Table 13 Patient Factors to be Assessed in the Population Pharmacokinetic Analyses

Table 3.1. Patient Factors to be Assessed in the Population Pharmacokinetic Analyses

Investigator	Hysterectomy (yes/no and date)	Thyroxine, Total-T4 by RIA
Geographical Location (Country)	Length of Time Postmenopausal	Thyroid Stimulating Hormone
Dose	Family History of Osteoporosis	T3 Uptake
Duration of Therapy	Hematocrit	Follicle Stimulating Hormone (FSH)
Age	Hemoglobin	Estrogen
Ethnic Origin	Leucocyte Count (WBC)	Plasma Vitamin D
Height	Platelet	Phosphorus
Weight	UA-Bilirubin	Parathyroid Hormone
Body Mass Index	UA-Creatinine (at Visit 2)	Blood Urea Nitrogen
Calculated Lean Body Mass	UA-Glucose	Calcium
Systolic Blood Pressure	UA-Protein	Total Protein
Diastolic Blood Pressure	UA-Urobilinogen	Albumin
Pulse	Gamma Glutamyl Transferase (GGT)	Glucose, Fasting
Percent Compliance	Alanine Transaminase (ALT/SGPT)	Total Bilirubin
Alcohol Use (designated as more than 3 drinks per week)	Aspartate Transaminase (AST/SGOT)	Serum Creatinine
Smoking (identified as current smoker and number of years patient has smoked)	Alkaline Phosphatase	Bone Specific Alkaline Phosphatase
	Creatine Phosphokinase	Osteocalcin
Creatinine Clearance (estimated by Cockcroft-Gault formula using either age and weight or age and calculated lean body mass)	Cholesterol	Bone Mineral Density (BMD)
	High Density Lipoprotein (HDL)	Type I Collagen Fragment
Previous Hormone Replacement Therapy (yes/no)	Low Density Lipoprotein (LDL)	
Previous Thiazide Diuretics Therapy (yes/no)	Triglycerides	Substudy Code

The patient factors are listed by category. No relationship to priority is implied.
A complete list of definitions and equations is provided in Appendix 7.a.

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2. Age

Age in study GGGK ranged from 45 to 81 years old. According to the sponsor, clearance decreased by 24% over this age range in the index data set, however this is less than the within-patient variability of 31%. Due to this and the failure to be retained in the final population pharmacokinetic model, the sponsor concluded that this effect is not clinically significant and does not necessitate dosage adjustment.

Table 14 Effect of Age on Clearance Estimates (GGGK)

Age (years)		Population Estimate of Clearance [a] (L/Hr)
45	(population minimum)	50.7
67	(population average)	43.3
81	(population maximum)	38.6

a For a typical nonsmoker with typical creatinine clearance for age.

3. Weight and Body Mass Index

According to the sponsor, *'Patient weight ranged from 33 to 133 kg in this study population. The inclusion of weight as a covariate did not improve the goodness-of-fit statistics (DMOF < 10.828 points). Therefore, the effect of weight on raloxifene disposition was not significant in this patient population. Body mass index ranged from 15 to 50 kg/m^2 in this study population. The effect of body mass index was not significant in this patient population."*

4. Race/Ethnicity

According to the sponsor, *'inclusion of ethnic origin as a covariate did not improve the goodness-of-fit statistics (DMOF < 10.828 points). Therefore, the effect of ethnic origin on raloxifene disposition was not significant in this patient population."*

As can be seen in Table 15 the numbers of non-Caucasians are small and are probably insufficient to detect an effect if one should exist.

Table 15 Race and Ethnicity of Subject in Study GGGK

Race/Ethnicity	%	Number of Subjects [a]
Caucasian	97.5	1669
Asian	1.0	17
Hispanic	0.7	12
African Descent	0.5	9
Other	0.2	3
Total	100	1710 of 1712

a - estimated from percentages.

5. Smoking Status

Smokers comprised 17% of the population. Based upon the total number of subjects in the pharmacokinetic study as reported by the sponsor this calculates to be 291 subjects. The mean clearance in smokers (49.9 L/hr) is 15% higher than the mean clearance in the typical non-smoker (43.3 L/hr). The typical non-smoker in this study is 67 years old, and has a mean creatinine clearance (CGLF) of 39 ml/min).

According the to sponsor, the increase in clearance is less than the within-patient variability of 31%. Consequently, the sponsor concluded that this effect is not clinically significant and does not necessitate dosage adjustment.

The basis of this difference of clearance in smokers is unknown, however according to the sponsor the results are consistent with earlier data from traditional pharmacokinetic studies.

6. Alcohol Consumption

According to the sponsor, *'In this study population, 82% of the patients were categorized as nondrinkers while 18% of the patients were categorized as drinkers (>3 drinks per week). The inclusion of the effect of alcohol as a covariate did not improve the goodness-of-fit statistics (DMOF < 10.828 points). Therefore, the effect of self-reported alcohol consumption was not significant in this study population.'*

7. Renal Function (CGLF)

Population analysis indicates that clearance decreases with renal function. For the typical 67 year old female nonsmoker population analysis indicates that there is a 14% decrease in raloxifene systemic clearance (from 43.3 L/hr to 37.2 L/hr). This 14% decrease occurs linearly with a 56% decrease in creatinine clearance from the mean value of 38.8 ml/min to the minimum value of 17 ml/min observed in the study population.

The sponsor claimed that these clearances were normalized to lean body mass, however this is erroneous as normalization would give units of volume/time x mass^{-1}. In actuality the Cockcroft-Gault formula for estimating creatinine clearance estimates the formation of creatinine based upon lean body mass. This estimation of creatinine formation based upon lean body mass is inherent to the formula whether the estimated creatinine clearance is subsequently normalized to body mass or not.

The formulae used by the sponsor follow:

Modified Cockcroft-Gault Method for Estimating Creatinine Clearance

$$\text{CGLF (ml/min)} = \frac{((140 - \text{current age (years)}) \times \text{FLBM}}{(72 \times \text{serum creatinine concentration (mg/dL)})}$$

Female Lean Body Mass

$$\text{FLBM (kg)} = [0.29569 \times \text{weight (kg)}] + [0.41813 \times \text{height (cm)}] - 43.2933$$

The modified Cockcroft-Gault method differs from the original Cockcroft-Gault method in the manner that female lean body mass is estimated.

The sponsor concluded that since the decrease in clearance is less than the within-patient variability of 31%, this effect is not clinically significant and does not necessitate dosage adjustment.

This is a reasonable conclusion, especially since the drug is also glucuronidated and eliminated in the feces. Consequently renal elimination only contributes a fraction of the total body clearance and modest alterations in renal elimination should not necessitate dosage adjustments with creatinine clearances above approximately 20 ml/min. Below approximately 20 ml/min there is insufficient information to guide dosing.

8. Other Patient Specific Factors

No other patient specific factor (See Table 13 Patient Factors to be Assessed in the Population Pharmacokinetic Analyses page 17) was identified that might effect raloxifene pharmacokinetics.

Patient specific factors included laboratory tests associated with liver damage, however the range of values for these tests were limited and were as follows:

serum bilirubin concentration	(range 3 to 34 mmol/L)
ALT	(range 4 to 164 IU/L)
AST	(range 10 to 123 U/L)

However, traditional PK studies performed earlier have clearly demonstrated altered clearance with hepatic impairment.

F. Concentration Effect Relationships

Concentration effect relationships were investigated for,

1. Efficacy
2. Discontinuations
3. Treatment Emergent Adverse Effects and Serious Adverse Events

1. Efficacy

In subsection 3.5.5.3., Evaluation of Raloxifene Steady-State Concentration Effect on Bone Mineral Density, the sponsor stated *"The effect of raloxifene steady-state concentrations on observed change of BMD was first evaluated graphically in patients participating in the pharmacokinetic portion of the study. Since no significant correlation between concentrations and change of BMD was observed, no further pharmacokinetic/pharmacodynamic model was developed."*

There was no discernable correlation between the change in total lumbar spine BMD or femoral neck BMD and raloxifene concentration. This lack of correlation is probably due to the wide range of concentrations seen with each dose level, and the large degree of overlap in observed concentrations between doses (See Figure 3 Pharmacodynamic Effect vs. Steady State Raloxifene Concentrations).

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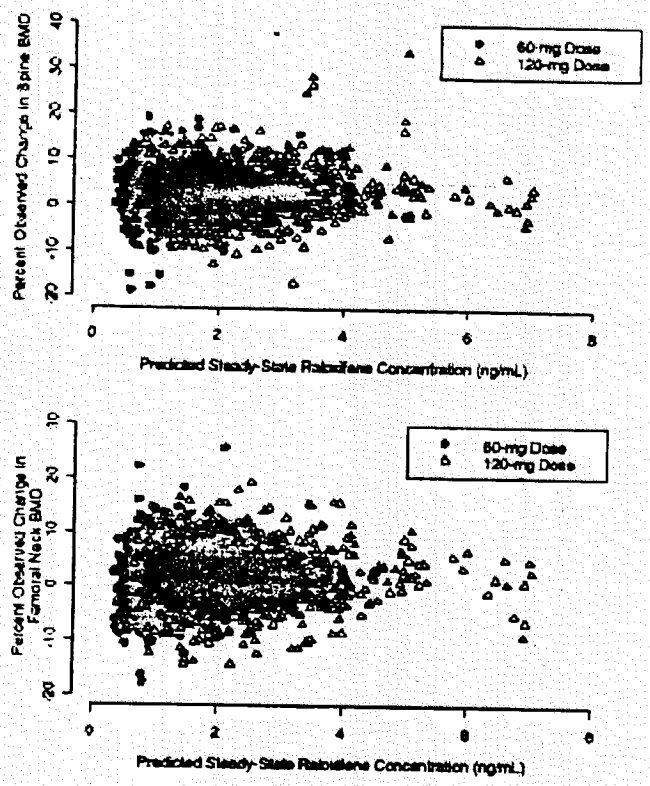
Figure 3 Pharmacodynamic Effect vs. Steady State Raloxifene Concentrations



Percent Change in Total Lumbar Spine Bone Mineral Density (Upper Panel) and Femoral Neck Bone Mineral Density (Lower Panel) Versus Predicted Raloxifene Steady-State Concentration (GGGK, 0-36 Month Data)

2. Discontinuations

a) Introduction

Discontinuations due the following causes were evaluated for any potential relationship to concentration:

a) Lack of efficacy (Protocol Completed)
b) Adverse Effects
c) Death

Table 16 shows the breakdown of the reasons for all discontinuations. In summary the following conclusions are demonstrated by Table 16:

There are statistically significant differences in:

- The total number of discontinuations in both the 60 and 120 mg groups compared to placebo.
- The number of discontinuations due to adverse events in the 60 mg group compared to placebo.
- The number of discontinuations due to a lack of efficacy in both the 60 and 120 mg groups compared to placebo.
- The number of deaths in the 120 mg group compared to 60 mg group.

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Table 16 Reasons for Study Discontinuation: Comparison of Overall Study Population and PK Study Population (all PK Data Observations)

Reason for Discontinuation (Raloxifene Treated Patients)	Overall Study Population			PK Study Population			PK Data Observations		
	60 mg Dose	120 mg Dose	Total	60 mg Dose	120 mg Dose	Total	60 mg Dose	120 mg Dose	Total
	(N= 2557)	(N= 2572)	(N= 5129)	(N= 885)	(N= 889)	(N =1774)	(N= 4835)	(N= 4802)	(N= 9637)
Total Discontinued	585 (22.9%) a	567 (22.0%) b	1152 (22.5%)	166 (18.8%)	157 (17.7%)	323 (18.2%)	588 (12.2%)	515 (10.7%)	1103 (11.4%)
Adverse Event	*279 (10.9%) a*	*248 (9.6%)*	*527 (10.3%)*	*97 (11.0%)*	*92 (10.4%)*	*189 (10.7%)*	*329 (6.8%)*	*299 (6.2%)*	*628 (6.5%)*
Personal conflict or other patient decision	161 (6.3%)	160 (6.2%)	321 (6.3%)	36 (4.1%)	32 (3.6%)	68 (3.8%)	127 (2.6%)	118 (2.5%)	245 (2.5%)
Lack of Efficacy	*28 (1.1%) c*	*25 (1.0%) c*	*53 (1.0%)*	*8 (1.0%)*	*3 (0.3%)*	*11 (0.6%)*	*42 (0.9%)*	*16 (0.3%)*	*58 (0.6%)*
Protocol variance	42 (1.6%)	45 (1.7%)	87 (1.7%)	8 (1.0%)	8 (1.0%)	16 (1.0%)	31 (0.6%)	24 (0.5%)	55 (0.6%)
Protocol entry criteria not met	29 (1.1%)	21 (0.8%)	50 (1.0%)	5 (0.6%)	4 (0.5%)	9 (0.5%)	10 (0.2%)	4 (0.1%)	14 (0.2%)
Unable to contact patient (lost to follow- up)	16 (0.6%)	21 (0.8%)	37 (0.7%)	4 (0.5%)	4 (0.5%)	8 (0.5%)	18 (0.4%)	14 (0.3%)	32 (0.3%)
Death	*13 (0.5%)*	*28 (1.1%) d*	*41 (0.8%)*	*3 (0.3%)*	*9 (1.0%)*	*12 (0.7%)*	*12 (0.3%)*	*25 (0.5%)*	*37 (0.4%)*
Patient moved	16 (0.6%)	19 (0.7%)	35 (0.7%)	5 (0.6%)	5 (0.6%)	10 (0.6%)	19 (0.4%)	15 (0.3%)	34 (0.4%)
Patient completed protocol, but had an adverse event	1 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total Continuing	1972 (77.1%) a	2005 (78.0%) b	3977 (77.5%)	719 (81.2%)	732 (82.3%)	1451 (81.8%)	4247 (87.8%)	4287 (89.3%)	8534 (88.6%)

NOTE: Chi- square tests were used when total count >= 10, else Fisher's exact test was used

a pairwise comparison statistically significant ($p < 0.05$) different from placebo

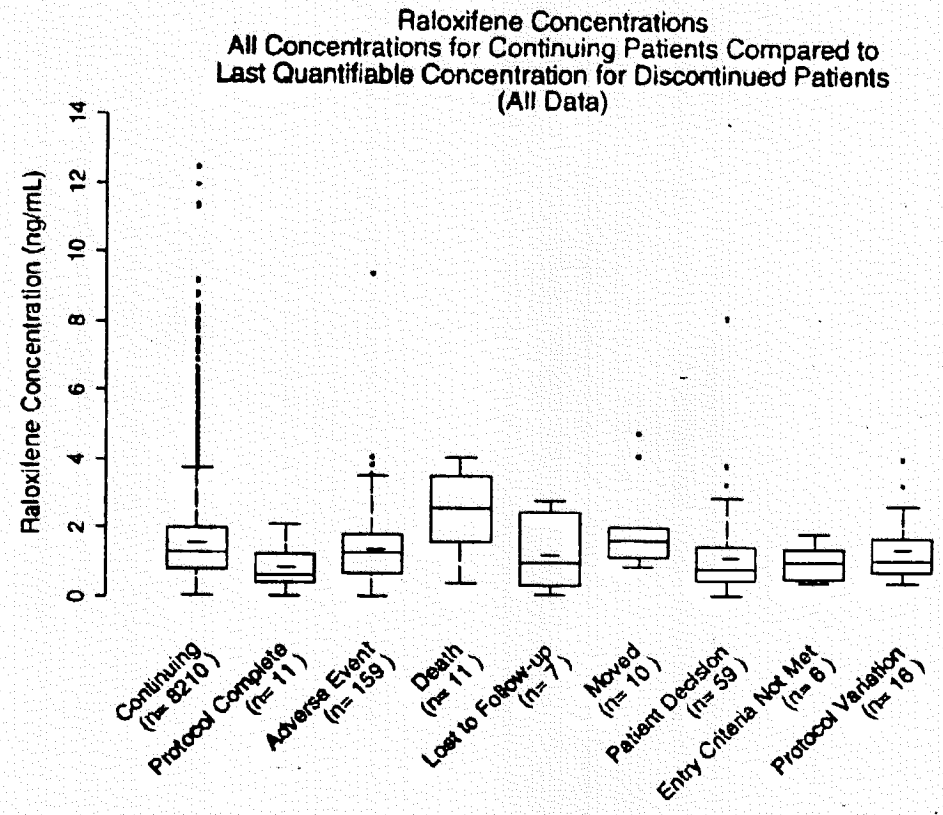
b pairwise comparison statistically significant ($p < 0.01$) different from placebo

c pairwise comparison statistically significant ($p < 0.001$) different from placebo

d pairwise comparison of 60 mg dose statistically significant ($p < 0.05$) different from 120 mg dose

Box and whiskers plots of the last quantifiable concentrations plotted for each reason for discontinuing are shown in the following figure (Figure 4). The boxes show the interquartile ranges and the whiskers the 80% confidence interval (i.e. 10% and 90% limits).

Figure 4 Raloxifene Concentrations: All Concentrations for Continuing Patients Compared to Last Quantifiable Concentration for Discontinued Patients (All Data)



Graphs are also available by dose.

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b) Discontinuations Due to Lack of Efficacy

Subjects on 60 mg daily who were discontinued from the protocol due to a lack of efficacy had lower mean concentrations than shown in Figure 4 above.

According to the sponsor, *'There was a statistically significant decrease of 28% (p= 0.04) in plasma raloxifene concentrations between patients in the 60-mg treatment group who discontinued the study due to protocol completion (lack of therapeutic efficacy) and those continuing in the study at 36 months. A 22% decrease was found in the 120-mg group but the difference was not statistically significant. These differences in plasma raloxifene concentrations, however, were less than within-subject variability (31%) of plasma raloxifene pharmacokinetics. Consequently, the concentrations were still within the range of concentrations from subjects who completed the protocol.'*

The sponsor concluded that there was 'no clinically relevant relationship exists between raloxifene steady-state plasma concentration and patient discontinuation due to lack of therapeutic efficacy'.

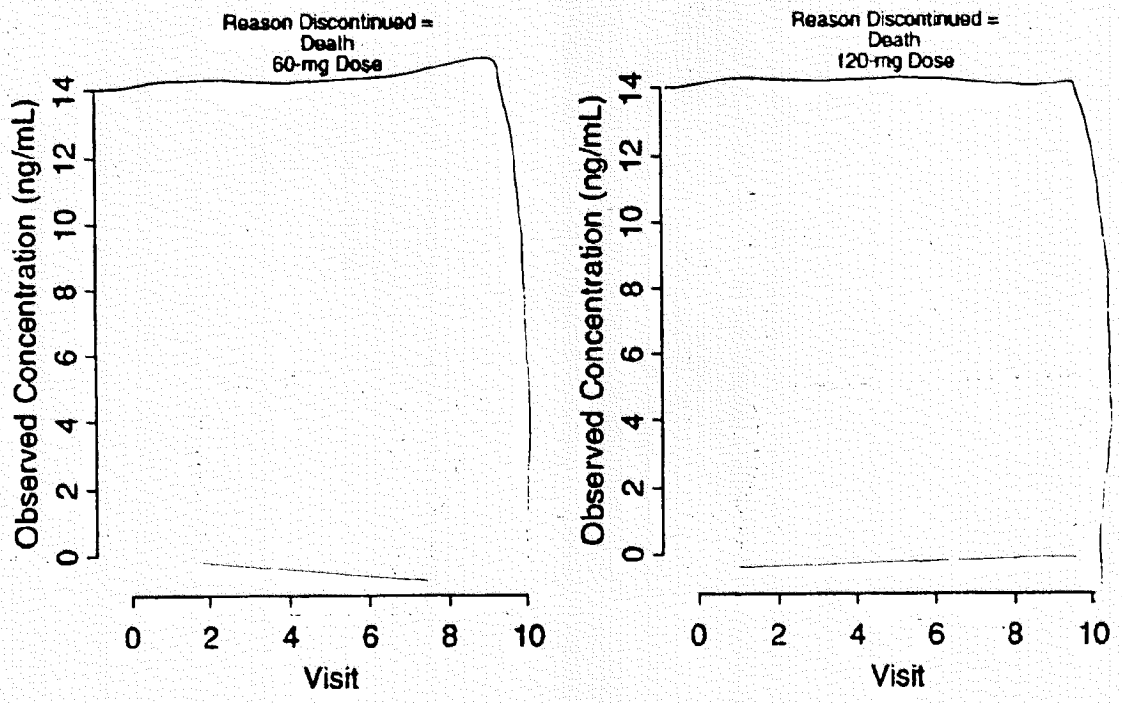
c) Discontinuations Due to Adverse Effects

There was no indication of any relationship between discontinuations due to adverse events and raloxifene concentrations.

d) Discontinuations Due to Death

The last quantifiable raloxifene concentrations are higher in those subjects who died compared to the mean concentrations in those who didn't. Plots of the concentrations in the subjects who died are shown in Figure 5.

Figure 5 Raloxifene Concentrations in Subjects who Died



Details of these subjects are shown in Table 17 Subjects Who Died and had Quantifiable Raloxifene Concentrations. Five of the subjects either died suddenly or had too few samples to assess a pattern relating to raloxifene concentrations. Of the rest, 2 of 7 had decreasing concentrations and both of these subjects had GI disorders. The remaining 5 of 7 had increasing concentrations over time and this might be due to decreasing elimination as these subjects got progressively sicker.

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Table 17 Subjects Who Died and had Quantifiable Raloxifene Concentrations

	Subject	Dose	Number of Samples	Raloxifene Concentration	Cause of Death
1	5065	120	5	Stable	Cardiac Arrest
2	5179	120	4	Increasing	GI Carcinoma
3	5273	60	3	Decreasing	Intestinal Gangrene
4	5451	60	5	Increasing	GI Carcinoma
5	5133	120	1	Can't assess	Hepatoma
6	86	120	3	Increasing	Hepatoma
7	3508	120	3	Increasing	Lung Disorder
8	929	120	2	Stable?	Heart Failure
9	335	120	1	Can't assess	Arrhythmia
10	2618	120	3	Decreasing	GI Carcinoma
11	2650	120	3	Stable	Cerebral Hemorrhage
12	4170	60	4	Increasing	Sepsis

3. Treatment Emergent Adverse Events and Serious Adverse Events

a) Treatment Emergent Adverse Events

Treatment emergent adverse events were defined as events that began or were preexisting and then worsened in severity after randomization.

Only those adverse events that met the following criteria were evaluated for a relationship to raloxifene concentrations:

- Incidence $\geq$ 1% in pooled raloxifene groups
- Incidence on raloxifene greater than the incidence on placebo (overall $p<0.05$ based on chi-square test)
- Occurred temporally within 1 week of sampling for raloxifene concentrations (i.e. 1 week before or after sampling; a 2 week interval)

According to the sponsor, *'Plasma raloxifene concentrations that were temporally associated with these adverse events were compared graphically and statistically to plasma raloxifene concentrations that were not temporally associated with these events.*

The effect of raloxifene concentrations on the occurrence of adverse events was evaluated using logistic regression. If the relationship between plasma raloxifene concentration and adverse event was found to be statistically significant, the data were then further analyzed by dose (60 mg and 120 mg). If the result within both treatment groups was not statistically significant, it was concluded that the correlation was due to the effect of dose on concentration and not between concentration and adverse event. A statistically significant result was not considered clinically relevant unless the change in the plasma raloxifene concentrations was greater than within-patient variability estimated by the population pharmacokinetic model.

Treatment emergent adverse effects that were identified are listed in Table 18.

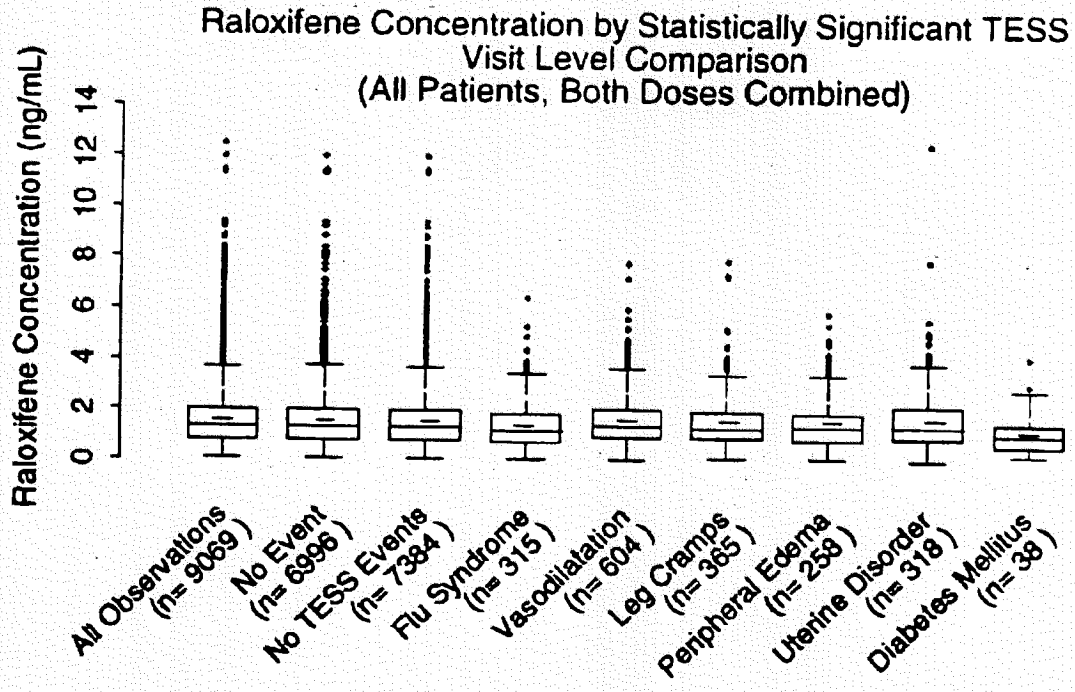
Table 18 Treatment Emergent Adverse Effects

Adverse Effect	Significant Relationship with Concentration	Dose Levels with Statistically Significant Relationships with Concentration
Flu Syndrome	YES	60 mg group only
Vasodilation	NO	x
Leg Cramps	NO	x
Peripheral Edema	NO	x
Uterine Disorders	YES	120 mg group only
Diabetes Mellitus	NO	x

According to the sponsor; *'No statistically significant relationship was identified between raloxifene concentration and leg cramps, vasodilatation, peripheral edema, or diabetes mellitus. The mean and range of plasma raloxifene concentrations in patients with these adverse events appear comparable to those for patients without these adverse events. Statistically significant relationships were identified with flu syndrome, only in the 60-mg treatment group, and with uterine disorder, only in the 120-mg treatment group. In both of these cases, the mean differences in plasma raloxifene concentrations were approximately 10% and were negligible in comparison to within-subject variability (31%) of plasma raloxifene pharmacokinetics."*

The lack of a clear relationship with mean concentration is demonstrated graphically in Figure 6.

Figure 6 Raloxifene Concentrations for Treatment Emergent Adverse Events

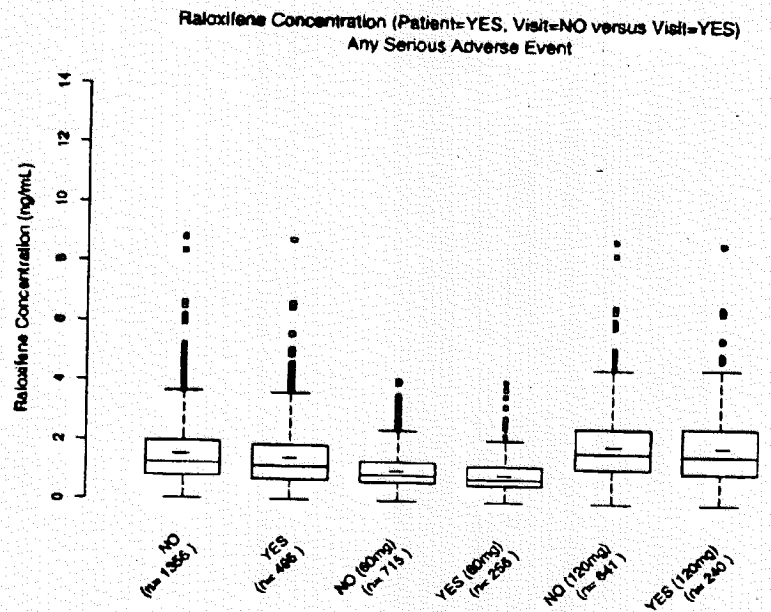


b) Serious Adverse Events

All raloxifene plasma concentrations from individuals with serious adverse events were pooled and compared to plasma concentrations from the rest of the patient population. In addition, concentration data from a subgroup of patients with serious adverse events were analyzed for potential relationships to the occurrences of venous thromboembolism (VTE). VTE includes deep thrombophlebitis, pulmonary embolus, and retinal vein thrombosis.

The sponsor failed to find any relationship between raloxifene plasma concentrations and the group of pooled serious adverse effect (See Figure 7). This is not surprising since there is no reason to expect that dissimilar types of serious adverse events would be related to each other. Consequently, this does not exclude the possibility of a relationship.

Figure 7 Raloxifene Concentrations and Serious Adverse Events



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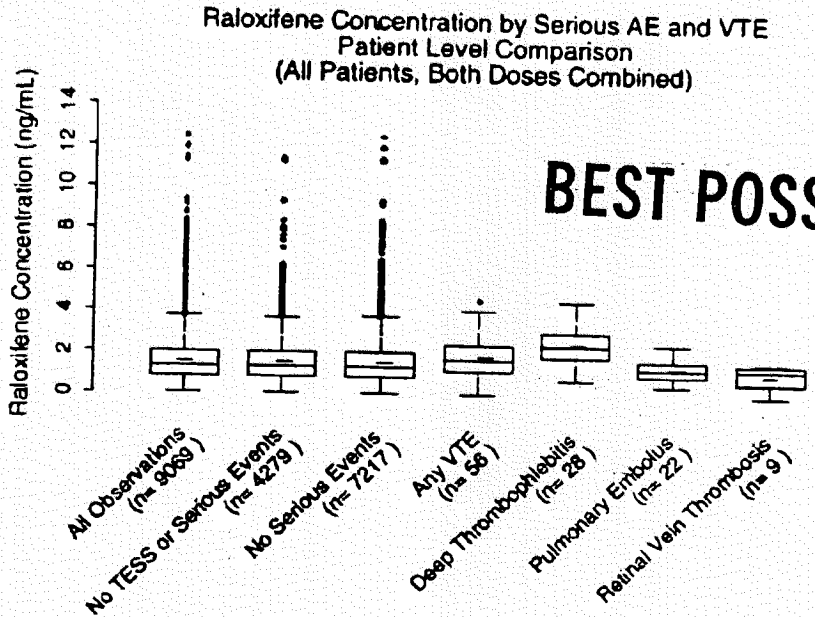
As can be seen from Figure 8 those subjects with deep thrombophlebitis may have higher mean plasma concentrations than usual.

Figure 8 Raloxifene Concentration by Serious AE and Venous Thromboembolic Event



However the number of subjects with venous thromboembolic events and raloxifene concentrations (n=5) is too small and the variability of concentrations from other subjects is too wide to draw any firm conclusions. This is seen more clearly by looking at the individual concentration data in Table 19.

Table 19 Available Individual Concentration Data in Subjects with Thromboembolic Events

Event	Number of Subjects	Raloxifene Dose	Raloxifene Concentration (ng/ml)
Venous Thromboembolism(VTE)	5 (Total)		
Deep Vein Thrombophlebitis (DVT)	3	60 mg 120 mg 120 mg	4.09ng/ ml 2.04 ng/ml 3.35 ng/ml
Pulmonary Embolus (PE)	1	60 mg	1.57 ng/ml
Retinal Vein Thrombosis (RVT)	1	120 mg	0.071 ng/ml

VII. DRUG INTERACTIONS

A. Population Pharmacokinetic Data - Concomitant Medication

The effect of concomitant medication on raloxifene concentrations was evaluated by a two-way mixed effects ANOVA on log transformed concentration data (geometric mean concentrations). Concomitant medication was included as a fixed effect and subject as the random effect.

According to the sponsor, *"Factors that make this approach particularly applicable for the current study include:*

1) *a large sample size (9637 raloxifene observations from 1774 Patients)*
2) *a strategy to define the temporal relationship between raloxifene plasma concentration and concomitant medication administration*
3) *the long t1/2 (28 hours) of raloxifene and daily dosing*
4) *the exclusive metabolism of raloxifene by glucuronidation*

The analysis was used only to exclude drug interactions but not to define them since the data are confounded by the underlying disease for which the concomitant medication was used."

A medication was classified as concomitant if used within one week **prior** to sampling to determine raloxifene concentration.

Drugs were grouped by pharmacologic class (See Table 20).

Individual drugs that fell into three categories were also examined. The individual drugs and their categories follow:

Highly Glucuronidated Drugs

Acetaminophen
Oxazepam
Ketoprofen
Morphine

Highly Protein-bound Drugs

Ibuprofen
Naproxen
Diazepam
Warfarin
Gemfibrozil

Drugs Previously Studied in Traditional Pharmacokinetic Drug Interaction Studies

Amoxacillin
Digoxin
Warfarin
Cholestyramine

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Table 20 Grouping of Concomitant Medications by Pharmacological Class (GGGK, 0-36 Month Data)

Drug Category	Products	Number of Concomitant Medication Records [a]	Number of Quantifiable Raloxifene Observations [b]
NSAID's	acetylsalicylic acid, diclofenac, ibuprofen, ketoprofen, nabumetone, naproxen, oxaprozin, piroxicam	5246	3183
Benzodiazepines	alprazolam, bromazepam, carbamazepine, clonazepam, diazepam, flunitrazepam, lorazepam, midazolam, nitrazepam, oxazepam, temazepam	1712	1153
Beta Blockers & Agonists	atenolol, metoprolol, propranolol, salbutamol, salmeterol, terbutaline, timolol	1633	1114
Antimicrobials	amoxicillin, azithromycin, cephalexin, cetirizine, ciprofloxacin, clarithromycin, doxycycline, erythromycin, metronidazole, nitrofurantoin, penicillin, tetracycline, trimethoprim/ sulfamethoxazole	1325	831
Calcium Channel Blockers	amlodipine, diltiazem, felodipine, lorazepam, nifedipine, nimodipine, verapamil	1276	891
Thyroid Hormone	levothyroxine, thyroid	1157	872
H2-Antagonists & Proton Pump Inhibitors	cimetidine, famotidine, nizatidine, omeprazole, ranitidine	1144	776
Hypolipidemics	cholestyramine, fluvastatin, gemfibrozil, lovastatin, nicotinic acid, pravastatin, simvastatin	976	721
Diuretics	chlorthalidone, furosemide, hydrochlorothiazide, indapamide	960	687
Glucocorticoids	beclomethasone, budesonide, cortisone, fluticasone, hydrocortisone, mometasone, prednisone, triamcinolone	914	563
GI Other	bisacodyl, cisapride, dimethicone, docusate, laxatives, loperamide, magnesium/aluminum hydroxide, psyllium	876	583
H1-Antagonists	chlorpheniramine, cinnarizine, diphenhydramine, loratadine, terfenadine	815	534
Estrogen Preparations	estrogen-containing products	801	594
ACE Inhibitors & Angiotensin Antagonists	captopril, enalapril, lisinopril, losartan	647	471
Nitrates	glyceryl trinitrate, isosorbide	541	348
Antidepressants	amitriptyline, fluoxetine, paroxetine, sertraline	420	280
Alpha Agonists & Antagonists	caffeine/ergotamine, phenylephrine, phenylpropanolamine, pseudoephedrine	225	174
Anticholinergics	atropine, ipratropium, meclizine	208	160
Iron	ferrous sulfate, iron	126	90
Muscle Relaxants	carisoprodol, quinine	116	85
Guaifenesin	guaifenesin	115	84
Theophylline	theophylline	81	53
Opioid Analgesics	morphine, pethidine	73	37
Non-benzodiazepine hypnotics	zopiclone	69	52
Bisphosphonates	alendronate	66	23
Hypoglycemics	glibenclamide	60	49
Antipsychotics	levomepromazine	47	39

a Total number of patient visits (pharmacokinetic study population) at which the concomitant medication was reported. Includes medication records with and without concentration data associated with them.

b Total number of quantifiable raloxifene observations temporally associated with the concomitant medication records. Includes both treatment groups.

Abbreviation: NSAID's = nonsteroidal anti-inflammatory drugs.

Analysis of variance of geometric mean ratios found statistically significant differences ($p \leq 0.05$); or trends, with the following classes of drugs or individual agents (Table 21).

Table 21 Statistically Significant Drug Interactions

Concomitant Medication	p- Value	
	60 mg Dose	120 mg Dose
NSAID's	0.01	—
Calcium Channel Blockers	—	0.04
Thyroid Hormone	0.06	—
H_1-Antagonists	0.06	—
Guaifenesin	0.03	—
Naproxen	—	0.04
Cholestyramine	0.002	—

The greatest differences based on the geometric mean ratios included a 16% decrease with guaifenesin and a 36.1% decrease with cholestyramine, both occurred with raloxifene doses of 60 mg daily. It should be noted however that no medication resulted in statistically significant differences with both dose levels (60 and 120 mg). Detailed results from the analysis of variance can be found in Table 22 and Table 23.

According to the sponsor, "A statistically significant result was not considered clinically relevant unless the effect on plasma raloxifene concentration was greater than the within-patient variability estimated by the population pharmacokinetic model."

That is unless the difference was greater than 31% the sponsor did not consider it clinically relevant. Consequently, only cholestyramine was considered by the sponsor to have a clinically relevant effect on raloxifene concentrations.

Table 24 shows the percent difference in raloxifene *arithmetic* mean concentrations in the presence of concomitant medications compared to *arithmetic* mean concentrations in the absence of concomitant medications. Those percentage differences greater than ~10% are highlighted in bold type. Fourteen groups of medications had *arithmetic* percentage differences of greater than 10%. Sometimes only one dose level or the other had a 10% or greater difference and in some cases such as warfarin the reported difference for both dose levels combined was greater than the percentage increase with each individual dose level.

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