

CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

N DA 20815
Lilly Research Laboratories
Pharmacological Class: SERM
Review Written:

Team Leader's Memo: Raloxifene for Postmenopausal Osteoporosis (PMO)

Raloxifene is a selective estrogen receptor blocker (SERM). It is like the previously approved (for treatment of breast cancer) SERM, tamoxifen, in some ways and differs in other ways. It appears that both may have protective effects reducing bone loss and the risk of breast cancer. However, the stimulatory effect of tamoxifen on uterus is not seen with raloxifene. Venous thrombosis is increased in frequency by raloxifene, but the frequency may be similar to that of estrogen. Adequate studies to compare these treatments have not been done.

Efficacy evaluation

The principal efficacy study for raloxifene in PMO is GGGK, which compares raloxifene with placebo, a double-blind, randomized comparison. The intention is to allow an indication for both treatment and prevention of osteoporosis. The efficacy demonstrated has been small. Other measures may be required to restore bone in severe cases of PMO. In patients with little bone loss, but in whom risk factors, including BMD indicate that pharmacological intervention is desirable to prevent further decline in bone strength, raloxifene would probably be adequate.

The population for study GGGK is ambulatory and postmenopausal women with low bone density. Patients with LS BMD T-score ≤ -2.5 and no prevalent vertebral fracture are admitted to Substudy I and those with one moderate or two mild vertebral fractures and low BMD to Substudy II. Patients were excluded for abnormal uterine bleeding, primary osteoporosis, hyperparathyroidism, history of deep vein thrombosis, thromboembolic disorders, cerebrovascular accident within the previous 10 years unless due to an accident, history of acute or chronic liver disease, impaired kidney function, renal lithiasis, excess alcohol consumption, or use of a number of drugs that might affect bone metabolism.

The proposed package insert does not exclude patients with these conditions. It simply says, "Evista is indicated for the treatment and prevention of osteoporosis in postmenopausal women." This statement is followed by instructions for diagnosing osteoporosis, i.e., history or radiographic documentation of osteoporotic fracture or bone densitometry. A number of risk factors for osteoporosis are provided, including bone density T-score ≤ -1 . Venous thromboembolism is discussed extensively in the Warnings section of the insert. Although the excess incidence of thrombosis is discussed, the only recommendations about limiting use of the drug are made in connection with

prolonged immobilization. [It is recommended that Evista be discontinued at least 72 hours prior to and during prolonged immobilization, and that patients move about frequently during prolonged travel.] The safety of raloxifene in women with a history of deep vein thrombosis, thromboembolic disorders, or cerebrovascular accident within 10 years is uncertain. In order to assure applicability of this data to a general population of postmenopausal women, it would be preferable either to include these women in the study, or to specify in the label that adequate studies have not been done on safety of raloxifene in those populations.

It is strange that in the placebo group, the fracture risk increased as BMD increased, and in treated patients, the fracture risk neither increased nor decreased as LS BMD increased. It is possible that the fracture risk increased in the placebo patients as the BMD increased, because the BMD was increased by collapsed vertebrae. Increased fracture risk might account for the increased fractures, which increase apparent BMD. The lack of correlation between BMD and fracture risk, however, seems to indicate that BMD is not predictive of fracture risk in PMO, when BMD is increased by raloxifene. There was still a small difference between drug and placebo with respect to fracture risk.

This study demonstrates that raloxifene is effective in patients who did and those who did not present with a spinal fracture. For this reason it is regarded as useful for treatment of patients who have established osteoporosis. However, it is important to understand the magnitude of this efficacy. I am omitting the data on 120 mg dose of raloxifene, because it is not a dose to be marketed and results are not very different.

In the overall population, there were 240 women with fractures in 2292 women, 10.5%. In the patients treated with raloxifene 60 mg/d, there were 157 of 2259 women who had fractures, 6.9%. This is a reduction of 3.6% over the 3 years of the trial. In Substudy 1 (no fracture at baseline) there were incident fractures in 68/1522 placebo-treated women, 4.5%, and 35/1490 = 2.3% of those treated with 60 mg, a 2.2% difference. In Substudy 2, there were 172/770 = 22.3% placebo women with incident fractures, and 122/769 = 15.9%, a difference of 6.4%.

Study	Placebo			Raloxifene 60 mg/d			Pbo-Rlx Differ- Ence
	Number treated	Number with Fx	% of women	Number treated	Number with Fx	% of women	
Overall	2292	240	10.5%	2259	157	6.9%	3.6%
Sub-study 1	1522	68	4.5%	1490	35	2.3%	2.2%
Sub-study 2	770	172	22.3%	769	122	15.9%	6.4%

Those who had a spinal fracture at baseline got somewhat more reduction in fractures than those without a fracture. In Substudy 2, placebo patients had 22.3 fractures per 100 women. Treatment with raloxifene reduced the number of fractures per 100 women to 15.9%, but that was still more than twice the number

of fractures prevented: 6.4 per 100 women treated for 3 years. To look at it another way, the majority of women (even those who have vertebral fractures at baseline) do not benefit from a year's treatment with raloxifene. The placebo fracture rate on average was 7.4% per year, indicating that 92.6% of patients did not need treatment to be fracture free for a year. In a prevention population, where the benefit from drug was 2.2% (4.5%-2.3%), 95.5% of the placebo patients are expected to be fracture-free over the 3 years. More specific therapy is not currently available, but the likelihood that a fracture would occur, is increased by choosing to treat patients with a significant likelihood of fracture.

Adverse events (AEs)

During the third year of the study, there was an excess of patients reporting diabetes as an AE. Treatment-emergent diabetes was reported by 11/2502 placebo subjects (0.4%) and 13/2460 = 0.5% of raloxifene 60 mg patients. Patients with pre-existent evidence of diabetes were 74 and 97. The number of these who got treatment-emergent diabetes was 3 (4.1%) and 18 (18.6%) placebo and raloxifene 60 mg subjects, respectively. All together, it was 14 (0.5%) and 31 (1.2%) who reported treatment-emergent diabetes. 0.3% of placebo and 0.9% of raloxifene 60 mg patients met the criteria for extremely high fasting glucose.

Deep thromboses were reported on 5 and 17 of the placebo and raloxifene patients respectively.

Cervical polyps were reported on 10 (0.4%) and 23 (0.9%) of the patients. No pathology is available. This is of interest, because other SERMS have tended to have pronounced effects on uteri. Uterine bleeding was worked up in 62 placebo and 68 raloxifene patients. The only diagnosis on these patients that was significantly different from placebo was for uterine polyps, 3 and 13. Endometrial carcinoma was reported in 4 and 4 cases.

Breast neoplasm was reported in 81 placebo and 56 raloxifene patients. Studies are ongoing that are expected to show a protective effect on the breast.

There is adequate evidence that fractures are reduced to warrant labeling the drug for this purpose. The drug is effective in preventing fractures, but only modestly so. Adverse events are mostly not serious, but one is - venous thrombosis. There is no discussion of who should receive raloxifene from the standpoint of risk factors for venous thrombosis. It should be pointed out that efficacy is very small in some situations, so care should be taken in electing this drug for patients who have risk factors for venous thrombosis.

Recommendations: Raloxifene should be approved.

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U.S. FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND ENDOCRINE
DRUG PRODUCTS

HFD-510

MEDICAL REVIEW

Supplemental NDA for Raloxifene Hydrochloride
Evista®

COMPANY: Lilly Research Laboratories

PHARMACOLOGICAL CATEGORY: SERM/bone antiresorptive

ROUTE OF ADMINISTRATION: Oral

PROPOSED INDICATIONS: Treatment of Postmenopausal Osteoporosis

PROPOSED DOSAGE: 60 mg once daily

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I. Clinical Background

Previously Approved Indications: 60 mg once-daily raloxifene was approved by the Agency in December 1997 for the prevention of postmenopausal osteoporosis. Raloxifene is also approved for use in over 40 foreign countries.

Post-Marketing Experience in USA: From the time period of 12/9/1997 through 12/8/1998, the sponsor received 4 spontaneous reports with a fatal outcome. The four cases as described by the sponsor are provided below.

- 1). In the first report a 57-year old female with a history of migraine headaches (>10 years), breast cancer, a family history of myocardial infarction and cardiovascular disease (father died at age 52 years), and migraines (sister and father) was hospitalized after being found unconscious. The patient was taking several concomitant medications including sumatriptan succinate, amitriptyline, and fluoxetine. The patient experienced a large cerebrovascular accident in the left hemisphere of the brain, diagnosed by a CT scan. A doppler ultrasound of the carotid arteries indicated a large plaque of the left internal carotid occluding over 90% of the lumen. A post-mortem examination was not performed. A causality assessment by the reporting physician was not provided.
- 2). An 81 year old female, died three days after taking a single dose of raloxifene. The patient had been inactive (extended immobility) for approximately 5 years and had a history of mild obesity and occasional smoking. No autopsy was performed. It was presumed that the patient died of a pulmonary embolism.
- 3). The third report involved a fatal myocardial infarction in a 53-year old female 1 week after raloxifene was prescribed. The patient had multiple pre-existing risk factors, including long standing obesity, hypercholesterolemia, chronic hypertension, and a history of smoking one packet of cigarettes per day.
- 4). The remaining report involved ventricular tachycardia in a 56-year old female with multiple preexisting medical disorders, including breast cancer, schizophrenia, alcoholism, chronic obstructive pulmonary disease, and hypertension. It was reported that the patient had been abusing alcohol around the time of the episode of ventricular tachycardia. She was also taking concurrent unspecified anti-depressants, anti-hypertensives, and anti-psychotic medication.

II. Preclinical Pharmacology/Toxicology

Pharmacological Mechanism

Multiple Pathways for Estrogen Responses

The estrogen receptor is a nuclear transcription factor activated by ligand binding in order to assume a conformation permitting binding to specific DNA sequences called estrogen response elements (ERE) and subsequent activation or inhibition of gene expression. The biological effects produced by endogenous estrogens are mediated through the estrogen receptor. Likewise, modulation of the estrogen receptor plays a central role in raloxifene's mechanism of action. Scatchard plot analyses of [3 H]-raloxifene or [3 H]-17 β -estradiol binding to recombinant

human estrogen receptors reveal that these two ligands compete for a single high affinity binding site with respective K_d values of 54 and 86 pM. Similar binding profiles have been demonstrated for both the alpha and beta forms of the estrogen receptor.

The mechanism of action of raloxifene as an estrogen agonist in bone and other tissues is the subject of current research. Emerging evidence from several groups indicates the presence of multiple transcriptional pathways for ligand-bound estrogen receptors and the existence of multiple estrogen receptor subtypes. The estrogen receptor contains multiple transcriptional activating functions (ie, AF-1 and AF-2) which account for some of the tissue-selective effects of tamoxifen. Furthermore, McDonnell and colleagues proposed that unique ligand-induced receptor conformations, as discerned in estrogen receptor protease protection assays, may be responsible for the range of pharmacological effects observed for SERMs, including raloxifene. As a consequence of the unique estrogen receptor:raloxifene conformation, this complex binds to sequences of the DNA distinct from the ERE in tissues where raloxifene exerts estrogen agonist effects.

Effects of Estrogen and Raloxifene in Bone

In ovariectomized (ovx) rats, raloxifene and estrogen produce similar antiresorptive action on bone, resulting in similar effects on bone mineral density, and on biochemical markers of bone metabolism.

While estrogen prevented bone loss in ovx rats, in simultaneously-tested hypophysectomized-ovx rats, the antiosteopenic effect of estrogen was completely absent. However, the uterine stimulatory capacity of estrogen was unaffected in the hypophysectomized-ovx animals, thereby providing strong evidence that the mechanism for the bone and uterine effects of estrogen are different. Similarly, ovx rats given raloxifene had the expected antiosteopenic effect, while ovx-hypophysectomized rats given raloxifene did not respond. These observations support the principle that raloxifene and estrogen share at least one mechanism with respect to their effects on bone. Interestingly, the antiosteopenic effect of a bisphosphonate (alendronate) was not lost in ovx-hypophysectomized rats, indicating the estrogen/raloxifene mechanism for inhibiting resorption of bone is distinct from that of the bisphosphonates.

Effect of Raloxifene on Bone Mineral Density

In a 12-month rat study, animals were treated with one of four therapies: sham, ovx, ovx + estradiol (EE, 0.1 mg/kg/day), or ovx + raloxifene (rlx, 3mg/kg/day). The ovx animals had progressive declines in vertebral BMD from months four through ten. From month ten to 12 the BMD increased slightly. The BMD in the EE and rlx groups also declined over the 12-month study; however the declines were significantly less when compared with the ovx group ($p=0.0001$). The decline in the EE group was significantly less than that seen in the rlx group ($p=0.01$). There was no evidence that the relative increases in vertebral BMD in the EE and rlx groups compared with the ovx group decreased over time. That is, the lines for EE and rlx maintained a significant parallel relationship with the ovx line throughout the study. A similar pattern of change in BMD was seen at the tibia.

In a 24-month monkey study, animals were treated with one of five therapies: sham, ovx, ovx + Premarin 0.04mg/kg/day (PR), ovx + rlx 1mg/kg/day (rlx 1), or ovx + rlx 5mg/kg/day (rlx 5). Every six months lumbar spine and whole body BMD were measured by DXA. Somewhat unexpectedly, the percent change in lumbar spine BMD increased slightly during the study in the ovx animals. Of the active treatment, the greatest increase in BMD was seen with PR, followed

by rlx 5; these increases were statistically significant when compared with ovx. Although the rlx 1 group had an increase in lumbar spine BMD, the difference was not statistically significantly different from ovx. In general, the slope of lines depicting the change in lumbar spine BMD vs. time were positive for all groups and there was no evidence (the BMD in the rlx 1 group did decrease slightly from month 18 to 24) that the lines in the active-treatment groups were converging with the line depicting the change in BMD in the ovx group. When compared with ovx, whole body BMD increased significantly in the PR group, but not in the Rlx groups.

These results indicate that, raloxifene (when given to rats and monkeys at doses considerably higher than the dose proposed for marketing in humans) has dose-related bone sparing properties that are less than those provided by 0.1mg/kg/day of estradiol and 0.04mg/kg/day of Premarin. The effect of raloxifene on BMD, at least at the lumbar spine, appears to be maintained relative to "placebo" for at least 12 months in the rat and 24 months in the monkey.

Effect of Raloxifene on Bone Histomorphometry and Strength

In a 35-day study of ovariectomized rats, treatment with 0.1 mg estradiol/kg/day prevented ovariectomy-induced increases in radial growth and cancellous bone turnover and the decrease in cancellous bone area. In comparison to the changes noted in the ovariectomized rats, raloxifene, at a dose of 3 mg/kg/day, prevented cancellous osteopenia as well as the changes in radial bone growth and bone resorption, but was less effective than estradiol in reducing cancellous bone formation.

In a 12-month rat study (described above), vertebral force-to-failure decreased over time in all treatment groups. When expressed as an integrated measure over the entire length of the study, the estrogen and raloxifene groups had higher force-to-failure values than the ovx-treated animals; however, there were no significant differences in the force-to-failure among the estrogen, raloxifene, and ovx groups when measured at months 10 and 12. Overall, there was no significant difference in vertebral force-to-failure between the estrogen and raloxifene groups. Although the femoral shaft BMDs were significantly greater in the estrogen and raloxifene groups relative to the ovx group, the values for femoral shaft load-to-failure were not significantly different between the active-treatment groups and the ovx group. Estrogen and raloxifene did, however, appear to attenuate the loss of femoral neck strength seen in the ovx animals.

The effects of Premarin and raloxifene on bone strength in the 24-month monkey study cited above are best summarized by the comments of Dr. Gemma Kuijpers:

- Premarin and raloxifene increased vertebral ultimate load; Premarin, but not raloxifene, increased vertebral ultimate stress.
- No significant biomechanical effects of Premarin or raloxifene were noted at the humerus.
- $F\mu$ decreased in ovx, reversed completely by Premarin, partially by rlx 1 and rlx 5 (results not statistically significant).

Toxicology Studies

Acute Toxicity

No mortality occurred in mice or rats administered a single 5000-mg/kg oral dose of raloxifene HCl. An intraperitoneal dose of 2000 mg/kg given to rats produced 20% mortality. No effects were seen in dogs or monkeys given a single oral dose of 300 mg/kg.

Repeated-Dose Toxicity

B6C3F1 mice administered raloxifene HCl in the diet for 3 months at average daily doses up to approximately 120 mg/kg had decreases in body weight gain with no associated toxicologically important effects. The most notable treatment-related finding was the estrogen antagonist effect of decreased uterine weight. The 6-month and 1-year dietary studies in Fischer 344 rats at doses up to approximately 25 mg/kg produced similar findings. In males, there were treatment-related decreases in food consumption and body weight gain. In female rats, decreased uterine weights and moderate elevations in serum alkaline phosphatase occurred at all doses. Moderate increases in adrenal weights were also seen in rats that received raloxifene, but these increases were not associated with any substantive histologic changes. Mineralization of the corticomedullary tubules of the kidneys occurred in both male and female rats of all dose groups. In a 6-month study in dogs at doses up to 30 mg/kg, the only treatment-related findings were decreased prostate weights in two of the four high-dose dogs, and aspermatogenesis and slight prostatic atrophy in one of those two dogs. The effects on the prostate are consistent with the pharmacological activity of raloxifene. No effects were observed on female dogs. There were no proliferative changes and no ocular effects in the chronic studies in rats and dogs. In subchronic studies conducted with CD-1 mice, Fischer 344 rats, and cynomolgus monkeys using raloxifene HCl doses up to approximately 1700, 700, and 1000 mg/kg, respectively, results were similar to those of the subchronic and chronic studies described previously. The primary findings in rodents included reduced food consumption and reduced body weight; decreased uterine and pituitary weights; and uterine hypoplasia, vaginal mucoid metaplasia, and ovarian changes. However, in female mice, body weight was increased at raloxifene HCl doses ≥ 184 mg/kg. The most important effects seen in monkeys treated for 1 month were decreased food consumption, various stool abnormalities in high-dose animals, reduced thymus weights in males, and reduced uterine weights and the presence of ovarian cysts at all doses. With the exception of the abnormal stools in monkeys given 1000 mg/kg, all of the changes produced by raloxifene treatment were attributable to its estrogen agonist/antagonist activity.

A 1-year toxicity study was conducted in cynomolgus monkeys to evaluate the effects of raloxifene HCl on intact females, OVX females, and juvenile males at daily raloxifene HCl doses of 0, 15, 30, or 100 mg/kg. Increases (2- to 6-fold above control values) in serum alanine transaminase (ALT) were observed in all groups of raloxifene-treated OVX females, but only in the mid- and high-dose groups of intact females. Serum ALT values in males were unaffected. Other serum enzymes associated with impaired liver function were not similarly increased, and there were no significant morphologic hepatocellular changes in any treated animals. Because estrogen has been shown to induce elevations in serum transaminases in the absence of hepatocellular damage, the increased serum ALT values seen in this study were likely related to the estrogenic activity of raloxifene in the liver and were not an indicator of hepatocellular damage. Reduced uterine weight and generalized atrophy of the uterus occurred in intact females treated with raloxifene. In raloxifene-treated OVX females, the uteri were indistinguishable (in weight and morphology) from those of the OVX control group. Ovarian weights were significantly increased in the mid- and high-dose groups compared to the control. Ovaries in raloxifene-treated animals had developing follicles and/or corpora lutea, but no follicular cysts were seen in any treated animal. Pituitary weights were reduced in males at all dose levels and thymus weights were decreased in high-dose males, but neither of these changes was associated with abnormal morphologic tissue changes. There were no proliferative lesions in any tissues or organs and no ocular effects.

Oncogenic Studies

In assessing the oncogenic potential of raloxifene, Fischer 344 rats were maintained for 2 years on diets containing raloxifene HCl that provided averaged daily doses up to 52 mg/kg in males and 279 mg/kg in females. In the high-dose group, systemic exposure to raloxifene in male and female rats was approximately 49 and 397 times greater, respectively, than the steady state plasma concentrations of raloxifene in postmenopausal women given a raloxifene HCl dose of 60 mg. There was an increased incidence (13% compared to 0% in the control) of benign ovarian neoplasms of granulosa/theca cell origin in the high-dose females. This effect was considered to have resulted from the extremely high systemic exposure of female rats to raloxifene (397 times greater than clinical exposure) which likely produced an exaggerated perturbation of normal estrogen physiology in the rat. In the mid-dose group where systemic exposure was approximately 90-fold above the clinical exposure level, no increase in ovarian neoplasia was observed. Because it is known that the factors contributing to ovarian neoplasia in rodents are not operative in postmenopausal women in whom the ovaries are senescent, the ovarian tumors observed in the high-dose rats are not considered to represent a clinical safety concern. No other neoplasms showed an increased incidence in males or females. An oncogenic study in mice was also conducted. Groups of 60 male and 60 female CD-1 mice (5 to 7 weeks of age) were maintained for 21 months on diets containing raloxifene HCl which provided average daily doses up to 210 mg/kg in males and 242 mg/kg in females. In the high-dose group, the mean plasma concentrations of raloxifene in males and females were approximately 23 and 32 times greater, respectively, than the plasma raloxifene concentrations in postmenopausal women given a daily raloxifene HCl dose of 60 mg. There were increased incidences of neoplasia in the testes, prostate, and ovaries. Significant increases in testicular interstitial cell tumors and prostatic adenomas and adenocarcinomas were seen in the mid- and high-dose groups, and prostatic leiomyoblastoma in the high-dose group. The incidence of these proliferative changes in the low-dose group was comparable to that of the control group. In females, dose-related increases in the incidence of ovarian neoplasia were observed in all treatment groups. These consisted of benign and malignant neoplasms of granulosa/theca origin (granulosa cell tumor, thecoma, and luteoma) and benign neoplasms of epithelial origin (tubular and papillary adenoma).

Special Studies

Several special studies with raloxifene have also been conducted. Results from these studies have indicated the following: 1) raloxifene showed no antigenic potential in a guinea pig model; 2) the estrogen receptor concentrations in the uteri of raloxifene-treated mice were elevated compared to controls, but testicular androgen receptors were not affected by raloxifene treatment; 3) raloxifene caused slight dermal and ocular irritation in rabbits; 4) inhalation of raloxifene HCl did not cause mortality in rats exposed to an aerosol concentration of 1.87 mg/L for 1 hour; and 5) inhalation exposure of monkeys for 8 hours to dry powder aerosols of raloxifene HCl did not affect pulmonary function at airborne concentrations up to 26.9 mg/m³.

Genotoxicity

Raloxifene was not genotoxic in any of the following assays: the Ames test for bacterial mutagenesis with and without metabolic activation; the unscheduled DNA synthesis assay in rat hepatocytes; the mouse lymphoma assay for mammalian cell mutation; the chromosomal aberration assay in Chinese hamster ovary cells; the in vivo sister chromatid exchange assay in Chinese hamsters; and the in vivo micronucleus test in mice.

III. Human Pharmacology/Pharmacokinetics

Absorption, First-Pass Effect, and Enterohepatic Cycling

Raloxifene undergoes rapid absorption, extensive first-pass glucuronidation, and enterohepatic cycling after oral administration. Based on plasma concentration versus time profiles of raloxifene and total raloxifene in hydrolyzed plasma (TRHP), absolute bioavailability of raloxifene is 2.0%, and absorption is estimated to be 63% following oral tablet dosing. TRHP represents the total concentration of raloxifene and all its metabolites.

Multiple peaks and plateaus are evident in plasma concentration-time profile for raloxifene, each of the monoglucuronide conjugates, and TRHP following oral and intravenous (IV) administration (Fig 1.1). Metabolite concentrations peak as early as 0.5 hour after the dose. Maximum plasma concentrations of raloxifene and secondary peaks for raloxifene metabolites typically occur at 6 hours after oral administration, approximately 1 to 2 hours after a meal. Peak concentrations observed shortly after a meal are likely to be influenced by biliary secretion and enterohepatic cycling. Probe studies with cholestyramine and ampicillin were conducted in order to assess the impact of interrupting enterohepatic cycling by either binding raloxifene and the glucuronide conjugates to prevent reabsorption or by decreasing β -glucuronidase producing enteric bacteria. Administration of cholestyramine or ampicillin with raloxifene HCl decreased raloxifene plasma concentrations; thus, providing strong evidence that raloxifene undergoes enterohepatic cycling.

The administration of raloxifene HCl with food leads to a small increase in the extent of raloxifene absorption (GGHN). Since raloxifene undergoes extensive first-pass metabolism, this enhancement of absorption resulted in a modest increase in TRHP concentrations. Based on the impact of coadministration of food and raloxifene HCl on single dose pharmacokinetics, average predicted raloxifene steady-state concentrations are similar to those predicted when raloxifene HCl is administered while fasting. Therefore, raloxifene HCl can be administered with and without food.

Distribution

Steady-state volume of distribution (V_{ss}) was 7.5 L/kg following intravenous administration. Similarly, V_{ss} determined following oral administration and corrected for bioavailability is also much larger than total body water. The high values of V_{ss} following both oral and intravenous administration indicate raloxifene distributes extensively in the body. Neither raloxifene nor its metabolites are distributed into the cellular components of blood.

Raloxifene and its two monoglucuronide conjugates are highly bound (>95%) to plasma proteins including both albumin and α -1-acid glycoprotein but plasma protein binding does not limit the large volume of distribution of raloxifene. In vitro analyses indicate plasma protein binding of warfarin, phenytoin, and tamoxifen was not altered by raloxifene or its monoglucuronide conjugates over the range of clinically relevant drug concentrations. Plasma protein binding may contribute to the limited glomerular filtration of raloxifene and the monoglucuronides.

Metabolism

Raloxifene undergoes extensive presystemic glucuronidation and systemic clearance of raloxifene approximates liver blood flow. Following IV administration, raloxifene represented only 65% of the TRHP at 0.5 hour. Raloxifene accounted for about 1% of the plasma radioactivity after oral administration of ^{14}C -raloxifene HCl solution. Raloxifene is metabolized to raloxifene-4 ϵ -glucuronide (primary metabolite), raloxifene-6- glucuronide, and raloxifene-6,4 ϵ -diglucuronide. In vitro studies indicated that raloxifene-4 ϵ -

glucuronide and raloxifene-6-glucuronide exhibited minimal binding to the classic estrogen receptor and therefore would not be expected to contribute to the pharmacological activity of raloxifene in vivo. Sulfate conjugates were not detected in either plasma or urine.

The terminal phase of raloxifene and its metabolites concentration-time profiles declined in parallel. Oral $t_{1/2}$ values for raloxifene are longer than those following intravenous administration. These results suggest that raloxifene interconverts and equilibrates with its glucuronide conjugates at nonenteric sites and that raloxifene half-life following oral dosing is formation-rate limited. The premise regarding presystemic and systemic clearance of raloxifene was explored using composite compartmental models for raloxifene and its metabolites. Results from these qualitative analyses support the hypotheses that raloxifene concentrations in the systemic circulation result primarily from hydrolysis of the glucuronides to reform raloxifene. Thus, half-life is attributed to enterohepatic circulation, systemic regeneration and extensive distribution of raloxifene and raloxifene conjugates in the body. The glucuronide conjugates serve as the predominate source of raloxifene in the body.

Excretion

The disposition of raloxifene was determined following oral administration of ^{14}C -raloxifene. The majority of the radioactivity was excreted as raloxifene in the feces within 5 days. Since approximately 63% of a dose of raloxifene was absorbed after oral administration of a tablet, raloxifene present in the feces primarily represents biliary excretion of raloxifene or the glucuronide conjugates followed by hydrolysis to raloxifene rather than nonabsorbed raloxifene. Less than 6% of the dose was recovered in the urine as glucuronide conjugates. Negligible amounts of raloxifene are excreted unchanged in the urine.

APPEARS THIS WAY
ON ORIGINAL

IV. Clinical Study

Comparison of Raloxifene and Placebo in the Treatment of Postmenopausal Women with Osteoporosis

Study GGGK

Primary Objective: To examine the effect of treatment with raloxifene, compared with placebo, on the rate of change in lumbar spine (LS) and femoral neck BMD and on the rate of new vertebral fractures in osteoporotic postmenopausal women with and without prevalent vertebral fractures.

Design: This is a multicenter, double-blind, placebo-controlled, randomized clinical study with a completed 36-month core treatment phase and an ongoing 12-month extension phase. This study consists of two parallel studies in separate populations: Substudy I consists of women with low BMD (lumbar spine or femoral neck BMD T-score of -2.5 or less) and Substudy II, which consists of women with at least one prevalent vertebral fracture. Patients were randomized 1:1:1 to either placebo once per day, raloxifene 60 mg once per day or raloxifene 120 mg once per day. Furthermore, patients were randomized 2:1 into Substudy I and II. All patients were instructed to take supplements of approximately 500 mg of elemental calcium per day and approximately 400 to 600 IU of vitamin D per day. Study medication was to be discontinued immediately in the event of an illness or condition leading to a prolonged period of immobilization and was not to be restarted until the inciting condition or illness had resolved and the patient was fully mobile. In addition, any patient who planned to undergo elective surgery was to discontinue study medication approximately 72 hours prior to admittance to the hospital and was not to restart medication until recovered to the point of prior mobility. When a patient discontinued, for any reason, from the study after Visit 2 she was to be seen by the investigator as soon as possible and all procedures required for Visit 11 (Month 48) were performed (if appropriate in the opinion of the investigator or sponsor).

Patient Population: In order to enter into this study women had to be: ambulatory, postmenopausal (serum estradiol < 73 pmol/L and FSH > 30 IU/L), expected to have a life expectancy of at least 5 years, and be no older than 80 years. To be included in Substudy I, patients had to have a femoral or LS BMD T-score of less than or equal to -2.5 . To be included in Substudy II, patients had to have at least one moderate or at least two mild vertebral fractures in the presence of low BMD or at least two moderate vertebral fractures, regardless of BMD. Some of the exclusion criteria included patients with: abnormal uterine bleeding, primary osteoporosis, hyperparathyroidism, a history of deep venous thrombosis (DVT), thromboembolic disorders, or cerebral vascular accident within the previous 10 years except for patients with a history of DVT due to accidents, hx of acute or chronic liver disease, impaired kidney function (serum creatinine > 225 $\mu\text{mol/L}$ or > 2.5 mg/dL), active renal lithiasis, a current history of excess alcohol consumption (> 4 drinks per day), treatment with therapeutic doses of any of the following medications more recently than 6 months prior to beginning the study: androgen, calcitonin, estrogen, and progestin, a history of treatment with therapeutic doses of systemic corticosteroids for more than one month during the 12 months prior to beginning the study, a history of receiving therapeutic doses of fluorides for more than 3 months during the 2 years prior to study entry, or for more than a total of 2 years in any period of time, and a history of participation in a study examining raloxifene.

Endpoints/Methods: For point of reference, Visits 1, 2, 3, 4, 5, 6, 7, 8, and 9 correspond to baseline and Months 0, 3, 6, 12, 18, 24, 30, and 36, respectively. Femoral neck BMD (DXA –

Hologic, Lunar, or Norland machines) measurements were performed at screening, again in the period beginning with Visit 1 and ending with Visit 2, and at Visits 5, 7, and 9. Posterior/anterior LS BMD measurements were obtained in duplicate in the period beginning with Visit 1 and ending with Visit 2. Follow-up LS BMD determinations were performed at Visits 5, 7, and 9. At screening, patients were interviewed about any clinically evident vertebral and nonvertebral fractures that had occurred before entering the study. At each follow-up visit, patients were interviewed about new nonvertebral fractures or clinical signs or symptoms of vertebral fractures that occurred since the most recent visit. Nonvertebral fractures were documented with the radiologist's written report or radiographs. Vertebral fractures were documented by centralized reading of spinal radiograph. Standing height was measured with stadiometers at baseline and Visits 4, 5, 7, and 9. Since serial height measurement was not a primary outcome of this study, specific height measurement with a wall-mounted stadiometer was not required, although recommended when available. Standardization of wall-mounted stadiometers also was not performed throughout the study. At screening, lateral and posterior/anterior thoracic and lumbar spinal radiographs were taken to determine the presence of vertebral fractures at baseline. Depending on the absence or presence of prevalent fractures, eligible patients were enrolled either into Substudy I or II. To determine the rate of incident vertebral fractures and deformities, lateral films of the thoracic and lumbar spine were repeated at Visits 7 and 9 (see below). Total body (n=2609) and radial (n=2743) BMD were assessed in a subset of patients at Visits 2 and 7. Markers of bone metabolism (osteocalcin, alkaline phosphatase [alk phos], carboxy-terminal propeptide of type I procollagen [PICP], urinary calcium excretion, and urinary creatinine were measured at Visits 2, 4, 5, 7, and 9 in a subset of 2600 patients. All patients had measurements of 25-hydroxyvitamin D and parathyroid hormone (PTH) at Visits 1, 2, and 4.

In a subset of patients, the following cardiovascular risk factors were measured at Visits 2, 4, 5, 7, and 9: apolipoprotein A1, apolipoprotein B, total cholesterol, HDL-C, LDL-C, triglycerides, fibrinogen, and HbA1c. Electrocardiograms were obtained at Visits 1 and 7.

In a subset of patients, pelvic examinations and uterine ultrasonography were performed at Visits 1, 5, 7, and 9. Mandatory mammography was performed at Visits 1, 7, and 9; mammography was optional at Visit 5. If mammography was not acceptable to the patient, ultrasonography of the breast was performed.

In a subset of 65 women, bone biopsies of the iliac crest were performed at baseline and after 2 years of therapy.

Statistical Analyses: See statistical review by Dr. Haberman. Analyses were performed using the intent-to-treat (ITT) principle, with patients allocated to assigned treatment regardless of compliance or other postbaseline factors. Patients had to have at least one postbaseline value to be included in the analyses. Missing postbaseline values were imputed by carrying forward the previous value (LOCF). Analyses on completers were performed separately. All safety and efficacy analyses were performed on the entire study cohort. Primary efficacy analyses were also performed separately on each Substudy population.

For the primary efficacy outcome, vertebral fracture, the following definitions were used:

- Prevalent vertebral fracture: any baseline adjudicated vertebral fracture.
- Incident vertebral fracture: any postbaseline adjudicated vertebral fracture; can be subclassified as follows 1) new vertebral fracture, 2) worsening vertebral fracture, and 3) clinical vertebral fracture (an incident vertebral fracture present on a radiograph taken at a visit where a patient reported signs and symptoms indicative of a possible fracture).