

Table 22 Groups of Concomitant Medications: Mixed Effects Analysis of Variance of Log-Transformed Concentration Data (GGGK, 0-36 Month Data)

Concomitant Medications	60- mg Treatment Group				120- mg Treatment Group			
	Geometric Means		Ratio of Means	p- Value	Geometric Means		Ratio of Means	p- Value
	CM Absent	CM Present			CM Absent	CM Present		
NSAID's	0.922	0.976	1.059	0.01	1.729	1.778	1.028	0.24
Benzodiazepines	0.942	0.921	0.977	0.51	1.771	1.706	0.963	0.31
Beta Blockers & Agonists	0.940	0.937	0.997	0.92	1.755	1.723	0.981	0.61
Antimicrobials	0.943	0.913	0.968	0.19	1.752	1.760	1.004	0.87
Calcium Channel Blockers	0.938	0.962	1.026	0.51	1.716	1.871	1.090	0.04
Thyroid Hormone	0.934	1.026	1.099	0.06	1.750	1.778	1.016	0.74
H ₂ -Antagonists & Proton Pump Inhibitors	0.941	0.917	0.974	0.50	1.757	1.711	0.974	0.50
Hypolipidemics	0.935	0.982	1.050	0.25	1.749	1.803	1.031	0.59
Diuretics	0.934	0.994	1.064	0.15	1.729	1.835	1.061	0.18
Glucocorticoids	0.942	0.891	0.945	0.12	1.750	1.786	1.020	0.62
GI Other	0.942	0.897	0.952	0.27	1.749	1.804	1.031	0.51
H ₁ -Antagonists	0.935	1.018	1.089	0.06	1.754	1.746	0.995	0.92
Estrogen Preparations	0.941	0.925	0.984	0.74	1.746	1.850	1.060	0.25
ACE Inhibitors & Angiotensin Antagonists	0.940	0.920	0.979	0.68	1.774	1.671	0.942	0.22
Nitrates	0.936	1.030	1.101	0.12	1.749	1.859	1.063	0.36
Antidepressants	0.941	0.862	0.917	0.16	1.754	1.745	0.995	0.93
Alpha Agonists & Antagonists	0.938	1.044	1.113	0.16	1.750	1.936	1.106	0.21
Anticholinergics	0.940	0.902	0.960	0.54	1.781	1.612	0.905	0.23
Iron	0.941	0.841	0.894	0.38	1.752	1.787	1.020	0.81
Muscle Relaxants	0.939	0.959	1.021	0.83	1.752	1.873	1.069	0.54
Guaifenesin	0.941	0.791	0.840	0.03	1.752	1.835	1.047	0.56
Theophylline	0.940	0.950	1.011	0.94	1.753	1.781	1.016	0.92
Oploid Analgesics	0.940	0.932	0.992	0.94	1.752	1.817	1.037	0.72
Non-benzodiazepine hypnotics	0.939	1.096	1.167	0.25	1.753	1.717	0.980	0.87
Bisphosphonates	0.940	0.950	1.011	0.95	1.753	1.549	0.883	0.33
Hypoglycemics	0.940	0.885	0.942	0.70	1.751	2.152	1.229	0.29
Antipsychotics	0.940	0.841	0.895	0.57	1.753	1.773	1.012	0.95

Table 23 Individual Concomitant Medications: Mixed-Effects Analysis of Variance of Log Transformed Concentration Data (GGGK, 0-36 Month Data)

Concomitant Medications	60- mg Treatment Group			120- mg Treatment Group			p- Value
	Geometric Means		Ratio of Means	Geometric Means		Ratio of Means	
	CM Absent	CM Present		CM Absent	CM Present		
Acetaminophen	0.946	0.907	0.959	1.754	1.747	0.996	0.88
Ibuprofen	0.938	0.953	1.015	1.742	1.842	1.058	0.11
Naproxen	0.941	0.922	0.980	1.745	1.935	1.109	0.04
Amoxicillin	0.940	0.941	1.002	1.752	1.802	1.029	0.61
Diazepam	0.940	0.931	0.991	1.759	1.720	0.978	0.82
Digoxin	0.938	1.134	1.210	1.749	1.972	1.128	0.19
Oxazepam	0.940	0.905	0.963	1.749	2.022	1.156	0.16
Warfarin	0.940	0.791	0.841	1.752	1.859	1.061	0.60
Ketoprofen *	0.938	1.119	1.192	1.752	1.923	1.098	0.45
Gemfibrozil *	0.940	0.942	1.003	NA	NA	NA	NA
Cholestyramine	0.942	0.602	0.639	1.754	1.370	0.781	0.24
Morphine	0.939	0.812	0.865	1.753	1.851	1.056	0.71

a NA - Not Assessable - One evaluable patient with six records.
Abbreviations: CM = concomitant medication.

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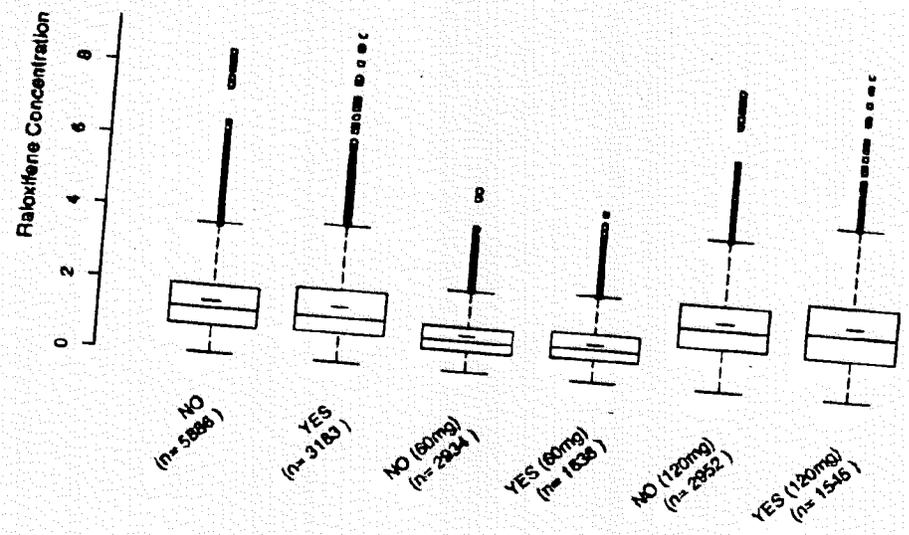
Table 24 Percent Difference in Mean Raloxifene Plasma Concentrations in the Presence of and Absence of Concomitant Medications

MEDICATION CATEGORY	Both Doses		60 mg Dose		120 mg Dose	
	N	% Difference	N	% Difference	N	% Difference
All Observations	9069	—	4572	—	4497	—
No Concomitant Medications	2170 (23.9%)	—	1194	—	976	—
ANY Concomitant Medication	6899 (76.1%)	5.8		1.7	3521	2.1
NSAID's	3183	6.4	1638	6.5	1545	7.9
PARACETAMOL	1539	0.3	740	-3.5	799	-0.2
BENZODIAZEPINES	1153	-3.9	21	-3.9	1132	-6.6
Beta-blockers & Agonists	1114	4.4	551	5.5	563	2.7
IBUPROFEN	980	3.2	482	1.3	498	2.8
Calcium Channel Blockers	891	7.8	453	3.4	438	10.7
THYROID Medications	872	10.7	375	9.6	497	3.6
ANTIMICROBIALS	831	-4.4	437	-4.2	394	-2.3
H ₂ Antagonists & Proton Pump Inhibitors	776	2.6	349	-3.2	427	0.0
HYPOLIPIDEMICS	721	-2.3	431	9.9	290	-0.3
DIURETICS	687	9.4	324	3.1	363	9.0
Estrogen Preparations	594	2.7	298	-2.2	296	5.2
GI - other	583	3.4	269	-5.6	314	3.4
Glucocorticoids	563	5.2	273	-0.5	290	6.1
H ₁ Antagonists	534	0.6	275	8.5	259	-2.7
ACE Inhibitors & Angiotensin Antagonists	471	-0.9	207	-2.8	264	-5.8
NAPROXEN	418	8.0	226	-2.3	192	18.7
NITROGLYCERINE	348	7.6	207	7.7	141	19.2
ANTIDEPRESSANTS	280	-2.5	126	-8.6	154	-4.5
ALPHA	174	3.1	90	6.7	84	2.3
AMOXACILLIN	160	-11.3	83	-17.2	77	-6.6
ANTICHOLINERGICS	160	-5.6	92	10.8	68	-10.0
DIAZEPAM	152	-2.9	80	2.2	72	-3.8
DIGOXIN	124	23.3	44	2.3	80	16.1
OXAZEPAM	94	19.5	31	10.1	63	7.3
IRON	90	6.5	38	-13.1	52	7.0
MUSCLE RELAXANTS	85	-7.9	50	-9.3	35	2.0
GUAIFENESIN	84	-1.6	41	-18.4	43	5.5
WARFARIN	64	32.6	19	-18.3	45	25.9
KETOPROFEN	62	21.7	30	37.3	32	11.7
THEOPHYLLINE	53	-5.6	31	-0.9	22	-0.6
ANTIPSYCHOTICS	52	-2.9	19	-22.1	33	12.5
HYPOGLYCEMICS	49	14.8	25	-7.7	24	28.0
CHOLESTYRAMIE	47	-30.7	33	-16.8	14	-26.8
GEMFIBROZIL	47	-4.8	41	6.3	6	83.2
Nonbenzodiazepine Hypnotics	39	5.4	21	16.0	18	-8.7
OPIOIDS	37	-4.8	17	-1.5	20	-10.0
BISPHOSPHONATES	23	17.3	8	-9.4	15	11.8
MORPHINE	17	-8.3	8	-25.5	9	-2.9

n.b. *Italicized* names are single medications.

Figure 9 graphically shows mean raloxifene concentrations with and without concomitant medications. The mean concentrations are shown for both dose levels as well at the concentrations at the 60 and 120 mg dose levels. As expected the overall mean falls between the means for the 60 and 120 mg dose levels.

Figure 9 Mean Raloxifene Concentrations in the Presence and Absence of Concomitant Medications at Various Dose Levels.



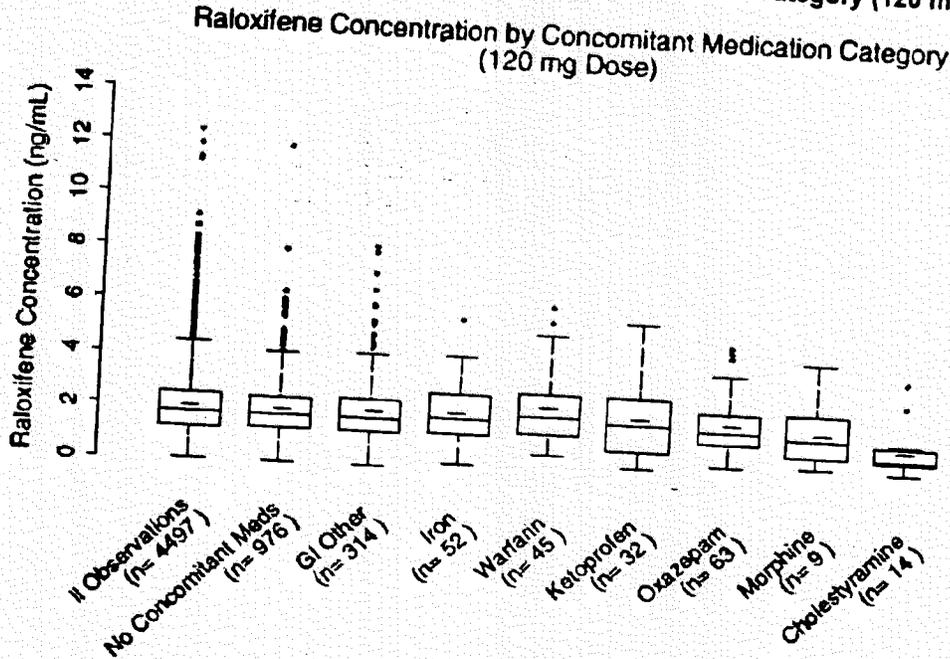
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Considering the large number of concomitant medications, since most would not be expected to interact, no difference is expected in mean raloxifene concentrations between those subjects taking concomitant medications and those not taking concomitant medications.

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Figure 10 graphically demonstrates raloxifene concentrations in the presence and absence of various concomitant medications.

Figure 10 Raloxifene Concentration by Concomitant Medication Category (120 mg Dose)



We can see that the number of observations in most categories is small and the overlap in concentrations between those on concomitant medications and controls is large.

1. Reviewer Comments:

There are a number of issues with this study.

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Effect on Pharmacokinetics of Raloxifene - This study evaluates the effects of other drugs on raloxifene pharmacokinetics. There is no evaluation of the effect of raloxifene on the pharmacokinetics of these other drugs.

Pharmacodynamic Interactions - This study evaluates only pharmacokinetic interactions. There is no evaluation of pharmacodynamic interactions. For example, in a traditional interaction study raloxifene did not effect the pharmacokinetics of warfarin, however it did effect warfarin pharmacodynamics. The present study would not identify such a pharmacodynamic interaction.

Confounding Due to Multiple Medications - Over 50% of subjects received ≥ 2 concomitant medications (See Table 25), and 20% of subjects received 4 or more concomitant medications. Consequently, interacting effects could cancel each other out, be additive, or might not be attributable to the correct medication. Thus, it makes it difficult to evaluate interactions. In addition, only medications of interest are included in these numbers, so the percentage of subjects on 2 or more concomitant medications could be higher.

Table 25 Number of Concomitant Medications of Interest Simultaneously Associated with Individual Raloxifene Observations: Frequency and Percent of Raloxifene Observations

Number of Concomitant Medications of Interest Associated with a Single Raloxifene Observation	Number of Raloxifene Observations	% of Raloxifene Observations	Cumulative % of Raloxifene Observations
0	2275	23.6	23.6
1	2487	25.8	49.4
2	1802	18.7	68.1
3	1140	11.8	79.9

Grouping of Concomitant Medications - There were 1493 different drug substances concomitantly administered, due to this large number of different substances, concomitant medications were grouped for analysis by pharmacologic effects or organ system effected.

Since the study was to evaluate pharmacokinetic interactions, any grouping of individual drugs might minimize the chance of detecting interactions. For example, if only a single drug in the group results in a pharmacokinetic interaction a lack of effect may be due to the other agents tempering the overall effect on the mean raloxifene concentration.

In addition, grouping by pharmacologic effect isn't justifiable, unless a specific pharmacologic effect would effect the pharmacokinetics (e.g. heart rate and organ blood flow in a drug with high intrinsic clearance). Neither is grouping to include both drugs with antagonistic effects and drugs with agonist properties rational. Such a grouping might result in no net change in the mean concentration if the agonists and antagonists have opposing effects on raloxifene pharmacokinetics.

As an example of the inappropriateness of the groupings used, the group GI-other contains an antifatuant, antacids, various types of antidiarrheals and various types of laxatives.

Assay Limitations - There is a lack of information on potentially interfering substances. This should not be a problem for the [] method, but needs to be considered for the [] method. Results could be spurious if assay interference causes a bias in the measured raloxifene concentration in the opposite direction of the effect of the pharmacokinetic interaction. Thus, results regarding drug interactions or the lack thereof from the population pharmacokinetic studies must be interpreted cautiously.

Temporal Association - Concomitant medications were included for evaluation if they were temporally administered within 1 week prior to sampling for raloxifene concentrations. If a drug causes induction of raloxifene elimination or takes time to decrease absorption the full effect might not be apparent within 1 week. In addition, some of these medications might have only been taken a single time and thus the interactions might not be detectable several days later. This might be particularly true for NSAID's, the category with the largest number of episodes of concomitant administration. Consequently, the temporal sampling scheme could result in erroneous conclusions.

Metric Evaluated - Raloxifene concentrations over the entire 24 hours dosage interval were grouped together and the mean concentration was evaluated. Metrics such as Cmax, or Cmin are more appropriate to evaluate as they would be expected to have smaller intrasubject variability (*vide infra*). Other metrics such as clearance, volume of distribution, AUC are usually better indicators of changes in pharmacokinetics, however there is one caveat to this. If pharmacokinetic parameters, such as clearance or volume of distribution were evaluated, their estimation would require bayesian analysis. This would

temper the individual estimates by the mean estimate and differences would be more difficult to detect using a population analysis.

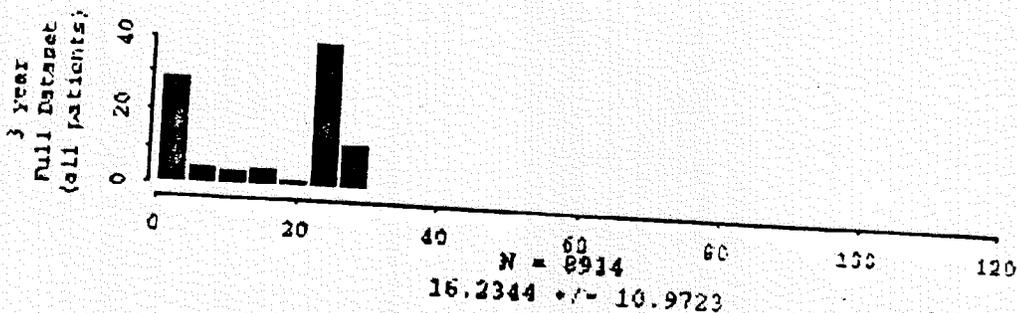
Within Subject Variability and Clinical Significance - The use of mean concentrations resulted in a 31% within subject (or intrasubject) variability. This was used to define the clinical significance of potential interactions, (i.e. differences in mean concentrations had to be > 31% to be considered clinically significant by the sponsor).

The use of intrasubject variability to determine clinical significance is the preferred approach. However, in the present case the manner in which the metric used was determined may have resulted in an inflated value for the intrasubject variability. Consequently, potentially clinically significant interactions may have been labeled as non-clinically significant by the sponsor.

Between Subject Variability - The mean half-life of raloxifene is approximately 32.5 hours (range 16 to 92 hours). By using a 6 hour time to peak the degree of peak to trough (pre-dose) fluctuation will average ~1.5 fold (range 1.15 to 1.85 fold). In addition, those subjects with a lower degree of fluctuation would have a lower clearance, a longer t1/2 and consequently more drug accumulation. Consequently, an extremely large between subject variability would be expected by using mean concentrations. Consequently, the ability to detect a statistically significant interaction is greatly diminished.

Sampling Times - Most samples were taken around the trough, although many of the samples seem to have been taken after 24 hours (See Figure 11). Consequently, some of the concentrations could have been lower than the pre-dose concentrations, thus contributing to the degree of fluctuation, increasing the within subject variability, and possibly spuriously altering the mean concentrations.

Figure 11 Frequency of Sampling Times Post-Dose



Number of Evaluable Subjects - The sample size for evaluation of interactions was often small, for example the group of chronically administered medications with the largest number of samples is the beta agonists and antagonists with 1114 quantifiable raloxifene concentrations. At an average of 5.4 observations per subject there are 206 subjects using 2 different pharmacologic classes (19 subjects per class). Assuming 25% of subjects on a single medication, approximately 5 subjects were receiving a single concomitant medication per pharmacologic class. In addition, this number has to be divided among several different medications. Consequently, the number of subjects receiving a particular medication by itself is very small, and the number of subjects taking a single concomitant medication would not be much greater for any other group.

Sample Size Required - The within, as well as the between subject variability are both quite large. Thus, normally we would expect the need for large numbers of subjects to detect any statistically significant difference. Consequently, the high variability would tend to underestimate the statistical and clinical significance of any pharmacokinetic interaction.

Data Exclusion - Only those samples with quantifiable raloxifene concentrations were included for analysis (i.e. samples with concentrations below the limit of quantification were excluded.). Consequently, if enhancement of raloxifene elimination, a decrease in absorption or some other factor decreases raloxifene concentrations it might not be detected.

No Evaluation of Certain Medications - The sponsor appropriately excluded many medications from analysis because too few individuals were receiving them. Although, if any of these drugs did result in a large interaction that could be detected with even a few subjects, they would not have even a chance of being detected in the present analysis. This will always be a potential deficiency with both population as well as conventional interaction studies.

Lack of Detection of Known Interactions - Perhaps the most interesting observation is that the detection of known interactions is either not conclusive from this population pharmacokinetic study or not detected at all.

In a previous interaction study cholestyramine resulted in a 60% decrease in the extent of raloxifene absorption. Due to the normally low raloxifene concentrations, i.e. frequently below the limit of quantification this could be quite significant clinically. In contrast, the population pharmacokinetic data only detected a statistically significant 36% decrease in mean concentration ($p = 0.002$) at the 60 mg dose, however, the difference was not statistically significant at the 120 mg dose level.

In addition, no interaction was detected with antimicrobial agents although interactions are expected, as antimicrobial agents are known to alter the GI fauna. They would thus be expected to alter enterohepatic recycling resulting in a pharmacokinetic interaction. Such an interaction has been previously demonstrated for ampicillin in a conventional clinical pharmacology interaction study and this information is included in the package insert that is currently on the market.

Other Drug Interactions - A major utility of a population approach is in the ability to identify potential interactions, i.e. to generate hypotheses. In spite of this the sponsor used the approach to exclude interactions and not for identification.

In spite of the claimed lack of clinically significant interactions, the statistically significant differences in mean raloxifene concentrations with the following drugs or categories of drugs suggests that interactions with the following agents should be evaluated more thoroughly. (See Table 22 and Table 23)

- NSAID's especially Naproxen
- Calcium Channel Blockers
- Thyroid Hormones
- Estrogen Preparations
- Guaifenesin

Due to a variety of factors, it's not possible to confirm or deny these interactions with a population approach. As raloxifene concentrations vary widely and the changes seen were modest, additional studies to evaluate the potential of these medications to effect raloxifene concentrations are not warranted at this time.

B. Glucuronidation

Based upon the individual medications singled out for analysis, the sponsor also concluded that there were no clinically significant drug interactions with other highly glucuronidated drugs.

Since raloxifene is glucuronidated competitive inhibition by other glucuronidated compounds is a potential mechanism for a pharmacokinetic drug interaction. Acetaminophen (n obs = 1539), oxazepam (n obs = 94), ketoprofen (n obs = 62), and morphine (n obs = 17) were the highly glucuronidated drugs examined. For oxazepam, ketoprofen and morphine graphical analysis showed a trend to higher mean raloxifene concentrations in the presence of some of these medications (See Figure 10). This trend to higher

concentrations raises a concern that there might be a drug interaction, even though one cannot be conclusively demonstrated from the present study. The trend to higher raloxifene concentrations seem to be more pronounced with the higher raloxifene dose of 120 mg, as would be expected for a competitive interaction. However, the visual inspection of the graphical analysis is partially at odds with the % differences reported in Table 24. In addition, these medications tend to be administered pm and thus may not have always been administered concurrently with raloxifene, thus skewing the results downward. These factors strength the concern that such an interaction might be occurring with raloxifene. Consequently, a conclusion of no interaction cannot be established from this study.

C. Highly Protein Bound Drugs

The sponsor also concluded that there were no clinically significant drug interactions based upon interactions with highly protein bound drugs.

The current study does not allow this conclusion to be made. Although clinically significant interactions based upon alterations in protein binding are rare. Such interactions to be clinically significant generally require a concomitant effect on elimination, or raloxifene to be a high intrinsic clearance compound so that an effect on absorption can occur. An interaction of both protein binding and metabolic elimination is uncommon and since raloxifene is glucuronidated it is unlikely to have high intrinsic clearance.

D. Methylprednisolone

The effect of raloxifene on the pharmacokinetics of methylprednisolone was examined in a classical multiple-dose crossover design. Raloxifene 2 x 60 mg or placebo was administered po on days 1-4 followed by 1 x 60 mg or placebo on days 5 - 11 each treatment period. Methylprednisolone 32 mg (2 x 16 mg) was administered po on day 11 of each treatment period.

The pharmacokinetic metrics of methylprednisolone after a single oral dose of 32 mg are very similar in the two treatments arms (See Table 26).

Table 26 Pharmacokinetic Metrics of Methylprednisolone

	After Placebo [Mean ± SD] (n = 16)	After Raloxifene [Mean ± SD] (n = 16)
C _{max} (ng/mL)	277 ± 64	298 ± 91
t _{max} (h)	1.9 ± 1.0	1.6 ± 0.8
AUC (0-∞) (ng/ml x hr ⁻¹)	1300 ± 540	1330 ± 590
Cl/F (L/h)	28 ± 9	29 ± 13
t 1/2 (h)	1.85 ± 0.43	1.85 ± 0.46

In addition, when 90% confidence intervals for these metrics are examined and the T_{max}'s are compared there is no indication of any effect of raloxifene on methylprednisolone pharmacokinetics (See Table 27).

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Table 27 Pharmacokinetic (PK) Interaction of Raloxifene on Methylprednisolone (M) after Repeated Administration of Raloxifene or Placebo

PK Metric for M	Between Subject CV (%)	Within Subject CV (%)	Mean Raloxifene Group (1) N = 16	Mean Placebo Group (2) N = 16	Ratio (1)/(2)	90% Confidence Limits on Ratio	
						Lower	Upper
AUC _(0-∞) ^a (ng/ml x hr ⁻¹)	42.5	13.6	1223	1214	100.8	92.7	109.7
C _{max} ^a (ng/ml)	30.4	22.1	282.6	270.0	104.7	91.4	119.9
t _{1/2} ^b (hours)	24.5	5.2	1.848	1.848	100.0	96.8	103.3
		Median Raloxifene group		Median Placebo group			
T _{max} ^c (hours)		1.5		2		(p-value = 0.5625)	

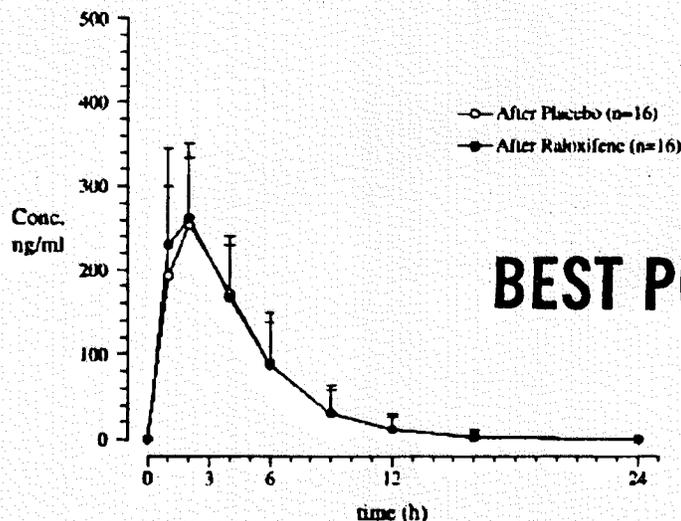
a CV, geometric means, ratio and corresponding confidence limits are back-transformed from the logarithmic scale.

b for t_{1/2}, arithmetic means are reported.

c for T_{max}, medians and the two-sided p-value of the Wilcoxon signed rank test are reported.

The lack of an interaction is demonstrated graphically in Figure 12.

Figure 12 Methylprednisolone Mean Concentration vs. Time Profiles in the Presence and Absence of Raloxifene



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Figure GGIP.A.1. Mean (+ sd) Plasma Concentrations of Methylprednisolone Following a Single Oral Dose of 32 mg Methylprednisolone After Multiple Administration of Placebo or Raloxifene in 16 Postmenopausal Women

The only obvious drug related side effects were associated with methylprednisolone. No side effects clearly associated with raloxifene were apparent in the 16 subjects in this study.

In conclusion, it appears that the administration of raloxifene has no effect on the pharmacokinetics of methylprednisolone in postmenopausal women when given as a single oral dose.

Conclusions regarding any effect on metabolite kinetics, specifically *methylprednisone*, or the lack thereof cannot be made. Although the effect of raloxifene on *methylprednisone* is unknown, since *methylprednisone* is inactive and is readily inter-converted with methylprednisolone, a significant interaction is highly unlikely.

Sampling for determination of raloxifene concentrations were limited and were only reported as a mean of two trough concentrations, one 24 hours before dosing with methylprednisolone and one immediately prior to dosing. Consequently, no determination of the effects of methylprednisolone on the pharmacokinetics of raloxifene can be made.

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IX. COMMENTS FOR THE SPONSOR

Labeling regarding the lack of effects of other drugs on raloxifene pharmacokinetics is unacceptable due to a number of reasons, some of which follow. The population pharmacokinetic approach is primarily useful for detecting potential drug interactions. It is less useful for ruling out drug interactions.

Confounding Due to Multiple Medications - Over 50% of subjects received ≥ 2 concomitant medications, and 20% of subjects received 4 or more concomitant medications. Consequently, interacting effects could cancel each other out, be additive, or we may not be able to attribute effects to the appropriate medication.

Grouping of Concomitant Medications - There were 1493 different drug substances concomitantly administered. Due to this large number of different substances, concomitant medications were grouped for analysis by pharmacologic effects or organ system effected.

Since the study was to evaluate pharmacokinetic interactions, any grouping of individual drugs might minimize the chance of detecting interactions with individual drugs. For example, if only a single drug in the group results in a pharmacokinetic interaction a lack of effect may be due to the other agents tempering the overall effect on the mean raloxifene concentration.

In addition, grouping by pharmacologic effect isn't appropriate, **unless** a specific pharmacologic effect would be expected *a priori* to effect the pharmacokinetics of a drug (e.g. heart rate and/or organ blood flow in a drug with high intrinsic clearance). An example where grouping could result in spurious results include grouping drugs with both antagonistic and agonist properties. Such a grouping might result in no net change in the mean concentration if the pharmacologic effects of the agonists and antagonists have opposing effects on raloxifene pharmacokinetics.

Assay Limitations - There is a lack of information on potentially interfering substances. This should not be a problem for the [] method, but needs to be considered for the [] method. Results could be spurious if assay interference causes a bias in the measured raloxifene concentration in the opposite direction of the effect of the pharmacokinetic interaction. Thus, results regarding drug interactions or the lack thereof from the population pharmacokinetic studies must be interpreted cautiously.

Temporal Association - Concomitant medications were included for evaluation if they were temporally administered within 1 week prior to sampling for raloxifene concentrations. If a drug causes induction of raloxifene elimination or takes time to decrease absorption, the full effect might not be apparent within 1 week. In addition, some of these medications might have only been taken a single time and thus the interactions might not be detectable several days later. This might be particularly true for NSAID's, the category with the largest number of episodes of concomitant administration. Thus, without more detailed temporal information the temporal sampling scheme could result in erroneous conclusions.

Variability and Clinical Significance - The determination of clinical significance was based upon the within subject variability of mean raloxifene concentration. It appears from the data that a number of samples were taken at greater than 24 hours post-dosing, especially at end of the study. Consequently, the variability of the mean concentrations may be spuriously high. Consequently, its' use would tend to underestimate the statistical and clinical significance of any pharmacokinetic interaction. Other metrics with lower intrasubject variability may be more appropriate.

Number of Evaluable Subjects - The sample size for evaluation of interactions was often small. For example the group of chronically administered medications with the largest number of samples is the beta agonists and antagonists with 1114 quantifiable raloxifene concentrations. At an average of 5.4 observations per subject there are 199 subjects using 2 different pharmacologic classes (28 subjects per drug). Based upon the data provided in the NDA, 25% of these subjects are taking a single concomitant

medication. Thus, approximately seven subjects per medication were receiving only raloxifene and that individual concomitant medication. Unless, the effect on raloxifene concentrations is dramatic an interaction is unlikely to reach statistical significance.

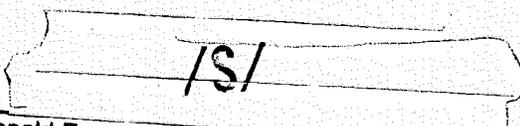
Data Exclusion - Only those samples with quantifiable raloxifene concentrations were included for analysis (i.e. samples with concentrations below the limit of quantification were excluded.). Consequently, if enhancement of raloxifene elimination, a decrease in absorption or some other factor decreases raloxifene concentrations it might not be detected.

Lack of Detection of Known Interactions - An interesting observation is that interactions that should occur are either not detected at all, or that the results from the population pharmacokinetic approach are much weaker. This tends to underscore the risk of concluding a lack of an interaction from the population pharmacokinetic approach.

In a previous interaction study cholestyramine resulted in a 60% decrease in the extent of raloxifene absorption. Due to the normally low raloxifene concentrations, i.e. frequently below the limit of quantification this could be quite significant clinically. In contrast, the population pharmacokinetic data only detected a statistically significant 36% decrease in mean concentration ($p = 0.002$) at the 60 mg dose, however, the difference was not statistically significant at the 120 mg dose level.

In addition, no interaction was detected with antimicrobial agents, although interactions would be expected as antimicrobial agents are known to alter the GI fauna. They would thus be expected to alter enterohepatic recycling resulting in a pharmacokinetic interaction. Such an interaction has been previously demonstrated for ampicillin in a conventional clinical pharmacology interaction study.

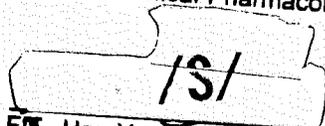
X. SIGNATURES



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9/15/99
Date



Hae-Young Ahn, Ph.D., Team Leader

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Date

OCPB Briefing Meeting: None

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Lilly; Indianapolis, IN

APPENDIX 1 - PROTOCOL SUMMARY - Combined Studies H3S-MC-GGGN / GGGP

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