suggestive of interconversion and possible equilibration between raloxifene and the glucuronide metabolites.

For raloxifene, female subjects achieved 40% higher C_{max} values, 30% larger AUC_{0-t}, and 30% smaller V_{ss}/F than men ($p<0.05$); however, when these pharmacokinetic parameters were normalized for lean body weight (LBW), the mean values of AUC_{0-t} and V_{ss}/F for raloxifene were not statistically significantly different between men and women. There was no statistically significant gender effect on λ_z, CL_p/F and $AUC_{0-\infty}$ for raloxifene. Gender does not appear to affect the pharmacokinetics of any of the raloxifene metabolites (raloxifene-4'-glucuronide, raloxifene-6-glucuronide, and TRHP).