CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-042

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	22-042
Submission Dates:	13 November 2006, 9 Feb 2007
Brand Name:	Evista®
Generic Name:	raloxifene HCl
Formulation:	60 mg tablets
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Sponsor:	Lilly
Submission Type; Code:	Original NDA; 000
Dosing regimen:	60 mg/day
Indication:	reduction in the risk of invasive breast cancer

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1 EXECUTIVE SUMMARY

Evista® is a selective estrogen receptor modulator (SERM). The current submission is the original NDA for Evista for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis or women at high risk for breast cancer.

To support the approval of reduction in risk of invasive breast cancer the sponsor conducted two new phase 3 studies (GGIO and GGJY), and used data from one previously submitted phase 3 study for osteoporosis (GGGK). All of the studies except for GGGK used the approved dose of 60 mg QD or placebo. GGGK had an arm with raloxifene 120 mg QD in addition to the 60 mg QD and placebo treatments. The primary endpoint for each of the studies differed. The primary endpoint for GGIO was incidence of coronary deaths and a co-primary endpoint was incidence of breast cancer. GGGK was an osteoporosis trial and the primary endpoint was related to new vertebral factures and bone mineral density (BMD) while a secondary endpoint was reduction in breast cancer. GGJY was an extension of GGGK and the primary endpoint was the incidence of invasive breast cancer.

In addition to the studies submitted to support the efficacy claim, the sponsor submitted a biomarker study (GGHW) in patients with primary breast cancer. The primary objective was to determine the short-term biologic effect of raloxifene treatment on an intermediate endpoint marker, Ki67, which is a proliferation-associated nuclear antigen. Subjects received either raloxifene 60 mg QD, raloxifene 300 mg BID or placebo for 14 days. Sparse samples for pharmacokinetics (Day 10 and 14) along with levels for Ki67, estrogen receptor and progesterone receptor measures (baseline and end of study) were taken throughout the study. No significant correlation between steady-state concentrations and change in Ki67 was observed upon analysis and no patient factors or laboratory measurements were found to influence the pharmacokinetics (PK) of raloxifene.

There was no formal PK/PD analysis done by the sponsor for the reduction in risk of breast cancer. The primary study supporting efficacy (GGIO) had sparse sampling from 250 of 10,000 patients under one dose level (60 mg QD) which made it difficult to elucidate a formal concentration/response relationship. In addition, the intrinsic and extrinsic factor results from study GGIO indicated that smoking, alcohol, age, weight or race had no effect on the steady state concentration of raloxifene. These results are identical to what was concluded for intrinsic and extrinsic factors with the original osteoporosis NDA.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 22-042. This clinical pharmacology information is considered acceptable.

Labeling Recommendations

There are no labeling recommendations. No changes were made by the sponsor to the relevant clinical pharmacology sections of the label.

Signatures:

Julie M. Bullock, Pharm.D. Reviewer Division of Clinical Pharmacology 5	Brian Booth, Ph.D. Deputy Director & Acting Team Leader Division of Clinical Pharmacology 5

Cc: DDOP: CSO - P Garvey; MTL - J Johnson; MO - P Cortazar; B Mann
DCP-5: Reviewer - J Bullock; Acting TL & DDD - B Booth; DD - A Rahman

OCP Briefing held Sept 5, 2007 and attended by: Brian Booth, Atik Rahman, Ting Ong, Leslie Kenna and Mike Orr

1.2 CLINICAL PHARMACOLOGY SUMMARY

Evista® is a selective estrogen receptor modulator (SERM) which inhibits estrogen-like action in reproductive tissues, such as the breast and uterus. Evista® (raloxifene) is currently approved for the prevention and treatment of osteoporosis in postmenopausal women (NDA 20-815).

Raloxifene pharmacokinetics were extensively described in the human pharmacokinetics, pharmacodynamics, and bioavailability section of the initial and subsequent regulatory submissions for the indication of prevention and treatment of osteoporosis in postmenopausal women. In brief, approximately 60% of an oral dose of raloxifene is absorbed. Metabolism is extensive and the majority is excreted in the feces. The terminal half-life is approximately 28 hours due to enterohepatic cycling.

Since the prevention (NDA 20-815/000; June 8, 1997) and treatment (NDA 20-815/SE1; March 30, 1999) of osteoporosis applications, the sponsor has conducted additional trials in which the population pharmacokinetics and pharmacodynamics of raloxifene in patients with primary breast cancer (GGHW) and the steady-state raloxifene concentration data (GGIO) in postmenopausal women were evaluated. No additional clinical pharmacology studies have been undertaken for the purpose of this submission.

Studies submitted with the current application to support the safety and efficacy for reduced risk of invasive breast cancer in postmenopausal women (PMW) with osteoporosis and postmenopausal women with an increased risk of breast cancer are below in Table 1.

TABLE 1. Studies submitted to support safety and efficacy.

Study	Population	Endpoints	Dose	submitted previously?	PK?
GGIO (RUTH)	10k PMW at risk for major coronary events	reduction in coronary deaths & reduction in breast cancer	60 mg QD or placebo	No	Yes
GGGK (MORE)	PMW with Osteoporosis	rate of new vertebral fractures & lumbar spine and femoral neck BMD	60 mg or 120mg QD or placebo	Yes	Yes
GGJY	PMW with osteoporosis	Incidence of invasive breast cancer	60 mg QD or placebo	No	No

GGIO was a Phase 3, multicenter, double-blind, placebo-controlled, randomized, parallel study enrolling 10,101 postmenopausal women at risk for major coronary events to one of two therapy groups: raloxifene 60 mg/day or placebo. The study had two primary objectives. The first was to evaluate the effect of chronic oral treatment with raloxifene, compared with placebo, on the combined coronary endpoint of coronary events in postmenopausal women at risk for major coronary events. A second primary objective was to determine the effect of raloxifene in reducing the incidence of invasive breast cancer. Concentration data was gathered from 253 patients following 12 and 24 months of treatment. Graphical visualization and descriptive statistical analyses of the raloxifene concentration data was the primary tequniqe of data evaluation. Similar to previous conclusions from past osteoporosis study analyses, there were no correlations between raloxifene concentrations and weight, age, race, smoking status or alcohol use.

GGGK was a randomized, double-blind, placebo-controlled, multinational study conducted in

postmenopausal women with osteoporosis. The primary objectives of GGGK were to assess the effects of raloxifene treatment, compared with placebo, on the incidences various osteoporosis markers, and safety. Assessment of the effect of raloxifene on incidence of all breast cancer was a secondary safety endpoint. Steady-state concentrations were evaluated in patients over 36 months of raloxifene treatment. This study was originally submitted and reviewed under a supplement to the osteoporosis NDA (NDA 20-815, SE1), and no new data was submitted. The results of the population PK and safety analysis from prior review indicated that age, weight, ethnicity, body weight, race, renal function, alcohol use and smoking status did not effect raloxifene pharmacokinetics. In addition there was no statistically significant effect of plasma raloxifene concentrations related to adverse events, treatment emergent side effects, or death.

In addition to the above studies submitted to support the efficacy claim, the sponsor submitted results from GGHW and a pharmacodynamic analysis of three phase 3 osteoporosis prevention studies. The details of these studies are listed below in Table 2.

TABLE 2. Supportive studies.

Study	Population	Endpoints	Dose	submitted previously?	PK?
GGHW	Patients with Breast cancer	Effect on Ki67	60mg QD 300mg BID placebo	No	Yes
GGGF GGGG GGGH	PMW	various osteoporosis markers	30, 60 or 120 mg/day	Yes	Yes

Study GGHW was a phase 3 study of raloxifene in patients with primary breast cancer. The primary objective of this study was to determine the short-term biologic effect of raloxifene treatment on an intermediate endpoint marker, Ki67, which is a proliferation associated nuclear antigen. Patients received either raloxifene 60 mg QD, raloxifene 300 mg BID or placebo for 14 days. Sparse samples for PK (Day 10 and 14) along with levels for Ki67, estrogen receptor and progesterone receptor measures (baseline and end of study) were taken during the study. A one-compartment model with first-order absorption (Ka) and first-order elimination was selected to describe the pharmacokinetics of raloxifene following oral administration. Each covariate was tested for a relationship with clearance or volume of distribution using both linear and nonlinear models. Since no significant correlation between steady-state concentrations and change in Ki67 was observed, no further pharmacokinetic/pharmacodynamic model was developed. In addition, no patient factors or laboratory measurements were found to influence the PK of raloxifene.

Since the analysis of the three phase 3 studies (GGGF, GGGG & GGGH) was reviewed with the original osteoporosis NDA (NDA 20-815, June 8, 1997) and the analysis is regarding osteoporosis markers, it was not reviewed for this application.

2 GENERAL ATTRIBUTES

Please see the original NDA 20-815 review.

2.1.1 What are the proposed mechanisms of action and therapeutic indications?

Evista is a selective estrogen receptor modulator (SERM) based on its ability to elicit prototypical estrogenic effects on the bone and on certain aspects of lipid metabolism while inhibiting estrogen-like action in reproductive tissues, such as the breast and uterus.

2.1.2 What are the proposed dosage and route of administration?

The proposed dose is 60 mg QD orally which is also the currently approved dose for osteoporosis prevention and treatment.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

No clinical pharmacology studies were conducted specifically for this indication. Three phase 3 studies were submitted to support the efficacy claims.

GGIO (RUTH) was a Phase 3, multi-center, double-blind, placebo-controlled, randomized, parallel study enrolling 10,101 postmenopausal women at risk for major coronary events to one of two therapy groups: raloxifene 60 mg/day or placebo. The study had two primary objectives. The first was to evaluate the effect of chronic oral treatment with raloxifene, compared with placebo, on the combined coronary endpoint of coronary events in postmenopausal women at risk for major coronary events. A second primary objective was to determine the effect of raloxifene in reducing the incidence of invasive breast cancer. Concentration data was gathered from 253 patients following 12 and 24 months of treatment.

GGGK (MORE) was a randomized, double-blind, placebo-controlled, multinational study conducted in postmenopausal women with osteoporosis. The primary objectives of GGGK were to assess the effects of raloxifene treatment, compared with placebo, on the incidences various osteoporosis markers, and safety. Assessment of the effect of raloxifene on incidence of all breast cancer was a secondary safety endpoint. Steady-state concentrations were evaluated in patients over 36 months of raloxifene treatment. The population pharmacokinetics from this trial were reviewed with the Original osteoporosis NDA 20-915 (March 20, 1998)

GGJY (CORE) was a double-blind, placebo-controlled, multinational study that enrolled postmenopausal women with osteoporosis who had been randomized in GGGK for an additional 4 years of follow-up. Subjects who were enrolled in GGGK on raloxifene 60 mg or 120 mg received 60 mg in GGJY and subjects on placebo continued to receive placebo. The primary objective of GGJY was to compare the long-term effect of raloxifene 60 mg/day versus placebo on the reduction in incidence of invasive breast cancer in postmenopausal women with osteoporosis. The secondary objectives were to assess the long-term effect of raloxifene 60 mg/day on the incidence of invasive, ER-positive breast cancer and non-vertebral fractures in postmenopausal women with osteoporosis.

P-2 was a randomized, double-blind, active-controlled, North American study conducted by the

NSABP under the auspices of the National Cancer Institute. Postmenopausal women were randomized to receive tamoxifen 20 mg/day or raloxifene 60 mg/day for 5 years. The primary objective was to compare the ability of raloxifene to reduce incidence rate of invasive breast cancer compared to tamoxifen.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The table below summarizes the efficacy endpoints for the studies GGIO, GGGK, and GGJY which used to support the efficacy claim.

TABLE 3. Efficacy endpoints in clinical studies.

Endpoint	GGIO	GGGK	GGJY
Coronary	Combined endpoints of coronary death, nonfatal MI, or hospitalized ACS other than MI.		
Invasive breast cancer	mammograms were obtained at randomization and every 2 years.	(secondary endpoint) mammograms obtained at baseline and throughout the study	mammograms at baseline and throughout the study
Osteoporosis		New vertebral fractures. Lumbar spine, and femoral neck bone mineral density.	(secondary) non-vertebral fractures

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Samples from GGHW were analyzed for raloxifene and total raloxifene hydrolyzed in plasma (TRHP) using a validated LC/APCI/MS/MS method at Lilly laboratory for Bioanlytical Resarch (Scarborough, Canada). There was no mention of where or how the samples from GGIO were analyzed.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The majority of the sponsor's exposure-response analysis focused on markers for osteoporosis and were not analyzed for the purpose of this NDA submission.

No formal PK/PD analysis was conducted by the sponsor with the data from study GGIO for time to event of breast cancer or the reduction of the risk of breast cancer endpoints. Only six subjects with PK sampling had a time-to-event code for breast cancer therefore no concentration/response analysis could be performed.

For our data investigation, the treatment/response (time to breast cancer event) showed a favorable outcome for raloxifene treatment with a mean time to event of 1284 months compared to the mean 1057 months for placebo (see Figure 1). Figure 1 does not include all patients who were enrolled in GGIO, it only includes patients who had a time to breast cancer event (52 for raloxifene and 76 for placebo), therefore the statistical significance of raloxifene prolonging

breast cancer events by 227 days was not evaluated for our analysis or by the sponsor.

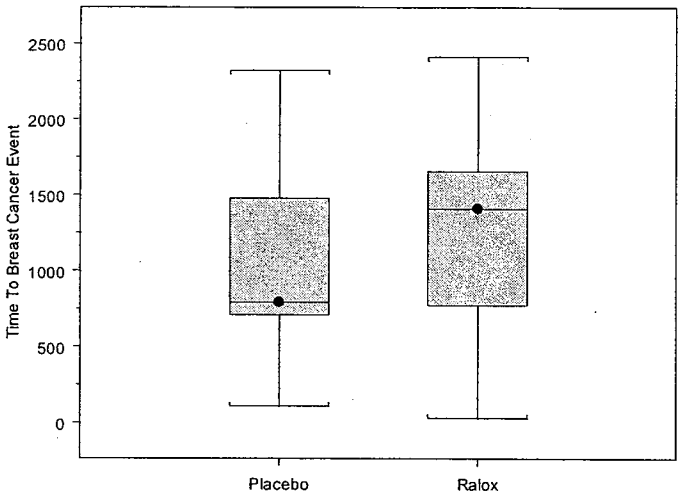


FIGURE 1: Time to Event (breast cancer event) versus treatment group in Study GGIO for patients who had a time to event code for breast cancer.

The exposure-response for study GGHW indicated that there was no significant correlation between change in Ki67 and steady-state raloxifene concentration (see Figure 2). Since Evista had no effect on the proliferation-marker Ki67 no further PK/PD relationship was explored.

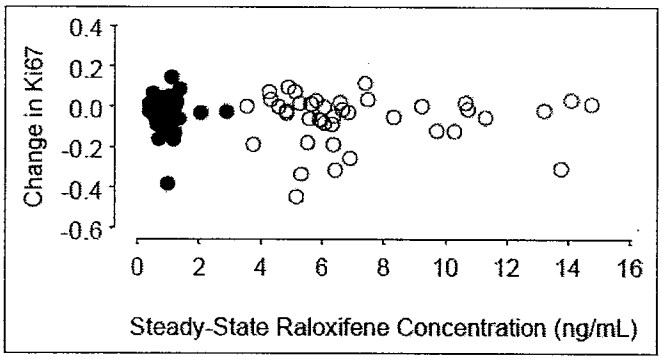


FIGURE 2: Change in Ki67 versus predicted raloxifene steady-state concentration in study GGHW

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The common safety observations from the studies were venous thromboembolic events (DVT, PE and other VTE's), hot flashes, leg cramps and peripheral edema all of which are reflected in the current US label for Evista®. As with past reviews of this data, there was no effect of raloxifene concentration on the occurrence of these adverse events within the studied exposure range, therefore no further analysis was performed for these AE's.

In study GGIO, there was a statistically significant increase in the incidence of death due to stroke in the raloxifene arm compared with the placebo arm. This increase had not been seen in

prior studies. There were insufficient concentration data from this study to analyze a concentration vs. effect relationship.

2.2.4.3 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose proposed for the indication is 60 mg QD, which is also the currently approved dose for Evista's osteoporosis labeled indication.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

Please seen the original and supplemental reviews for the osteoporosis NDA 20-815.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Intrinsic factors such as age and weight were evaluated from the GGIO dataset (total enrollment > 10,000 subjects). The steady state levels from the two visits were averaged for each patient and plotted against age, weight and race. The steady state values from study GGIO (1.3 ng/mL) were similar to trough concentrations from previous studies (1.1 ng/mL from GGGK).

There were no statistically significant contributions of age (range 55-83 years) or race identified from the 250 subjects who had sparse sampling performed during the trial (see Figures 3 and 4). However, due to the small number of patients (n = 1-3) in the Asian, Hispanic and 'Other' groups, these results should be interpreted with caution.

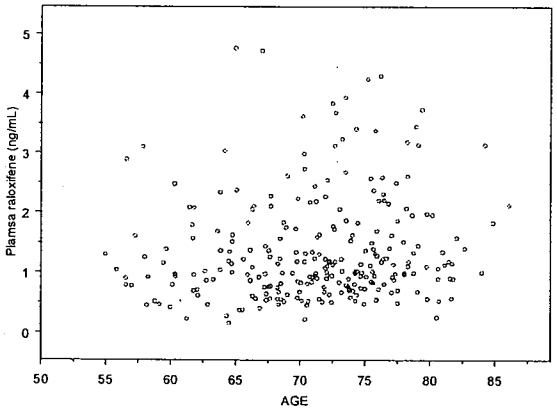


FIGURE 3: Raloxifene steady state concentration from study GGIO vs. Age

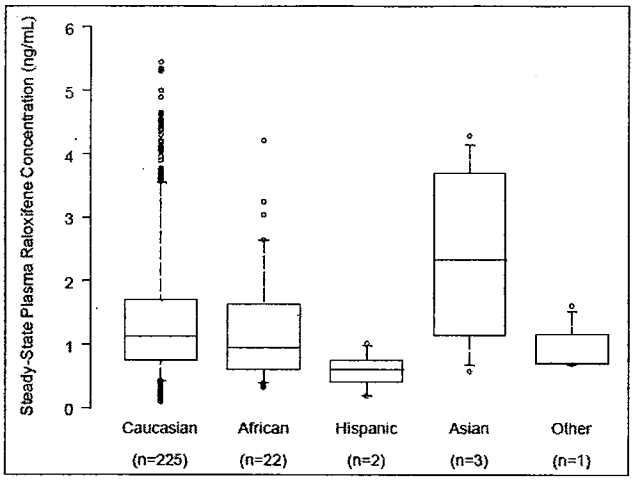


FIGURE 4: Raloxifene steady state concentration from study GGIO vs. Ethnic Origin (sponsor's graph).

There was a trend for decreasing raloxifene concentration with increasing body weight (Figure 4). However the inclusion of weight as a covariate in past population PK models (GGGK) did not improve the goodness-of-fit.

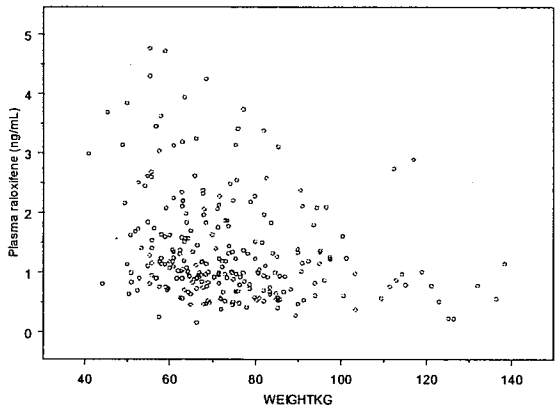


FIGURE 5: Raloxifene steady state concentration from study GGIO vs. Weight

These results from the intrinsic factor analysis for age, race and weight are consistent with results from previous osteoporosis NDA reviews.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The sponsor did not provide any specific studies or analyses to evaluating the effects of diet, smoking, or alcohol use on the PK of raloxifene. Data from GGIO was explored to look for trends with smoking status and alcohol use. Like previous findings from past analyses there were

no statistically significant contributions smoking status or alcohol use identified from the 250 subjects who had sparse sampling performed during the trial (see Figure 6 and 7).

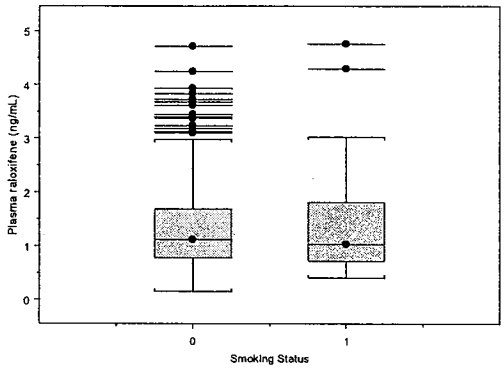


FIGURE 6: Raloxifene steady state concentration from study GGIO (n = 250) vs. Smoking status (0 = No; 1 = Yes)

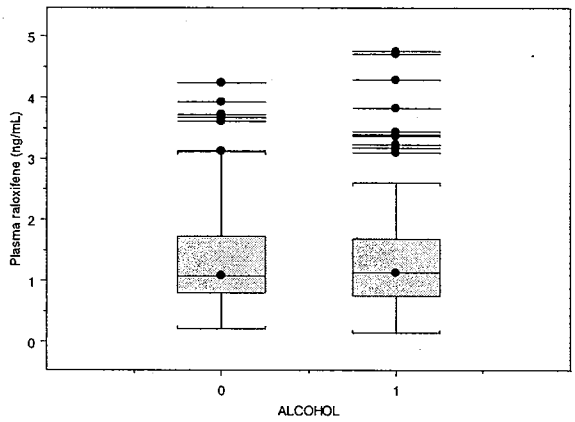


FIGURE 7: Raloxifene steady state concentration from study GGIO (n = 250) vs. Alcohol use (0 = No; 1 = Yes)

2.4.2 Drug-drug interactions

Please see the past clinical pharmacology reviews of NDA 20-815 and the approved label for Evista®.

2.5 GENERAL BIOPHARMACEUTICS

Please see the past clinical pharmacology reviews of NDA 20-815.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Samples from GGHW were analyzed for raloxifene and total raloxifene hydrolyzed in plasma (TRHP) using a validated LC/APCI/MS/MS method at Lilly laboratory for Bioanalytical

Research (Scarborough, Canada). This was the same method that was previously used and validated for the osteoporosis NDA.

There was no mention of where or how the samples from GGIO were analyzed.

Please see the relevant individual study reviews (Appendix 4.1) for details on the analytical methods.

3 DETAILED LABELING RECOMMENDATIONS

No changes in clinical pharmacology sections were made by the sponsor therefore no labeling recommendations are needed.

4 APPENDICES

4.1 INDIVIDUAL STUDY REVIEWS

4.1.1 GGGK

GGGK (MORE) was a randomized, double-blind, placebo-controlled, multinational study conducted in postmenopausal women with osteoporosis. The primary objectives of GGGK were to assess the effects of raloxifene treatment, compared with placebo, on the incidences various osteoporosis markers, and safety. Assessment of the effect of raloxifene on incidence of all breast cancer was a secondary safety endpoint. Steady-state concentrations were evaluated in patients over 36 months of raloxifene treatment. This trial was submitted to NDA 20-815 SE1 for the indication of treatment of osteoporosis in post menopausal women (March 30, 1999). The population pharmacokinetics from this trial were reviewed by Dr. Ronald Kavanagh.

The overall conclusion regarding the population PK was that there was no relationship between serious treatment emergent AEs and concentrations. In addition there was insufficient data (insufficient sample size, variability, inappropriate grouping of concomitant medications) to justify possible effects of concomitant medications on raloxifene.

4.1.2 GGJY

GGJY (CORE) was a double-blind, placebo-controlled, multinational study that enrolled postmenopausal women with osteoporosis who had been randomized in GGGK for an additional 4 years of follow-up. Subjects who were enrolled in GGGK on raloxifene 60 mg or 120 mg received 60 mg in GGJY and subjects on placebo continued to receive placebo. The primary objective of GGJY was to compare the long-term effect of raloxifene 60 mg/day versus placebo on the reduction in incidence of invasive breast cancer in postmenopausal women with osteoporosis. The secondary objectives were to assess the long-term effect of raloxifene 60 mg/day on the incidence of invasive, ER-positive breast cancer and non-vertebral fractures in postmenopausal women with osteoporosis. There were no pharmacokinetic samples taken during this extension study.

4.1.3 GGIO

Title: Raloxifene Hydrochloride or Placebo in Postmenopausal Women at Risk for Major Coronary Events

Objectives: The two primary objectives of GGIO were to assess whether in postmenopausal women at risk for major coronary events, chronic oral treatment with raloxifene HCl 60 mg/day,

compared with placebo, reduces the incidence of:

- The combined endpoint of coronary death, nonfatal (including silent) MI, or hospitalized ACS other than MI (coronary primary endpoint)
- Invasive breast cancer (breast cancer primary endpoint),

Design: Approximately 10,000 patients were to be enrolled and randomly assigned to one of two therapy groups: raloxifene HCl 60 mg/day or placebo for 5 years of which 4060 patient completed in the raloxifene group and 3979 completed in placebo. Efficacy was evaluated based on adjudication of endpoint events (coronary death, nonfatal MI, hospitalized ACS other than MI, invasive breast cancer, fractures, all breast cancers, all deaths, all hospitalizations, VTEs, strokes, revascularizations and amputations). Supporting clinical documentation, mammograms, or electrocardiograms were reviewed during the adjudication processes. Biochemical markers of CV risk, ie, lipid parameters and fibrinogen, were also collected. Safety was evaluated through the reporting and collection of adverse event (AE) data, vital signs, physical findings, and routine laboratory testing.

Pharmacokinetics: The raloxifene concentration evaluation included data from 253 patients. Two blood samples were collected from patients at Visits 5 and 7 following 12 and 24 months of 60 mg raloxifene HCl once daily, respectively. Samples were collected at least 1 hour apart during each visit. The pharmacokinetics of raloxifene in plasma were assessed for the 2-year data following the conclusion of the study. Graphical visualization and descriptive statistical analyses of the LY139481 concentration data using S-PLUS were the primary techniques of data evaluation.

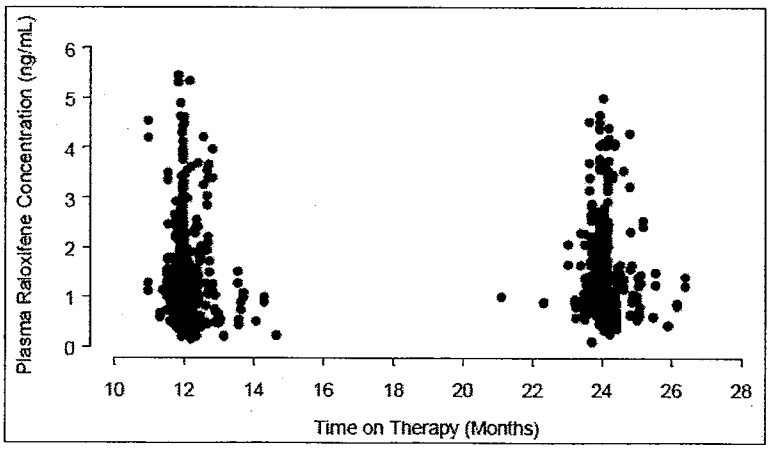
Pharmacokinetic Results: The overall mean steady state raloxifene plasma concentration in this patient population was 1.38 ng/mL (coefficient of variation percentage [CV%], 69.3%), which is similar to the mean concentration of 1.09 ng/mL (CV%, 56.4%) in postmenopausal women with osteoporosis in H3S-MC-GGGK (sponsors table 2.7.2.4).

Table 2.7.2.4. Mean Observed Steady-State Raloxifene Concentrations Following 60mg Daily Dose in GGIO

	12 Months	24 Months	Overall
Mean (ng/mL)	1.34	1.43	1.38
CV%	71.6	66.7	69.3
n [a]	483	400	883

Abbreviation: CV = coefficient of variation percentage.
[a] Number of quantifiable plasma concentrations obtained from patients for whom time of dose and time of sample draw were available.

In addition, there were no apparent changes in concentrations from month 12 to month 24 (see sponsor's graph below).



4.1.4 GGHW

Title: A Randomized Phase 3 Study of Raloxifene in Patients with Primary Breast Cancer

Objectives: The primary objective was to determine the short-term biologic effect of raloxifene treatment on an intermediate endpoint marker, Ki67, which is a proliferation-associated nuclear antigen, in postmenopausal women with newly diagnosed primary breast cancer, prior to surgical resection. The secondary objectives were to

1) determine the effect of raloxifene on estrogen receptor and progesterone receptor levels and on apoptosis;
2) determine raloxifene and total raloxifene in hydrolyzed plasma (TRHP) concentrations after administration of doses of 60 mg QD or 300 mg BID;
3) evaluate Ki67 and apoptosis in normal breast tissue (in patients undergoing mastectomy);
4) characterize the safety of raloxifene.

Design: This was a parallel, placebo-controlled, randomized, double-blind Phase 3 study. A total of 167 post menopausal women with newly diagnosed primary breast cancer who were scheduled for surgical resection of their primary tumor were enrolled. Fifty-three were randomly assigned to placebo, 58 to raloxifene 60 mg QD, and 56 to raloxifene 300 mg BID. Study drug was administered for 14 ± 1 days.

Pharmacokinetics/Pharmacodynamics: The population PK evaluation included data from 95 postmenopausal women. Single 10-mL blood samples were obtained on Day 10 and Day 14 for pharmacokinetic analyses. Ki67, a proliferation associated nuclear antigen, was measured at baseline and after 14 days of treatment. Apoptosis, estrogen receptor, and progesterone receptor measures also were taken at baseline and endpoint.

PK/PD model development: A total of 98 patients contributed 181 observations with valid raloxifene plasma concentrations. Nine observations were excluded due to inadequate dosing information thus only 165 observations from 95 patients were included in the dataset. Estimates of the pharmacokinetic parameters and error terms were obtained by fitting the concentration-time data by means of the nonlinear mixed-effects modeling program, NONMEM with PREDPP. The subroutine ADVAN2 was used in the evaluation of a one-compartment oral model. The covariates considered in the PK analysis are below in Sponsor's table GGHW.3.1.

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

Dose	Hematocrit
Age	Hemoglobin
Geographical Location (Country)	Leukocyte Count
Height	Platelets
Weight	Aspartate Transaminase
Body Mass Index	Alanine Transaminase
Calculated Lean Body Mass	Alkaline Phosphatase
Alcohol Use (designated as > 3 drinks per week)	Gamma Glutamyl Transferase
Creatinine Clearance (estimated by Cockcroft-Gault formula using age and either weight or calculated lean body mass)	Serum Creatinine
Smoking Status (identified as current smoker and number of years patient has smoked)	Calcium
Years Postmenopausal	Phosphorus
Systolic Blood Pressure	Total Protein
Diastolic Blood Pressure	Albumin
Pulse	Total Bilirubin

Previous PK analysis of clinical pharmacology studies from healthy women and women with osteoporosis show that a one-compartment model was preferable to a two-compartment model for describing the time course of raloxifene concentrations. The absolute bioavailability (Fabs) was fixed to 0.0199, which was determined previously in the absolute bioavailability study. Since a limited number of plasma samples were obtained during the early portion of the 24-hour dosing interval, the rate constant for appearance of raloxifene (Ka) could not be estimated; the value was fixed to 0.561 hr-1, which was determined from previous population pharmacokinetic analyses of clinical pharmacology studies. Based on these previous studies, a one-compartment model with first-order appearance (Ka) and first-order elimination was selected to describe the pharmacokinetics of raloxifene following oral administration for Study GGHW. This structural model was parameterized in terms of total CL and V. The effect of raloxifene steady-state concentrations on observed change in Ki67 was first evaluated graphically by the sponsor and since no significant correlation between concentrations and change in Ki67 was observed, no further pharmacokinetic/pharmacodynamic model was developed.

Assay Results: Raloxifene concentrations in plasma were determined using a validated liquid chromatographic/atmospheric pressure chemical ionization/tandem mass spectrometry (LC/APCI/MS/MS) method at Lilly Laboratory for Bioanalytical Research (Scarborough, Canada). The standard curve was linear and ranged from 0.050 ng/mL to approximately 5.000 ng/mL. Concentrations less than 0.050 ng/mL were reported as below quantitation limit (BQL) or <0.050 ng/mL. During the validation, both the intraday and interday coefficient of variation (relative standard deviation) and the absolute relative error were ≤10.0%. For all assay batches the expression of precision (CV%) was ≤15% and the absolute percent relative error was ≤5.1%.

The concentrations of total raloxifene in hydrolyzed plasma (TRHP) were determined using a validated LC/APCI/MS/MS method at Lilly Laboratory for Bioanalytical Research (Scarborough, Canada). Concentrations are expressed as the free base of raloxifene and represent the sum of raloxifene and its glucuronide conjugates. Two standard curves were used and each was linear within its range. The lower curve ranged from approximately 0.50 ng/mL to approximately 100 ng/mL and the higher curve ranged from approximately 10 ng/mL to approximately 1000 ng/mL. Concentrations less than 0.50 ng/mL were reported as BQL or <0.50 ng/mL. During the validation, both the intraday and interday coefficient of variation (relative standard deviation) and

the absolute relative error were ≤11.2%. The CV% for all assay batches for both ranges was ≤10.7% and the absolute percent relative error was ≤11.6%.

Efficacy Results: Reductions in Ki67 and estrogen receptor (ER) levels were seen for each raloxifene dose studied. A marginal statistical trend (p=0.07) for a reduction in the endpoint-over-baseline ratio in Ki67 levels for the raloxifene HCl 60 mg/day dose (Sponsor's Table 1).

Table 1. Primary Analysis Results for Ki 67 All Randomly Assigned Evaluable Patients

Comparison (sample size)	Statistics [Sqrt(n/2)*log(X_{n1}/X_{n2})]	Reduction from Placebo [(1-X_{n1}/X_{n2})*100]	p-value
RLX060/Placebo (n1=50/n2=44)	-1.811	31.2%	0.070
RLX600/placebo (n1=49/n2=44)	-1.284	23.4%	0.199

Abbreviations: RLX060 = raloxifene HCl 60 mg/day; RLX600 = raloxifene HCl 600 mg/day, n1, n2 = number of patients with non-missing paired data; X_{n1}, X_{n2} = the mean ratio of endpoint over baseline; n = the average of n1 and n2.

In addition, the median percentage change in Ki 67, which showed a statistically significant decrease for both raloxifene doses (Sponsor's Table 2). There was no statistically significant effect of raloxifene on apoptosis or on progesterone receptor (PR) levels.

Table 2. Change and Percentage Change from Baseline to Endpoint for Ki 67 and ER All Randomly Assigned Evaluable Patients

Tests (unit)	Treatment	n	Baseline (median)	Median Change (p-value[a])	Median % Change (p-value[a])	p-value[b]
Ki67	Placebo	44	15.75	0.55 (0.658)	5.07 (0.605)	0.053[c]
	RLX060	50	14.40	-2.60 (0.005)	-15.37 (0.002)	0.025[d]
	RLX600	49	16.00	-3.00 (0.001)	-14.84 (0.019)	0.049[d]
ER	Placebo	44	195.50	-9.00 (<0.001)	-10.44 (0.001)	0.006[c]
	RLX060	50	195.50	-39.00 (<0.001)	-22.52 (<0.001)	0.009[d]
	RLX600	49	199.00	-49.00 (<0.001)	-27.99 (<0.001)	0.003[d]

[a] Within-group p-value based on the Wilcoxon signed-rank procedure. [b] Between-group p-value based on ANOVA for the percentage change. [c] Overall p-value. [d] p-value for the pairwise comparison between raloxifene group (either dose) and placebo.

Note: One patient in the RLX060 group and two patients in RLX600 group had no measurements of ER at baseline and thus were excluded from the percentage change analysis for ER.

Abbreviations: ANOVA = analysis of variance; n = number of patients with non-missing paired data; RLX060 = raloxifene HCl 60 mg/day; RLX600 = raloxifene HCl 600 mg/day.

Safety Results: The safety data from this study are consistent with the safety profile demonstrated for raloxifene in previous studies. Raloxifene was no different from placebo in the reporting of treatment-emergent adverse events, serious adverse events, or early discontinuations due to an adverse event. There were no clinically relevant changes in vital signs or in safety laboratory values.

Pharmacokinetic Results: The overall mean steady-state raloxifene plasma concentrations were 0.94 ng/mL and 6.81 ng/mL for 60 mg QD and 300 mg BID, respectively. The overall mean steady-state TRHP concentrations were 190 ng/mL and 826 ng/mL for 60 mg QD and 300 mg BID, respectively. The variability between Day 10 and Day 14 concentrations was far higher for the 300 mg BID patients that for the 60 mg QD subjects for raloxifene, while variability was similar if not less for the 300 mg BID subjects with regards to TRHP concentrations (see sponsors Figures 5.2 and 5.3)

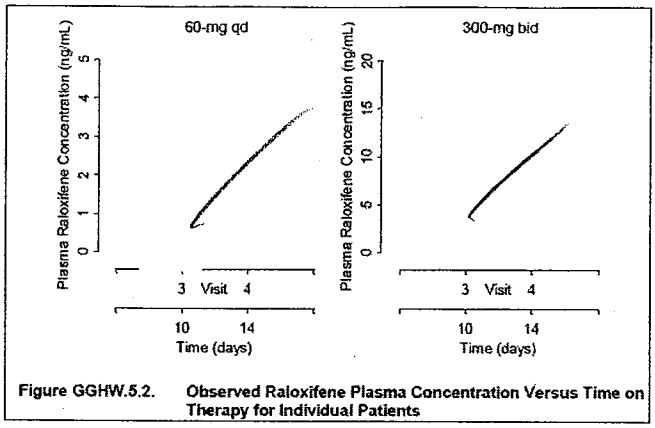


Figure GGHW.5.2. Observed Raloxifene Plasma Concentration Versus Time on Therapy for Individual Patients

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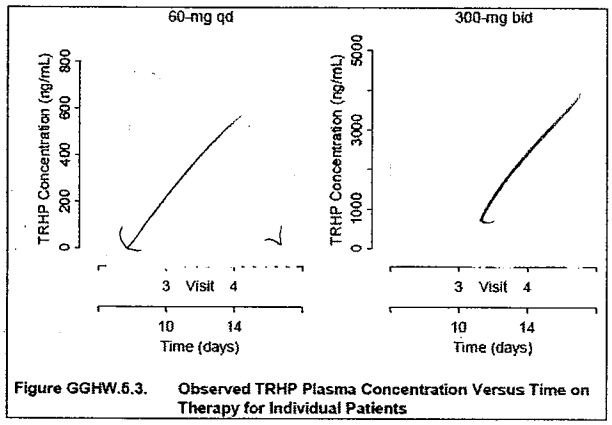


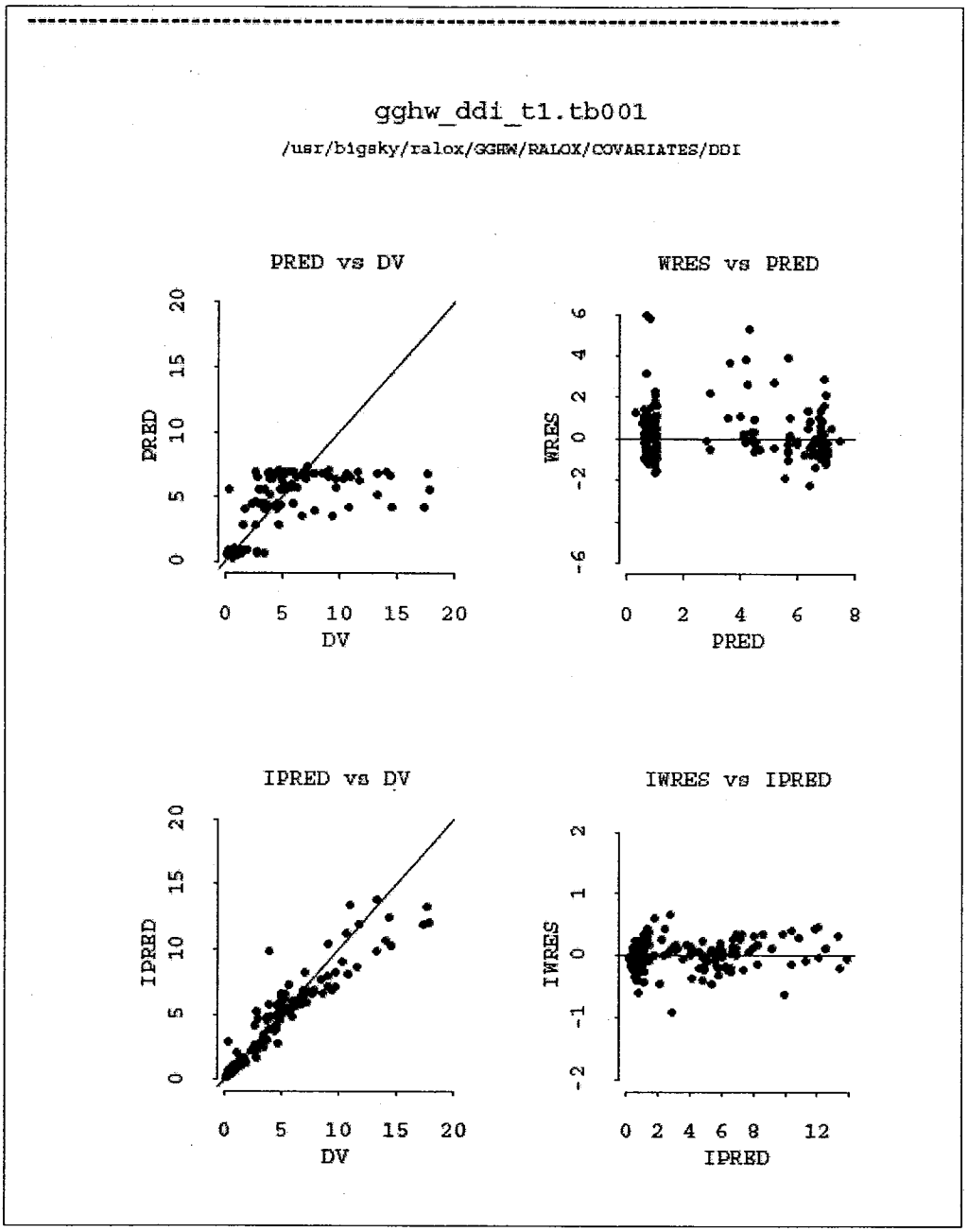
Figure GGHW.5.3. Observed TRHP Plasma Concentration Versus Time on Therapy for Individual Patients

Population PK Results: A one-compartment model parameterized in terms of CL, V, Ka, and bioavailability (F) was selected as the base structural model based on previous analyses. The final population model is below:

Final Model

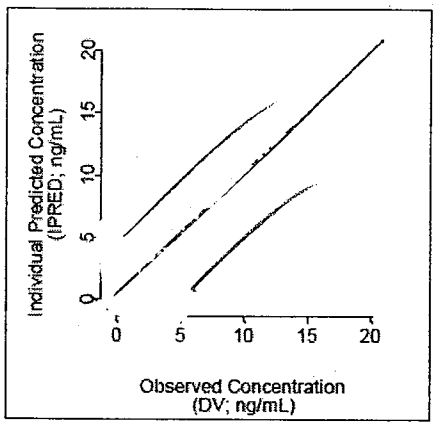
```
-------------------------------------------------------------------------------
Drug: Raloxifene     Protocol: H3S-MC-GGHW
Subject: Pop Ralox 1 Cmpt     Run: 001
Notes: Dose effect on F
-------------------------------------------------------------------------------
Kineticist:
Run on Computer: pks10.d50.lilly.com  Date: 08/09/1999  Time: 14:26:14
Output Path: /usr/bigsky/ralox/GGHW/RALOX/COVARIATES/DDI
Output File: gghw_ddi_001.op001
Input File:  gghw_ddi_001.inp
Data File:   gghw_pk_ralox_29JUN99.dat
Table(s):    gghw_ddi_t1.tb001 gghw_ddi_t2.tb001
MS Output:   gghw_ddi.ms001
-------------------------------------------------------------------------------
Subroutines: ADVAN2 TRANS2     Method: 1 INTER
686 Records     165 Observations     95 Patients
Obj Func: 179.983     # EVALS: 124     Sig. Digits: 3.4
-------------------------------------------------------------------------------

Parameter             Initial Estimate   Estimate   StdErr      %SE
---------             ----------------   --------   ------      ----
THETA #1   Ka         0.561 FIXED          0.561    Fixed         -
THETA #2   F          0.0199 FIXED        0.0199    Fixed         -
THETA #3   CL         (5,40,90)            52.7     3.70        7.02
THETA #4   V          (500,2500,5000)      2190      291       13.29
THETA #5   F_600mg    (0.1,1,3)           0.746    0.0722       9.68
OMEGA #1   E_CL       0.1                 0.170    0.0369      21.71
SIGMA #1   prop_err   0.05                0.0893   0.0150      16.80

;; Base Model:  Ka Fixed, Eta on CL.  FOCE with INTER
;;              MOF = 189.962
;; Absorption rate constant (1/hr), obtained from (GGGV,GGHK,GGHN,GGHO)
;; combined NONMEM analyses.  Fabs= 0.0199 from GGHH.

$PK
   I1 = 0
   IF(DDI.GE.60) I1=1
   TVKA  = THETA(1)
   KA    = TVKA                          ; Ka (1/hr)
   TVF1B = THETA(2)
   TVF1C = TVF1B*(1-I1)+TVF1B*THETA(5)*I1
   F1A   = TVF1C
   TVCL  = THETA(3)
   CL    = TVCL * EXP(ETA(1))            ; CL (L/hr)
   TVV   = THETA(4)
   V     = TVV                           ; V (L)
   F1    = F1A
   S2    = V

$ERROR
  DEL   = 0
  IF (F.EQ.0) DEL=0.000025;
  IPRED = F
  W     = IPRED+DEL
  IRES  = DV-IPRED
  IWRES = IRES/W
  Y     = W*EXP(ERR (1))

 MINIMIZATION SUCCESSFUL

CPU  Time: 0:00:42
Real Time: 0:00:41
-------------------------------------------------------------------------------
Report prepared Sun Aug  8 14:26:57 1999 on pks10
```

b(4)



Dose had a significant influence on bioavailability with the BA of the 300-mg dose 74.6% of that for the 60-mg dose. No patient factors or laboratory measurements were found to influence the pharmacokinetics of raloxifene. The variability for the final model was high with a between-patient variability in CL of 41.2% (21.7 %SEE) and a residual error of 29.9% (16.8 %SEE).

The goodness-of-fit for the population model is show graphically by the agreement between individual predicted value and observed concentrations



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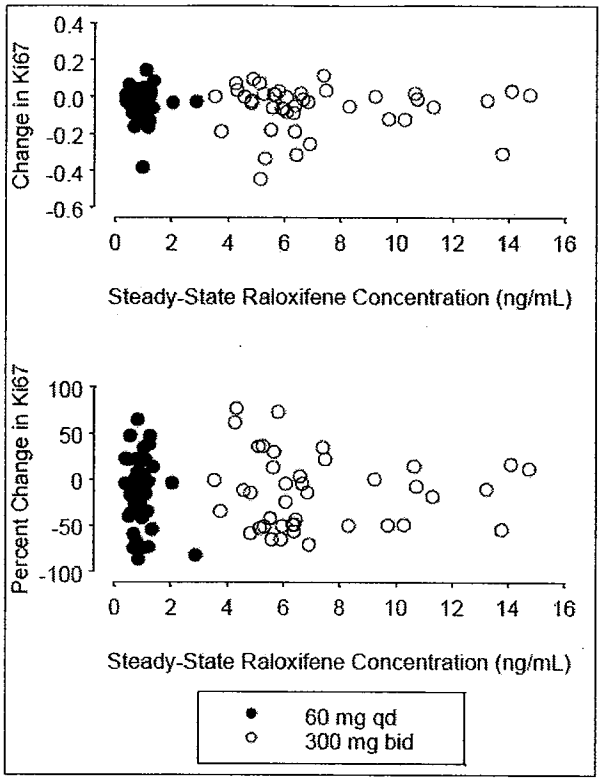
The final raloxifene model was used to calculate a 24-hour Css for each patient based on that individual's CL value. These Css values represent estimates of systemic exposure to raloxifene in individual patients. The range of Css values that represents approximately 95% of all patients in the GGHW study population are provided in the Sponsor's Table GGHW.5.5. These results are similar to those found in previous population PK analysis in women with osteoporosis.

Table GGHW.5.5. Average Raloxifene Concentration at Steady State

$C_{ss,B}$	60 mg qd	300 mg bid
Median value ng/mL	0.87	6.04
Range ng/mL	0.40 – 2.89	3.55 – 14.75

Pharmacodynamic Results:

The relationship of steady-state average concentration and observed change in Ki67 was evaluated graphically. Individual observed change in Ki67 data was plotted versus 24-hour Css, which represented best estimates of systemic exposure to raloxifene in individual patients based on individual's CL value calculated from the final raloxifene pharmacokinetic model. There are no discernible correlations between the change of Ki67 and raloxifene concentrations.



Conclusions: Higher steady-state raloxifene concentrations were achieved following 300-mg bid dosing regimen. The steady-state concentrations ranged from 0.40 to 2.89 ng/mL for the 60-mg dose, and 3.55 to 14.75 ng/mL for 300 mg bid dose. Pharmacokinetics of raloxifene are similar in breast cancer patients and postmenopausal women in osteoporosis prevention and treatment trials. There is no observed correlation between raloxifene concentrations and reduction of Ki67.

4.1.5 GGGF, GGGG, GGGH

These studies were originally submitted and reviewed with the osteoporosis NDA 20-815 (original submission, June 8, 1997. Reviewed by Carolyn D. Jones). No new data was submitted.

4.1.6 NSABP P-2 study

P-2 was a randomized, double-blind, active-controlled, North American study conducted by the National Surgical Adjuvant Breast and Bowl Project under the auspices of the National Cancer Institute. Postmenopausal women were randomized to receive tamoxifen 20 mg/day or raloxifene 60 mg/day for 5 years. The primary objective was to compare the ability of raloxifene to reduce incidence rate of invasive breast cancer compared to tamoxifen. No pharmacokinetic data was collected.

4.2 PAST CLINICAL PHARMACOLOGY REVIEWS CITED

4.2.1 Original NDA 20-815

Submitted on June 8, 1997 for the prevention of osteoporosis in PMW. Reviewed by Dr. Carolyn Jones. Includes information on the general clinical pharmacology, the population PK model development along with the analysis of the GGGF, GGGG and GGGH data.

4.2.2 sNDA 20-815, SE1-003

Submitted on March 30, 1999 for the treatment of osteoporosis in PMW. Reviewed by Dr. Ron Kavanagh. Includes information on the population PK model development along with the analysis of study GGGK.

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/s/

Julie Bullock
9/5/2007 03:01:23 PM
BIOPHARMACEUTICS

Brian Booth
9/5/2007 07:14:48 PM
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