

Diagnosis	Clinical Diagnoses for Patients with Endometrial Bleeding			p-value
	Plc (n=1999)	Rlx 60 mg (n=1948)	Rlx 120 mg (n=2010)	
Atrophy	26	35	24	0.2
Polyp	3	13	9	0.04
Myoma	2	3	1	0.5
Proliferative	3	0	3	0.3
Hyperplasia	1	2	0	—
Adenocarcinoma	1	2	1	—
Normal	2	0	0	—
SEETUS	0	1	2	—
Adenofibroma	1	2	1	—
Endometrial Fluid	1	0	2	—
Mucocele	0	1	0	—

SEETUS=spurious elevation of endometrial thickness of undetermined significance

Atrophy was the most common diagnoses for all groups. Polyp was reported by significantly more raloxifene-treated women than placebo-treated women (see consult from HFD-580).

Endometrial Thickness: A total of 1781 randomly assigned patients without a prior hysterectomy had both a scheduled baseline and at least one postbaseline endometrial thickness measurement. This total represents about 30% of all randomly assigned patients without prior hysterectomy at study entry.

The mean baseline endometrial measurements were comparable for the three groups: 2.97 mm. The mean changes from baseline to Endpoint were -0.27 mm, 0.06 mm, and -0.03 mm for the placebo and Rlx 60 mg and 120 mg groups, respectively. The difference between placebo and Rlx 60 mg was significant at $p < 0.05$. In a frequency distribution analysis, 31% of placebo patients compared with 36% of Rlx 60 mg subjects had increases in endometrial thickness in the range of 0 to 3 mm from baseline to endpoint. In addition, whereas only 3 placebo subjects (0.5%) had an increase in endometrial thickness of 6 to 9 mm, 8 (1.5%) of the Rlx 60 mg subjects had an increase in thickness of this magnitude.

There were 253 patients with a postbaseline endometrial thickness of > 5.0 mm; of these subjects 203 (58 placebo, 75 Rlx 60 mg, and 70 Rlx 120 mg) were investigated according to the uterine evaluation algorithm shown above. The most common clinical diagnosis for these women was atrophy followed by "spurious evaluation of endometrial thickness of undetermined significance." The percentages of patients in each group with the two aforementioned diagnoses were not significantly different. Polyp was the third most common diagnosis: 13 in placebo patients, 20 in Rlx 60 mg patients, and 15 in Rlx 120 mg patients ($p=0.4$). There were two cases of hyperplasia in the placebo and Rlx 60 mg groups and one case of adenocarcinoma in the placebo group.

Uterine-Related Serious Adverse Events: The following table provides the numbers and percentages of patients in each group reporting serious uterine-related adverse events.

Adverse Event	Incidence of Uterine-Related Serious Adverse Events			p-value
	Plc (n=1999)	Rlx 60 mg (n=1948)	Rlx 120 mg (n=2010)	
Any AE	19 (1.0%)	12 (0.6%)	11 (0.5%)	0.3
Uterine Atony ^a	11 (0.6%)	3 (0.2%)	5 (0.2%)	0.07
Carcinoma	4 (0.2%)	4 (0.2%)	1 (0.0%)	0.4
Uterine Disorder ^b	1 (0.1%)	1 (0.1%)	2 (0.1%)	—
Vag Hemorrhage	1 (0.1%)	2 (0.1%)	1 (0.0%)	—
Endometrial Disorder ^c	0 (0.0%)	2 (0.1%)	1 (0.0%)	—
Neoplasm: Endometrial	1 (0.1%)	2 (0.1%)	0 (0.0%)	—

Incidence of Uterine-Related Serious Adverse Events				
or Uterine Polyp				
Uterine Hemorrhage	1	1	1	—
Ruptured Uterus	1	1	0	—
Uterine Fibroids ^e	0	0	1	—
Enlarged ^d				—
Uterine Neoplasm	0	1	0	—

^a actual term most frequently referred to uterine or uterovaginal prolapse,

^b actual term most frequently referred to a report of intrauterine fluid, mild adenomyosis, and uterine abnormalities noted on TVU,

^c actual term referred to thickened endometrium,

^d actual term referred to leiomyoma,

^e actual term referred to adenofibroma with rare mitoses

It is noteworthy that the incidence of uterine or uterovaginal prolapse (atony) was lower in the raloxifene groups compared with the placebo group.

Endometrial Carcinoma: A total of nine cases of carcinoma have been reported: 4 in placebo patients, 4 in Rlx 60 mg patients, and 1 in Rlx 120 mg patients. The relative risk for endometrial cancer in the Rlx 60 mg group compared with the placebo group is 1.03 (0.26, 4.16). Five cases were brought to attention because of vaginal bleeding, three cases because of abnormal transvaginal ultrasound, and one case because of an abnormal Pap smear.

Endometrial Fluid: From the numbers reported it appears that raloxifene increases the risk for the development of fluid in the endometrial cavity. Approximately 6% of placebo women, 8% of Rlx 60 mg women, and 9% of Rlx 120 mg women ($p=0.06$) developed fluid in the endometrial cavity. The significance of this fluid accumulation is not clear.

Ovary

There were no significant differences among the three groups for the percentage of patients reporting treatment-emergent ovarian-related adverse events. Ovarian disorder was reported by 1.5% of placebo patients, 1.2% of Rlx 60 mg patients, and 1.2% of Rlx 120 mg subjects ($p=0.06$). Regarding ovarian cysts, 1.4% of placebo patients, 0.9% of Rlx 60 mg and 0.8% of Rlx 120 mg subjects were reported to have had this finding. Ovarian carcinoma was reported by four placebo, one Rlx 60 mg, and one Rlx 120 mg patients ($p=0.4$).

Breast (see consult from the Division of Oncology Drug Products)

Breast neoplasm was reported as a treatment-emergent adverse event by 81 (3.1%) patients in the placebo group, 56 (2.2%) patients in the Rlx 60-mg group, and 54 (2.1%) patients in the Rlx 120-mg group. This treatment-emergent adverse event was most frequently reported with the actual terms "breast neoplasm female" or "breast neoplasm benign female." The COSTART term breast neoplasm was used for various breast signs, symptoms and imaging findings that did not necessarily indicate a neoplastic process. Both raloxifene groups reported breast neoplasm less frequently compared with placebo ($p=0.034$ for Rlx 60-mg group and $p=0.019$ for Rlx 120-mg group). Twenty-three of the patients reported both a treatment-emergent adverse event of breast neoplasm and breast carcinoma (15 patients in the placebo group, 5 patients in the Rlx 60-mg group, and 3 patients in the Rlx 120-mg group).

These data are considered preliminary at this time due to the lack of adjudication for the cases diagnosed after approximately October 1998.

Venous Thromboembolism

Venous thromboembolism (VTE) is the most serious adverse event known to be drug induced. The data submitted in the original raloxifene NDA (prevention of PMO) showed a clear increase in the risk for VTE – retinal vein thrombosis, deep vein thrombosis, and pulmonary embolism – in women taking raloxifene.

The numbers from study GGGK reflect this increased risk. For all VTE events, the relative risk was 2.4 (1.2, 4.5) for Rlx 60 mg vs. placebo. For PE (+ DVT) the relative risk was 3.4 (1.0, 11.3) for Rlx 60 mg vs. placebo. Similar values were observed for comparisons between Rlx 120 mg vs. placebo.

As noted in the original raloxifene NDA submission, the risk for VTE is highest during the initial months of treatment, with a gradual decrease in risk over time.

Case-Cohort Analysis of Baseline Factors for Venous Thromboembolism: A case-cohort analysis was conducted to identify baseline factors, other than use of raloxifene, associated with increased risk for DVT/PE. The baseline factors included in this analysis were: age, weight, BMI, years postmenopausal, systolic blood pressure, diastolic blood pressure, pulse, LDL-C, HDL-C, hemoglobin A1c, apolipoprotein A1, apolipoprotein B, bone-specific alkaline phosphatase, osteocalcin, urinary type I collagen fragment to creatinine ratio, random urine creatinine, random urine calcium, serum 25-hydroxyvitamin D, serum parathyroid hormone Current alcohol use (at least three drinks per week), current tobacco smoker (yes/no), hysterectomy (yes/no), family history of osteoporosis (yes/no), family history of breast cancer (yes/no), prior HRT use (yes/no), prior thiazide diuretic use (yes/no), prior fluoride use (yes/no), prior bisphosphonate use (yes/no), prior MI (yes/no), prior percutaneous transluminal coronary angioplasty (PTCA) (yes/no), prior stroke (yes/no), and prior coronary bypass graft (yes/no).

When compared with the unaffected cohort, cases were significantly older, heavier, additional years postmenopausal had a higher mean systolic blood pressure, had greater use of thiazide diuretics, and greater prevalence of previous myocardial infarction.

Venous Thromboembolism Case-Control Study: To complement the case-cohort study, a nested case-control study was conducted from GGGK. This study was designed to identify risk factors for DVT/PE that either emerged after treatment initiation or that were not collected as part of the routine baseline assessment.

Eligible cases were defined as patients reported to have experienced a VTE (DVT, PE, cerebral venous sinus thrombosis, or retinal vein thrombosis) while enrolled in Study GGGK. For each reported case of VTE, 6 control patients were identified, without regard to treatment assignment, based on their geographic location (eg, country) and date enrolled (within approximately 30 days). Study procedures consisted of the administration of a risk factor assessment instrument (questionnaire), and laboratory analyses to determine (1) whether aPC resistance is associated with the development of VTE in this cohort and (2) whether raloxifene treatment confers a risk of VTE independently of aPC resistance. The risk factor assessment instrument includes questions related to prior VTE, varicose veins, visible swelling in legs, family history of deep vein clots, presence of inherited genetic tendencies, prior pregnancy, history of serious limb injuries, major surgeries requiring regional or general anesthesia, and history of cancer.

The first interim analysis was performed on data reported through 19 June 1998. A total of 41 cases of VTE and 249 matched controls completed the study procedures. The four cases of RVT and their matching controls were excluded from the primary analyses, leaving 37 DVT/PE cases and 225 geographically and time enrolled-matched controls.

Interim analysis of these data identified three factors not detected in the case-cohort analysis. These significant characteristics were: history of previous DVT or PE, visible swelling in the lower legs (may have actually occurred after the VTE), and history of major bone or joint surgery.

Cerebrovascular Accident

A total of 60 patients reported a treatment-emergent adverse event of cerebrovascular accident: 26 (1.0%) in the placebo group, 16 (0.6%) in the Rlx 60-mg group, and 18 (0.7%) in the Rlx 120-mg group. The difference among the three treatment groups and between the pooled raloxifene group and placebo was not statistically significant. Treatment-emergent cerebrovascular accidents were analyzed as reported by investigators and were not adjudicated.

In addition, the following treatment-emergent adverse event COSTART terms representing cerebrovascular accident events were assessed individually for potential differences among the three treatment groups: cerebral infarct and cerebrovascular disorder. In the cerebrovascular disorder category, the only relevant actual terms included in the analysis were "cerebral infarction," "cerebrovascular accident," and "stroke." There was no evidence of an overall difference among the three treatment groups or between the pooled raloxifene group and placebo in the number of patients reporting either of these cerebrovascular accident event terms. An analysis also was performed by pooling patients who reported one or more of the three terms: cerebrovascular accident, cerebral infarct, and cerebrovascular disorder. There were 30 (1.2%) patients in the placebo group, 20 (0.8%) patients in Rlx 60-mg group, and 18 (0.7%) patients in the Rlx 120-mg group in the pooled analysis. There was no evidence of an overall difference among the three treatment groups or between the pooled raloxifene group and placebo in the number of patients reporting one or more of these events.

Bone Histomorphometry

Bone biopsies were obtained at baseline and after 24-months of treatment from women in Substudy I (45) and II (20). A total of 25, 22, and 18 women were randomly selected from the placebo, Rlx 60 mg, and the Rlx 120-mg groups, respectively. The groups were well matched for baseline characteristics. The mean age was 68 years and all women were Caucasian.

Methods

Before the baseline biopsy was performed, the subjects took a total of 8 tetracycline tablets, 500 mg each, or 16 tablets, 250 mg each (days 1 and 2, then days 13 and 14). Tetracycline was to be taken on an empty stomach or with small piece of fruit or bread, but NOT with dairy products or calcium.

The biopsy was to be done on Day 17 but could have been done up to Day 24. Exact recording of dates of tetracycline administration was related as being important. The study nurse was to telephone the subject to remind the subject to take the tetracycline.

Before the second biopsy was performed (after two years of therapy) the patient was to follow a second labeling regimen. During the first labeling period (days 1 and 2) the subjects took a total of 8 demeclocycline tablets, 300 mg each, or 16 tablets, 150 mg each. During the second labeling period (days 13 and 14) the subjects took a total of 4 tetracycline tablets, 500 mg each, or 8 tablets, 250 mg each. Demeclocycline and tetracycline were to have been taken on an empty stomach or with small piece of fruit or bread, but NOT with dairy products or calcium.

The biopsy was done on the anterior iliac crest, 2 cm posterior to the anterior superior iliac spine and 2 cm inferior to the iliac crest. The biopsy was transverse. The follow-up biopsy was done on the opposite side of the body from the first biopsy.

Immediately after the biopsy sample is removed from the subject, the biopsy sample will be immersed in 4 to 10% phosphate buffered formalin. The vial of formalin will be in a container of crushed ice and should contain 50 to 100 mL cold formalin. The sample will be refrigerated (not frozen) for 24 hours. After refrigeration for 24 hours, the sample will be transferred to a solution of 70% ethanol in a plastic, sealed container so it will not break during shipping. The container should hold at least 15 mL of ethanol. The sample may be kept in the ethanol for up to 1 week before shipping. The sample in the ethanol can be sent to the laboratory at any temperature. It does not require dry ice.

Samples will be embedded in methyl methacrylate. They will be sectioned using a sledge microtome to sections of 5 to 8 m. The sections will be taken a third of the way through the core sample, and another set of sections 200 m below the first set. These sets will be stained with Goldner's stain, acid phosphates stain, and one section will be unstained.

Histomorphometric measurements of cancellous and cortical bone were performed. The section through the center of the core was measured first. If there was less than 20 mm² of cancellous bone, then another level (200 m away) was measured. Specimens were considered to be adequate for interpretation if the total measured area of the two levels of the cancellous tissue was 20 mm² or greater. Cancellous bone data were analyzed for patients from whom adequate biopsies were obtained both at baseline and at endpoint. The analyses of bone histomorphometry were completed by two investigators. One investigator reviewed 33 baseline samples, but due to patient decision only 26 endpoint samples were available for this investigator to review. Likewise, the second investigator reviewed 55 baseline samples, but due to patient decision only 39 endpoint samples were available for review. A total of 65 paired biopsies were evaluable, with 25, 22, and 18 patients in the placebo, Rx 60-mg, and Rx 120-mg treatment groups, respectively. All patients samples in these analyses met the 20-mm² area criterion.

Even when specimens were adequate for full interpretation, there were missing data for some of the histomorphometry variables. This occurred for tests which were dependent on measurement of mineral appositional rate (bone formation rates, activation frequency, and formation period) and is explained as follows: when regions of double tetracycline labeling are absent or inadequate for quantification in the biopsy specimen, it is not possible to measure the mineral appositional rate because this rate is determined by measuring the distance between the two separately administered labels and by relating this distance to the time interval between labeling periods. Absent double labels may occur as a result of sampling errors, and assigning values of zero to mineral appositional rates in these situations is inappropriate. Therefore, these

were handled as missing data. Fifty-six paired biopsies were evaluable for all indices and up to 65 paired biopsies were available for some indices.

Results

Structural Indices: There were no significant differences among the groups in the following parameters: bone area/tissue area, trabecular thickness, osteoid thickness, or wall thickness.

Surface-Based Indices: There were no significant differences among the groups in the following parameters: eroded perimeter, osteoclast number/cancellous tissue, osteoid perimeter, or osteoid surface/bone surface.

Dynamic Index: There were no significant differences among the groups in mineralization surface/bone surface.

Derived Dynamic Indices: There were no significant differences among the groups in the following parameters: bone formation rate/bone volume, bone formation rate/tissue volume, activation frequency, or mineral appositional rate. The formation period increased by 5.11 days in the Rlx 60 mg group and decreased by -5.38 days in the Rlx 120 mg group ($p=0.02$).

The sponsor reports that there was no evidence of osteomalacia, marrow fibrosis, cellular toxicity, or woven bone seen in any of the samples.

Vital Signs

Body Weight: There were statistically significant, but clinically irrelevant, increases in body weight in the two raloxifene groups compared with placebo. The mean change from baseline to Endpoint in the placebo group was -0.22 kg compared with a 0.26 kg increase in the Rlx 60 mg group ($p<0.001$) and a 0.28 kg increase in the Rlx 120 mg group ($p<0.001$). Subgroup analyses indicate that raloxifene-treated women in the lowest baseline weight tertile had the greatest placebo-subtracted weight gain: approximately 0.5 kg. Of some interest, 14% of placebo patients and 17% of Rlx 60 mg subjects gained at least 5% of baseline weight at Endpoint ($p<0.01$).

Height: The median changes in height from baseline to Endpoint were not significantly different among the groups. All treatment groups had median reductions in height of about 0.35 mm. It should be reiterated that there was no systematic use or standardization of stadiometers in this study. As a result, the height data need to be interpreted cautiously.

Systolic Blood Pressure: There were small (0.8-1.7 mmHg) changes in systolic blood pressure from baseline to Endpoint in the three treatment groups that were not statistically significant different.

Diastolic Blood Pressure: The mean diastolic blood pressures for all three groups decreased slightly from baseline to Endpoint and there were no statistically significant differences among the groups.

Heart Rate: The mean baseline heart rate in the Rlx 60 mg group was statistically significantly higher than the rate in the placebo group (72.1 vs. 72.6 bpm; $p<0.05$); although this difference is

of no clinical relevance. The mean changes from baseline to Endpoint in heart rate were, again, statistically significant, but not clinically significant.

Clinical Laboratory Tests

In the following analyses of safety laboratory tests, the various analytes have been assigned to laboratory groups. Analytes collected as numeric data included:

- **Serum Chemistry:** blood urea nitrogen (BUN), creatinine, fasting glucose, calcium, phosphorus, uric acid, creatine phosphokinase, sodium, potassium, and chloride
- **Serum Liver-Related Chemistry:** aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, total bilirubin, total protein, and albumin
- **Hematology (Red Blood Cell [RBC] and Related):** hemoglobin, hematocrit, erythrocyte count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC)
- **Hematology (White Blood Cell [WBC] and Related):** leukocyte count, segmented neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count.

Analytes reported as categorical (abnormal/normal) data included:

- **Red Blood Cell Morphology:** anisocytosis, microcytosis, macrocytosis, poikilocytosis, hypochromia, polychromia, spherocytes, target cells, elliptocytosis, schistocytosis, burr cells, and rouleaux
- **White Blood Cell:** bands, atypical lymphocytes, and probable myeloperoxidase deficiency
- **Urinalysis Chemistry:** protein, glucose, bilirubin, urobilinogen, and blood
- **Urinalysis Microscopic:** bacteria, yeast, red blood cells, white blood cells, epithelial cells, renal tubular epithelial cells, transitional epithelial cells, granular casts, or hyaline casts.

Because this study involves such a large cohort, it was possible for the sponsor to create internal population-based reference ranges. These population-based reference ranges for laboratory parameters are considered representative of this population. Using the distribution of the observed baseline laboratory data for the GGGK cohort as the reference, outliers and extreme outliers at endpoint were defined as follows:

Outliers:

Low outliers: below the 2.5 percentile of the baseline distribution

High outliers: above the 97.5 percentile of the baseline distribution

Extreme Outliers:

Low-extreme outliers: below the 0.5 percentile of the baseline distribution

High-extreme outliers: above the 99.5 percentile of the baseline distribution.

This approach seems reasonable.

Serum Chemistry

Urea Nitrogen: There was a statistically significant, but clinically irrelevant decrease in the median change from baseline to Endpoint in urea nitrogen in the Rlx 60 mg group compared with the placebo group. Using the sponsor's definition of high outlier, there were significantly fewer high outliers in the two raloxifene groups relative to the placebo group.

Serum Creatinine: There were no significant differences among groups in the median change from baseline to Endpoint for this parameter. There were statistically significantly fewer Rlx 60 mg subjects vs. placebo subjects categorized as high outliers.

Fasting Glucose: There were no significant differences among the three groups in the median change from baseline to Endpoint for this parameter. Approximately 4.0% of Rlx 60 mg subjects vs. 3.0% of placebo subjects ($p < 0.05$) met the criteria for high fasting glucose outlier. In addition, 8 (0.3%) of placebo patients, 21 (0.9%) of Rlx 60 mg patients ($p = 0.01$), and 19 (0.8%) of Rlx 120 mg patients ($p = 0.03$) met the criteria for an extremely high fasting glucose outlier.

Serum Calcium: The median changes in serum calcium from baseline to Endpoint were statistically significantly decreased in the two raloxifene groups compared with the placebo group. Additionally, whereas 1% of the placebo group met the criteria for low outlier, 3.5% and 3.8% of the Rlx 60 mg ($p < 0.001$) and 120 mg ($p < 0.001$) subjects, respectively, met this criteria. As for extremely low calcium outliers, 6 (0.2%) of placebo patients and 17 (0.7%) of Rlx 60 mg subjects ($p = 0.02$) met this criteria.

Serum Phosphorus: The median changes in serum phosphorus from baseline to Endpoint were statistically significantly decreased in the two raloxifene groups relative to the placebo group (about -0.06 mmol/L vs. -0.02 mmol/L; $p < 0.001$). Furthermore, about 5% of raloxifene-treated women compared with 2% of placebo-treated subjects ($p < 0.001$) had low outlier phosphorus values during the trial. Not unexpectedly, four times as many raloxifene-treated patients had extremely low phosphorus values compared with placebo-treated participants (16 subjects vs. 4 subjects; $p = 0.007$).

Serum Uric Acid: Uric acid levels increased in all treatment groups, although the median increase in the raloxifene-treated groups (about 10 $\mu\text{mol/L}$) was statistically significantly greater than the increase in the placebo group (6.0 $\mu\text{mol/L}$; $p < 0.001$). There were no significant differences among the groups for the percentages of patients who met the criteria for outlier or extreme outlier.

Creatinine Phosphokinase (CPK): The median change in CPK was 0.0 U/L in the placebo group and -5.0 U/L in the Rlx 60 mg group ($p < 0.001$) and -6.0 U/L in the Rlx 120 mg group ($p < 0.001$). There were slightly more patients in the Rlx 120 mg group with low outlier values than in the placebo group.

Serum Sodium: The median values for sodium changed very little in all three groups and there were no differences among the three groups in the percentages of patients with low or high outlier values.

Serum Potassium: The baseline values for potassium were slightly higher in the Rlx 60 mg compared with the placebo group. The median changes from baseline to Endpoint were also slightly greater in the two raloxifene groups vs. the placebo group; although the magnitude of the differences were not of clinical significance. The percentages of outliers were similar across groups.

Serum Chloride: The baseline levels of chloride were somewhat higher in the two raloxifene compared with the placebo group. Approximately 3.5% of raloxifene-treated subjects vs. 2.0% of placebo-treated women ($p < 0.01$) developed high outlier values during the trial. Whereas seven placebo subjects developed extremely high outlier values for chloride, 21 women in each raloxifene group developed extremely high values ($p < 0.01$).

Serum Liver-Related Chemistry

AST: The median levels of AST increased in all three groups from baseline to Endpoint and there were no differences among the groups. There were also no significant differences among the groups in the percentage of subjects who met outlier criteria. The percentages of patients who developed any postbaseline AST value $> 1.5x$, $> 2.0x$, or $> 3.0x$ the baseline value were very similar (not statistically significantly different) among the three groups.

ALT: There were very small, but statistically significant differences between the placebo and the two raloxifene groups in the median change in ALT from baseline to Endpoint. However, there were no differences among the groups in the percentages of patients who met outlier criteria. The percentages of patients who developed any postbaseline ALT value $> 1.5x$, $> 2.0x$, or $> 3.0x$ the baseline value were very similar (not statistically significantly different) among the three groups.

GGT: There were small and statistically significant decreases in the median levels of GGT from baseline to Endpoint in the two raloxifene groups compared with the placebo group. There were also 2% vs. 1% of raloxifene-treated compared with placebo-treated participants ($p < 0.01$) with low outlier values during the trial. The percentages of patients who developed any postbaseline GGT value $> 1.5x$, $> 2.0x$, or $> 3.0x$ the baseline value were very similar (not statistically significantly different) among the three groups.

Three placebo patients, 0 Rlx 60 mg subjects, and three Rlx 120 mg patients discontinued from the study because of "liver function tests abnormal."

Alkaline Phosphatase (Alk Phos): Given raloxifene's antiresorptive activity on bone, it is not surprising that the levels of Alk Phos decreased significantly in the active-drug groups. Nearly three times as many raloxifene women had low outlier values compared with placebo-treated women ($p < 0.001$). Similarly, there were three times as many active-drug treated subjects with extremely low outlier values when compared with placebo-treated women ($p < 0.001$).

Total Bilirubin: The median levels of total bilirubin changes very little in all three groups. There were statistically significantly more Rlx 120 mg-treated women (2.3%) compared with placebo-treated subjects (1.4%) with low outlier values ($p < 0.05$).

Total Protein: The median levels of total protein decreased by -1.0 g/L in the placebo group and by -2.0 g/L in the Rlx 60 mg group ($p < 0.001$) and by -3.0 g/L in the Rlx 120 mg group ($p < 0.001$). Four percent of placebo subjects and 7% and 8.0% of the Rlx 60 mg and 120 mg subjects, respectively, had low outlier values for total protein ($p < 0.001$). About 1% of the placebo patients developed an extremely low outlier value for total protein compared with about 2% of the Rlx 60-mg subjects and about 3% of the Rlx 120-mg patients ($p < 0.01$).

Albumin: There were also greater median reductions in the levels of albumin in the Rlx 60 mg and 120 mg groups (-1.0 g/L) compared with no change in the placebo group (0.0) ($p < 0.001$). Whereas 2% of the placebo subjects developed low outlier values, about 4% of the subjects in the two raloxifene groups developed low outlier values for albumin ($p < 0.001$). There were no extremely low outliers in any of the groups.

Hematology

Hemoglobin: There were small (statistically significant) decreases in the median levels of Hb in the two raloxifene groups (-0.19 mm/L-Fe) compared with the placebo group (-0.06 mm/L-Fe) ($p < 0.001$). There were no significant differences among groups in the percentages of patients with low outlier values.

Hematocrit: Like hemoglobin, there were small (statistically significant) reductions in the median levels of Hct in the two raloxifene groups (-0.01 l) compared with placebo (0.0 l) ($p < 0.001$). There were, however, no differences among the groups in the percentages of patients with low or outlier values.

Platelet Count: The median levels of platelets decreased by -10.0 GI/L in the placebo group and by -16.0 GI/L in the Rlx 60 mg group ($p < 0.001$) and by -17.0 GI/L in the Rlx 120 mg group ($p < 0.001$). There were no differences among the groups in the percentages of patients with low outlier values. None of the patients developed extremely low outlier values.

Urinalysis

Proteinuria: Significantly fewer Rlx 60 mg-treated women compared with placebo-treated women developed proteinuria (5.85 vs. 7.5%, respectively; $p = 0.02$).

Occult Blood: Significantly fewer raloxifene-treated women compared with placebo-treated subjects had occult blood in their urine (17% vs. 22%, respectively; $p < 0.001$).

It is reassuring that in no case did a patient with an extremely low outlier value for calcium, phosphorus, or total protein or an extremely high outlier value for chloride require specific intervention for the abnormality: all resolved spontaneously.

V. Sponsor's Conclusions

This 36-month analysis demonstrates that treatment with raloxifene decreases the rate of new vertebral fractures in osteoporotic postmenopausal women with and without prevalent vertebral fractures, and increases lumbar spine and femoral neck BMD significantly relative to placebo and baseline. In addition, raloxifene reduces total cholesterol and LDL-C while not affecting HDL-C

or triglyceride concentration. Raloxifene has an excellent safety profile with few minor adverse events; venous thromboembolism was the only serious adverse event of clinical significance. Furthermore, there were no stimulatory effects on the breast, and treatment with raloxifene decreased the incidence of breast cancer. There were no clinically relevant effects on the endometrium, and treatment with raloxifene did not increase the incidence of endometrial cancer. There were no clinically relevant safety laboratory changes. The sponsor concludes that 36 months of raloxifene treatment is well tolerated and substantially reduces the incidence of vertebral fractures in osteoporotic women with and without prevalent vertebral fractures. This study is continuing to evaluate the long-term effects of raloxifene on vertebral and nonvertebral fracture risk and other clinical outcomes.

VI. Medical Officer's Conclusions

The 3-year data from this large study of postmenopausal women with low BMD and/or prevalent vertebral fractures indicate that treatment with 60 mg once daily of raloxifene increases LS BMD by about 2.5% and reduces the incidence of vertebral fractures by 3.6% [RR=0.66 (0.55, 0.81)] compared with calcium and vitamin D treatment. The group of women defined as osteoporotic at baseline by low BMD alone or by the presence of vertebral fractures both accrued skeletal benefit; although the reduction in absolute risk for new fractures was only 2.2% in women without prevalent fractures.

Up to two thirds of postmenopausal vertebral fractures are asymptomatic. It is therefore difficult to assess the clinical significance of the majority of these fractures. In an analysis restricted to clinically manifest vertebral fractures (i.e., back pain), 3.1% of placebo-treated women vs. 1.8% of raloxifene 60 mg-treated subjects ($p < 0.001$) sustained clinically apparent fractures. Approximately 77 women (of similar demographics to this study population) would need to be treated with 60 mg per day of raloxifene for 3 years to prevent one clinically apparent vertebral fracture.

Like estrogen, raloxifene increases the risk for venous thromboembolic events (VTE); this remains the most serious adverse event associated with raloxifene use. As of May 1, 1999, there have been 11 cases of DVT/PE in placebo-treated women and 27 in Rlx 60 mg-treated subjects [RR = 2.47 (1.26, 4.86)]. It appears that the risk for VTE decreases after one year of treatment.

Other raloxifene safety issues of particular interest include the effects of the drug on the risks of breast, endometrial, and ovarian cancers. It is safe to say that the postmenopausal use of raloxifene for an average of about 3 years does not increase the risk for ER+ invasive breast (most likely decreases the risk), endometrial, or ovarian cancer. And appropriately so, the company is committed to examining the long-term effects of raloxifene on these organ systems.

In summary, raloxifene appears to be a modestly effective agent in the treatment of postmenopausal osteoporosis. For appropriately selected postmenopausal women, this drug's benefits will outweigh its risks, at least when taken for a period of up to 3 years.

VII. 4-Month Safety Update Review

Cutoff Dates

This review will be restricted to comparisons between the placebo group and the Rlx 60mg group (the dose proposed for marketing).

In this safety update of serious adverse events the following cutoff dates were used:

Deaths – June 1, 1999

VTE – May 1, 1999

Breast Cancer – May 1, 1999

Endometrial Cancer – May 1, 1999

Ovarian Cancer – May 1, 1999

Extent of Exposure

Patients in each group have had a median duration of exposure of about 3.89 years (~8449 patient-years).

Deaths

In an analysis of all deaths reported during study or after discontinuation from the study, there were 41/2576 placebo deaths and 26/2557 Rlx 60 mg deaths [RR = 0.64 (0.39, 1.04)]. In a survival analysis, the time to death during study was significantly later for the Rlx 60 mg group compared with the placebo group (log-rank p-value = 0.03).

VTE

There have been 11 cases of DVT/PE in placebo-treated women and 27 in Rlx 60 mg-treated subjects [RR = 2.47 (1.26, 4.86)]. In a survival analysis, the time to DVT/PE was significantly different for the Rlx 60 mg group compared with the placebo group (log-rank p-value = 0.01). At this time, the greatest risk for VTE appears to be during the first 2 years of treatment.

Breast Cancer

Lilly's adjudication board has not convened since October 28, 1998; thus the following data should be considered preliminary and subject to formal review by the Division of Oncology Drug Products.

There have been 41 breast cancers in placebo-treated women and 14 in Rlx 60 mg-treated subjects [RR = 0.34 (0.19, 0.61)]. In a survival analysis, the time to diagnosis of breast cancer was significantly different for the Rlx 60-mg dose relative to placebo (log-rank p-value < 0.001).

Endometrial Cancer

There have been 6 cases of endometrial cancer in the placebo group and 5 in the Rlx 60 mg group [RR = 0.85 (0.26, 2.79)].

Ovarian Cancer

There have been 6 cases of ovarian cancer in the placebo group and 4 in the Rlx 60 mg group [RR = 0.67 (0.19, 2.36)].

Comments

The data submitted and reviewed in this 4-month safety update do not raise any serious safety concerns. If anything, these data suggest a beneficial effect of the drug (60mg per day) on several parameters of safety.

**APPEARS THIS WAY
ON ORIGINAL**

VIII. Regulatory Recommendation

This Reviewer recommends approval of the 60 mg dose of raloxifene for the treatment of postmenopausal osteoporosis.

/S/
Eric Colman, MD *9/23/99*

cc: HFD-510/Div file
HFD-510/Ecolman/Groendle

/S/
9/24/99

**APPEARS THIS WAY
ON ORIGINAL**

Review and Evaluation of Clinical Data

NDA	20815 (S-003)
Sponsor:	Eli Lilly
Drug:	Raloxifene (Evista)
Proposed Indication:	Post-Menopausal Osteoporosis
Material Submitted:	Draft Label Change/Consult
Correspondence Date:	4/28/99
Date Received / Agency:	5/13/99
Date Review Completed	9/16/99
Reviewer:	Ranjit B. Mani, M.D.

DRAFT

1. Background

This is a brief review of a sponsor-proposed change in the draft label for raloxifene (Evista®) which is currently undergoing revision in connection with the Supplemental NDA described below. This review was initiated by an e-mail request from the Division of Metabolic and Endocrine Drug Products (HFD-510) on 9/16/99.

Raloxifene (Evista®) is a drug approved in this country for the prevention of post-menopausal osteoporosis. A Supplemental NDA for the use of this drug in the treatment of post-menopausal osteoporosis was submitted on 4/28/99. Both protocols used to support the latter indication, H3S-MC-GGGK and H3S-MC-GGNN, had included tests of cognitive function in relation to their secondary objectives. Our Division had reviewed the cognitive function data from these studies in consultation; please see my earlier review completed 7/16/99 for full details.

My earlier review, completed 7/16/99, was in reference to a section of the draft labeling for raloxifene submitted by the sponsor with the Supplemental NDA which contained the following statement in regard to cognitive function and affect (in the "Precautions" section):

In my review, and in supervisory comments made by Randy Levin, MD, it was recommended that the above statement be deleted from the labeling. We believed that both studies had serious deficiencies that rendered them incapable of supporting the sponsor's conclusions as summarized in the above statements. The sponsor's conclusions appeared to be based on post-hoc analyses of secondary outcome measures (some of which were not specified in the original protocols or amendments) which were of uncertain validity and reliability in a population of cognitively healthy individuals. Please see the discussion in my review of 7/16/99 for full details.