CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020815

Trade Name: EVISTA 60 MG TABLETS

Generic Name: RALOXIFENE HYDROCHLORIDE

Sponsor: LILLY RESEARCH LABORATORIES

Approval Date: 12/09/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020815

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020815

APPROVAL LETTER

NDA 20-815

DEC - 9 1997

Lilly Research Laboratories
Attention: Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Stotka:

Please refer to your new drug application dated June 8, 1997, received June 9, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Evista (raloxifene hydrochloride) Tablets 60 mg.

We acknowledge receipt of your pre-submissions dated March 13 and April 2, and 3, 1997, and your submissions dated June 12 and 27, July 3, 10, 18, and 21, August 1, 4, 5, 11(3), 15(2), 18, 20(2), 22, 25, 28(2), and 29, September 3, 4, 9(2), 12(3), 18, 19, and 26(2), October 1(4), 2, 6, 8(2), 10, 14, 15(6), 16, 17(2), 20(2), 22, 24, and 28(2), November 3, 10, 13(4), 17(5), 19, 21, 24, and 25(2), and December 3, 5, 8, and 9, 1997. The User Fee goal date for this application is December 9, 1997.

This new drug application provides for the use of Evista Tablets for the prevention of osteoporosis in postmenopausal women.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft package insert and patient package insert labeling dated December 9, 1997, and the draft packaging labeling dated June 8, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-815. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of the Phase 4 commitment

Submit protocols, data, and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of this commitment in your annual report to this application. The status summary should include expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to this Phase 4 commitment should be clearly designated "Phase 4 Commitment."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301)827-6392.

Sincerely yours,

12/9/97

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-815
HFD-510/Div. files
HFD-510/CSO/R.Hedin
HFD-510/EColman/GTroendle/GKuijpers/RSteigerwalt/SMarkofsky/DWu
/CJones/HAhn/ENevius/EGalliers
HFD-002/ORM (with labeling)
HFD-102/Office Director (with labeling)
HFD-101/L.Carter
HFD-820/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFI-20/Press Office (with labeling)
HFD-021/ACS (with labeling)

Drafted by: RH/November 25, 1997/N20815AP.LT1
Initialed by:
final:

APPROVAL (AP) [with Phase 4 Commitment]

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020815

MEDICAL REVIEW(S)

Memorandum
December 7, 1997
To:NDA File 20-815 (Evista,raloxifene hydrochloride)
From:Solomon Sobel M.D. Director,Division of Metabolic and Endocrine Drug Products 12/7/97
Subject:Approval of NDA
There are several issues which arose during the review of this NDA.

1.Should raloxifene, a selective estrogen receptor modulator (SERM), be considered as an estrogen for evaluation as such in applying our osteoporosis guidelines?

2.Do pre-clinical studies support the view that the bone effects of raloxifene result in normal histomorphology and mechanical strength?

3.Do clinical histomorphology studies (by biopsy) show normal bone after raloxiphene treatment?

4.In clinical studies, has raloxifene shown satisfactory benefit in regard to bone mineral density for at least 2 years?

5.Does the relative greater effect on bone mineral density of a comparative estrogen (conjugated estrogen) affect raloxifene's approval.

6.Does an apparent small decline of BMD at 2 years of treatment(in 2 studies) require further follow-up to study whether this decline is real and persistent with continued treatment before approval can be given?

7.Is a demonstration in improvement in respect to the incidence of fractures necessary before approval?

8.What can be definitively said about raloxifene's effect on breast and endometrial cancer?

9.What is the magnitude of the effect of raloxifene on the incidence of venous thromboebolism?

10. What is the significance of the finding of ovarian carcinomas in rats and mice treated with raloxifene?

1. In basic molecular biological research, there is evidence that there are multiple transcriptional pathways for ligand-bound estrogen receptors and the existence of multiple receptor subtypes.

It has been proposed, that unique ligand-receptor conformations may be responsible for the various pharmacodynamic effects of SERMs.
Experiments in ovariectomized rats
vs.hypophysectomized+ovariectomized rats, indicate that that the effects of estrogen may be dissociated in respect to bone vs. mammary-uterine effects.
Raloxifene shares estrogen's effects in these experiments in respect to the prevention of osteopenia but has no stimulatory effects on mammary and uterine tissues. This provides evidence that raloxifene acts as an estrogen, selectively, on bone.
Based on these considerations and the clinical effects of raloxifene in post-menopausal osteoporosis we have decided to treat raloxifene as an estrogen, to a substantial degree, in the context of the osteoporosis guidelines.

2.The effect on bone of raloxifene was carried out in studies ranging from a few weeks to 12 months in ovariectomized rats.
A 24 month study was performed in cynomologous monkeys.
In ovariectomized rats, raloxifene inhibited the decrease in bone mineral density. Both raloxifene and estrogen prevented bone loss and trabecular changes.
Biomechanical testing of rat vertebrae in a 12 month study suggested that raloxifene and estrogen increase bone strength in parallel with BMD.
The 2-year study in ovx monkeys showed that raloxifene and Premarin prevented osteopenia.The high dose raloxifene was moderately less efficacious than Premarin.
However, there were some aspects of the monkey study which clouded interpretation.
Both sham and ovx monkeys gained bone mass during the study. The BMD gain was probably due to the fact that the bone mass of the feral monkeys was not stabilized at the start of the study.
Nutritional and other growth factors may have been involved in the increase observed.

3.Study GGGM studied the histomorphologic effect of short term (6-month) therapy on the iliac crest of postmenopausal women.
Fifty-one subjects were randomly assigned to one of two double blind therapy groups(60 mg of raloxifene and 0.625 mg of Premarin).
Twenty-two subjects had evaluable bone biopsy data.
The results showed that raloxifene did not have a detrimental effect on bone histomorphometry. This was a short study and had few patients.
An ongoing placebo controlled study (GGHF) will further investigate histomorphometry.

4.Drs. Colman and Troendle have summarized the BMD changes and the findings of the pivotal studies show a small but consistent effect of raloxifene over placebo in increasing bone mineral density.

5.In study, GGGH where there were both a placebo and active control (Premarin) there was a considerably better effect of Premarin on BMD.
However, this does not affect the approval of raloxifene because advantages in safety in respect to effect on breast and endometrial tissues may make raloxifene the choice of therapy in some patients.
In general, issues of relative efficacy do not preclude the approval of a drug.

6.There is a concern that in the pivotal studies GGGG and GGGH the mean change in lumbar spine BMD in the groups randomized to a 60-mgm dose is showing a trend to decline (non-significant) at 24 months.
In view of the estrogen-like mechanism of action of raloxifene, there is no reason to believe this small decline is of significance.

7. Because we have good evidence that raloxifene exerts its effects through estrogen receptors, our guidelines permit approval based on 24 months of BMD data.

8.Pre-clinical data demonstrate that raloxifene is an estrogen antagonist in uterine and breast tissue.
Clinical data (through 30 months) suggest that raloxifene lacks estrogen-like effects on uterus and breast tissue.

9.The relative risk for thromboembolism of raloxifene as compared to estrogen is difficult to ascertain from the numbers of patients studied. The absolute risk for deep venous thrombosis and pulmonary embolism is about 1 case per 1000 persons/year.
The relative risk for these events during the first four months of treatment with raloxifene is 6.7(1.2,39)
This risk declines substantially with longer exposure, 1.8 (0.6,5.3).
This risk of thromboembolic disease appears acceptable for approval.

10.In rodents, raloxifene induced benign and malignant tumors in prostate, testis and ovary.
The carcinogenicity studies were carried out in intact animals.
The ovarian tumors are of particular concern because they occurred at a low human exposure level.
Because these studies were conducted in animals with intact hypothalamic-pituitary-ovarian axes, the pituitary gonadotrophin levels may have been increased in the long term carcinogenicity studies and may plausibly be the cause for the findings.
Raloxifene will be used in postmenopausal women where there is unlikely to be an increment in already high gonadotrophin levels.

Conclusion:
There is a difference of opinion between the medical office (Dr. Eric Colman) and the the medical group leader (Dr. Gloria Troendle).

Dr. Colman believes that it would be prudent to delay approving raloxifene until the Division receives further data. He recommends waiting for data (from ongoing studies) in respect to fracture incidence and also to wait for data in respect to the findings of BMD at three years.

Dr. Troendle has concluded that raloxifene is a reasonable alternative to estrogen for many women and might be preferred by some to bispohosphanates.

The Endocrinology and Metabolic Advisory Committee has voted in favor of approval.

I believe that there is sufficient evidence at this time to warrant approval of raloxifene for the prevention of post-menopausal osteoporosis for the reasons I have outlined above in the answers to the questions I have listed.

Solomon Sobel

Solomon Sobel M.D.

CC: Arch NDA 20-815
HFD-510
HFD-510/SSobel/GTroendle/EColman/RHedin

APPEARS THIS WAY
ON ORIGINAL

NDA 20815 Lilly
SERM for Osteoporosis 19 November, 1997
Raloxifene, Evista Review Completed 17 November, 1997

Team Leader's Comment

Raloxifene is the first selective estrogen receptor modulator (SERM) to have been presented in an NDA for osteoporosis. Three efficacy studies (GGGF, GGGG and GGGH) are currently on-going, and were subjected to an interim (24 months) analysis for this NDA. The studies will continue for a total of at least 36 months, and will then permit a 2-year open extension. Patients are being assigned to one of two doses of raloxifene (60 and 120 mg per day) or placebo. It is intended that another on-going study (GGGK) will also continue to a total of at least 36 months. The study is being done in 180 centers with 205 principal investigators. The total enrollment is more than 7000 women, and the primary endpoint is vertebral fracture rate. The last 36-month patient visit should be completed in October 1998.

The Division Guidance for osteoporosis drugs allows for approval after completion of two year studies with a BMD endpoint if the drug is an estrogen, and we agreed with the sponsor that in vitro and animal evidence showed that raloxifene binds to the estrogen receptor and has similar effects to estrogen on several parameters. However, now that we have all the data and see how much different results are for raloxifene and estrogen, and because of new information on receptor variability in different tissues, we are reluctant to say that this drug is indeed an estrogen. The margin of effectiveness is very small, and there is a great disparity in BMD and turnover marker results between raloxifene and CE. This may be just a quantitative difference on the basis of differential receptor binding, but that is as much a conjecture as the proposition that this drug is an estrogen.

The principal endpoints for the three efficacy studies submitted in this NDA are mean change from baseline in lumbar spine and total hip bone mineral density (BMD). GGGF and GGGG are very similar studies conducted in Europe and North America respectively. GGGH is a similar study but includes a conjugated estrogen (CE) arm.

The following table gives the mean percent change from baseline for BMD at several sites and the median percent change from baseline for biochemical markers and lipids. Results are shown here only for placebo, the 60mg dose of raloxifene, and in GGGH for conjugated estrogens (ERT). In

each cell, the results for placebo are followed by a slash and then by the value for Evista. In the GGGH column, Evista results are followed by results for conjugated estrogens 0.625mg (CE). The left column consists of a description of the various measurements made. Results are consistently better for Evista than for placebo, and show considerably less benefit than CE.

	GGGF	GGGG	GGGH
	Plbo/Evista	Plbo/Evista	Plbo/Evista/Estr
N	150/152	136/134	152/152/ 158
BMD			
Lumbar spine	-.80/+1.63	-1.16/+.78	-1.59/+.19/+3.8
Total hip	-.84/+1.58	-.76/+1.2	-.49/+.79/+2.4
Femoral neck	-1.34/+1.16	-2.4 /+1.9	-1.32/+.30/+1.5
Trochanter	-.62/+2.07		-.68/+.62/+3.2
Intertrochanter	-.69/+1.76	-.93/+1.34	-.45/+.86/+2.3
Ward's Triangle	-.35/+3.67		-3.17/+.52/+2.0
Total body	-.55/+1.42	-.92/+ .39	
Distal Radius	-2.02/-1.47	-1.9 /- .95	
Ultradist rad	-2.30/+ .26	-2.4 /-2.42	
Bone markers			
Osteocalcin	-9.4 /-23	-20/-32	-17/ -29/ -49
Total AlkP	-3.5 /-12.9	-1.8 /-14	
Bone spec AlkP	-9.7 /-14	+11/+.9	-4.5/ -10/-45
Type 1 Collag	- 15/-34	-9/-30	+5.5/-2.4/-59
Lipids			
Total Cholest	- 1.2/-6.4	-.49/-3.24	-.85/ -4.1/-2.2
LDL-C	- 1.0/-10.1	-1.57/-4.1	+1.3/ -8.2/-10.4
HDL-C	- 4.7/-3.7	-3.9 /-2.6	-4.2/-2.65/+6.3
Triglycerides	+ 2.8/-6.7	0/+1.5	-3.8/ -5.0/+26
ApoA1			0 / +3.5/+17

The effects of raloxifene on BMD are extremely small, and the radius does not appear to be protected from bone mineral loss to any meaningful extent. Bone markers indicate slowing of turn over, but differences between drug and placebo are small and differences between placebo and estrogen are much larger (vs 32 osteocalcin, vs 40 bone specific Alkaline phosphatase, and vs 53 type 1 collagen fragment).

There are multiple effects of estrogen that should be considered in the overall assessment of benefits and risks. Most of them are listed below with the relative effects seen with raloxifene. There is much overlap in the effects listed. It is likely that the effects on CHD derive from the effects on vascular endothelium, and from lipid and clotting effects. The effects on vascular endothelium also contribute to the effects on hot flushes and cognition.

General stimulatory effects on sexual endocrine tissues affect the vaginal mucosa and the endometrium and its potential for developing cancer, endometriosis and fibroids. However, the effects on bone are not yet connected with these other effects. It is of great interest to work out the common mechanisms by which bone might share similar connections.

The following table consists of a comparison of the effects observed on raloxifene and CE. In the right-hand columns B means that the drug (raloxifene or estrogen) was tested and found to be beneficial. BB means that the benefit appears to be better in the specified drug. ? means the effect was not tested for. In the case of fractures and atherosclerosis/CHD, estrogen has been tested in epidemiological studies and found to be beneficial but was not tested in these NDA studies. For breast cancer, estrogen has been found to increase the risk, but risk of cancer has not been tested in the NDA studies. No effect indicates that none was found in the NDA studies. A means that the effect is adverse and AA indicates results are more adverse with estrogen or with raloxifene. The summary column (+-) indicates those areas where evidence indicates an advantage of estrogen over raloxifene or lack of information on raloxifene (-), advantage of raloxifene over estrogen or lack of information (+), and inadequate information to make a choice (no entry).

Effects on\by		Ralox	Estrogen	Sum
Bone	BMD	B	BB	-
	Biochemical markers	B	BB	-
	Fractures	?	B?	-
Lipids	HDL-C	No effect	B	-
	LDL-C	BB	B	+
Coagulation - Clotting Factors		B	B	
	VTEs	A	A	
Atherosclerosis - CHD		?	B?	-
	Vascular endothelium	?	B	-
Endometrium - Cancer		No effect	A	++
	Endometriosis	?	A	
Breast Cancer		?B	AA	++
Fibroids		?	A	
Hot Flushes		A	B	-
Vaginal mucosa		No effect	B	
Cognition		?	B	-

The efficacy provided by the BMD lumbar spine and total hip (the primary endpoints in GGGF, GGGG, and GGGH) is meager: 2.4, 1.9, and 1.8 in the three studies for lumbar spine; 2.4, 2.0, and 1.6 for the total hip vs 5.4 (lumbar spine)

and 2.9 (total hip) for estrogen. Looked at in the same study (GGGH), mean change from baseline for raloxifene vs CE is 1.8 vs 5.4 and 1.6 vs 2.9. However, use of raloxifene prevents loss of bone density, and that is adequate for preventing osteoporosis in women who start early in menopause before their bones are at a level that is associated with fractures. The raloxifene sponsor presents studies to show efficacy for treatment of established osteoporosis. In one of the treatment studies (GGGN), lumbar spine BMD was increased 1.78 vs .96 and total hip .95 vs -.71, differences of .8 and 1.7 per cent change from baseline. This amount of bone restoration is not adequate to warrant use of a drug in the osteoporotic population.

Other benefits and risks are primarily related to the effects listed above for estrogen. There is apparent benefit to bone as measured by BMD and bone markers, and lipids appear slightly improved with increased HDL-C and very slightly decreased LDL-C. However, hot flushes and VTEs are increased. Compared to estrogen, there is less benefit from effects on bone density, or biochemical markers, less decrease in LDL-C, probably less effect on vaginal mucosa. There is decreased risk of endometrial cancer, and possibly of breast cancer compared to use of estrogen. It is not clear whether other benefits of estrogens are realized, such as reduced fractures, less cardiovascular risk, improved cognition. There have been no studies of direct effects on vascular endothelium, endometriosis, and fibroids, and these are areas in which such studies would not be expected.

In spite of all the negative aspects of this drug, I believe it is a reasonable alternative to estrogen for many women, and would be preferred to the difficulties of taking bisphosphonates. Also, it may be more effective than calcitonin, especially when calcitonin is used nasally.

Recommendations: Approvable for prevention of osteoporosis
Label for risks of VTEs, hot flushes

Gloria Troendle 12/3/97

Gloria Troendle
cc:ORIG NDA
DIV FILE
HFD-510/GTroendle/EColman/SSobel

APPEARS THIS WAY
ON ORIGINAL

NOV 24 1997

MEDICAL OFFICER'S REVIEW OF NDA 20-815

EVISTA®

RALOXIFENE HYDROCHLORIDE

DATE SUBMITTED: June 8, 1997
DATE RECEIVED, CDER: June 9, 1997
DATE RECEIVED, M.O.: June 15, 1997
DATE REVIEW COMPLETED: 11/19/97

DRUG NAME
GENERIC: Raloxifene Hydrochloride
TRADE: Evista

SPONSOR: Lilly Research Laboratories

PHARMACOLOGICAL CATEGORY: Selective Estrogen Receptor Modulator (SERM)

PROPOSED INDICATION: Prevention of Osteoporosis

APPEARS THIS WAY
ON ORIGINAL

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1. Materials Reviewed

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2. Preclinical Pharmacology/Toxicology (see Dr. Kuijpers' pharmacology review)

Pharmacologic 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]-17b-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). Sham and ovx animals had declines in BMD over the 12-month treatment period. However, the ovx animals had a larger decline in vertebral BMD as compared with

sham controls from months 0-6. From months 6-12, BMD declined in parallel in sham and ovx groups The BMD in the EE and rlx groups also declined over the 12-month study; however, the declines were signficantly 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 remained parallel 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. For sham controls, BMD increased by approximately 7% over 24 months. Somewhat unexpectedly, the percent change in lumbar spine BMD also increased slightly during the study in the ovx animals. Of the active treatment groups, 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 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 rxl 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 Histomophometry 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.
- In femoral neck, no significant biomechanical effects of Premarin or raloxifene were noted at the humerus.

- Fu decreased by ovx, Premarin increased femoral neck Fu; raloxifene had no significant effect.

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 six-month and one-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 six-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 pharmacologic activity of raloxifene. No effects were observed on females 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 one 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.

A one-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. 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 two 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. In the mid-dose group where systemic exposure was approximately 90-fold above the clinical exposure level, no increase in ovarian neoplasia was observed. 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/m^3 .

Reproduction and Developmental Toxicity Studies

In a reproduction study in rats, both males and females received daily oral raloxifene Hcl doses of approximately 5, 10, or 20 mg/kg. Treated females had atypical estrous cycles, decreased incidence of mating, and no pregnancies. Because there were no effects on sperm production, sperm quality, mating performance, or fertility in male rats treated for two weeks in a separate study at doses up to 100 mg/kg, the infertility observed in the reproduction study was attributed to effects on female rats. A subsequent study suggested that the effects of raloxifene on estrous cycling and fertility in rats are reversible after treatment is discontinued.

Female rats administered raloxifene HCl at doses of 0.1 mg/kg during the preimplantation period of pregnancy exhibited a delay in embryonic implantation and an increase in pre-and early postimplantation deaths. These effects resulted in a prolonged gestation length and a decrease in litter size. However, the process of parturition was unhindered, and neonatal survival, development, and morphology were not affected. In teratology studies, a no-observed-effect level of 0.1 mg/kg raloxifene HCl was established for fetal effects in CD rats, but fetal abnormalities were observed at the lowest doses tested in two strains of rabbits. The developmental deviation in rats was wavy ribs. In Dutch Belted rabbits at a dose of 10 mg/kg and in New Zealand white rabbits at doses

of 0.1 mg/kg, developmental toxicity was manifested as a low incidence of hydrocephaly (3 out of 56), and as a ventricular septal defect of the heart (3 out of 338), respectively. In a study designed to evaluate both developmental and postpartum toxicity in rats, daily oral raloxifene HCl doses of 1 or 10 mg/kg increased gestation length, and 10 mg/kg caused disrupted parturition resulting in maternal death, morbidity, and increased numbers of dead progeny. In the offspring, dose-related growth retardation occurred at maternal raloxifene HCl doses of 0.1 mg/kg, and altered patterns of development and epithelial mucoid change (metaplasia) in the vagina were seen at doses of 1 mg/kg. Changes in the pituitary content of growth hormone, luteinizing hormone, and prolactin were found in offspring from the 10-mg/kg treatment group. Immunologic evaluation of five- to six-week-old offspring suggested that treatment of dams with raloxifene can reduce the size of lymphoid compartments, such as the spleen and thymus, but does not affect the general integrity of immune responsiveness by natural killer cells and antibody-producing cells. In a reproduction study of the offspring from raloxifene HCl-treated females, reduced mating, fertility, and litter size were seen in the high-dose group (10 mg/kg). A high rate of uterine hypoplasia occurred in the female offspring, but there were no ovarian, vaginal, or malignant changes.

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.

3. Clinical Background

Foreign Experience
Raloxifene is not marketed in any foreign country.

Relevant NDAs
Raloxifene is the first drug in a new class of drugs: selective estrogen receptor modulator (SERM).

Relevant Literature
A MEDLINE search from 1985 through mid-1997 revealed 37 published papers. The majority of these studies were conducted in rodents, with few data from clinical trials. For the most part, the data from the published literature is included in the NDA submission.

Human Pharmacology/Pharmakinetics/Pharmacodynamics (see Biopharm Review)

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

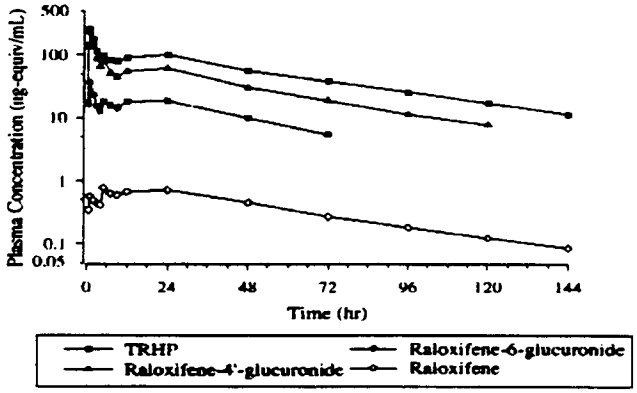


Figure 1.1. **Mean (n=8) Plasma Concentration versus Time Plots of Raloxifene, Raloxifene Metabolites, and TRHP after Administration of 2 x 60-mg Raloxifene HCl Tablets to Healthy Postmenopausal Women (Study GGHH)**

enteric bacteria. Administration of cholestyramine or ampicillin with raloxifene HCl decreased raloxifene plasma concentrations; thus, providing strong evidence that raloxifene undergoes enterohepatic cycling.

Due to extensive first-pass metabolism and enterohepatic cycling, Cmax and Tmax for raloxifene are inappropriate metrics for assessing rate of absorption.

The administration of raloxifene HCl with food leads to a small increase in the extent of raloxifene absorption. 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 (Vss) was 7.5 L/kg following intravenous administration. Similarly, Vss determined following oral administration and corrected for bioavailability is also much larger than total body water. The high values of Vss 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 a-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 of the TRHP at 0.5 hour. Raloxifene accounted for about of the plasma radioactivity after oral administration of 14C-raloxifene HCl solution. Raloxifene is metabolized to raloxifene-4¢-glucuronide (primary metabolite),

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 14C-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.

Raloxifene Pharmacokinetic Parameters

Single dose pharmacokinetic parameters for raloxifene obtained from 232 individual healthy postmenopausal female subjects in 11 of 20 clinical pharmacology studies have been evaluated. Because some subjects participated in more than one study or received more than one raloxifene HCl dose within a given study, the analysis included 494 raloxifene profiles from 232 subjects. Estimates of dose-normalized raloxifene pharmacokinetic parameters from these studies are presented in Table 1.3.

Table 1.3. Summary Statistics for Raloxifene Pharmacokinetic Parameters in Healthy, Postmenopausal Females

Estimates	C_{max}[a] (ng/mL)/(mg/kg)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$[a] (ng_hr/mL)/(mg/kg)	CL/F (L/hr/kg)	V_z/F (L/kg)
Oral Dose					
Mean	0.50	27.7[b]	27.2	44.1	2348
SD	0.26		12.1	20.3	1228
CV(%)	52	NA[d]	44	46	52
N[e]	494	462	465	465	465

[a] C_{max} and AUC values are dose/wt. normalized.
[b] Harmonic mean.
[c] Range for the pharmacokinetic profiles.
[d] Not applicable.
[e] Number of times the variable was evaluated in the 494 pharmacokinetic profiles.

A high first-pass effect, combined with enterohepatic cycling and metabolic interconversion contribute to large within- and between-subject variability in raloxifene pharmacokinetics. Within-subject coefficient of variation for AUC is approximately 30%. Between-subject coefficient of variation for raloxifene is approximately 50% for single dose pharmacokinetic parameters.

Raloxifene Multiple Dose Pharmacokinetics

Pharmacokinetics of raloxifene and raloxifene glucuronide metabolites are consistent following single and multiple doses. As was predicted from single dose studies, once-daily administration of raloxifene HCl for 10 to 14 days leads to steady-state concentrations which are approximately 4-fold higher than single dose concentrations. Based on population pharmacokinetic analyses, CL estimates for chronic administration(up to 24 months) of raloxifene HCl are comparable to values after single dose administration. Average steady-state raloxifene concentrations (Css,B) are predicted to range from following a 60-mg dose. Pharmacokinetic parameters of TRHP are also consistent following single and multiple doses of raloxifene HCl. TRHP average Css,B values are expected to range between following chronic administration of 60 mg raloxifene HCl.

Dose Proportionality

As dose is increased from 30 mg to 150 mg of raloxifene HCl, a slightly less than proportional increase in AUC is observed for both raloxifene and TRHP. This result is not caused by differences in formulation but is likely caused by a slight decline in the fraction of dose reaching systemic circulation with increasing dose. Population pharmacokinetic analyses indicated that the relative bioavailability of raloxifene from the 150-mg dose is 83% of the value for the 30-mg and 60-mg doses. The results for TRHP are similar.

4. Description of Clinical Data Sources

Study Type and Design

The proposed indication for raloxifene in this NDA submission is the prevention of osteoporosis. Two-year interim data from three placebo-controlled trials examining the effect of various doses of raloxifene on total spine and hip BMD provide the primary data in support of the prevention indication. A number of ongoing studies are also included in this submission; they provide important supportive data regarding the efficacy and safety of raloxifene. These studies are shown on the following page.

Study	Primary Objective	Study Population (Women)	Therapy
Ongoing Studies:			
GGGK	Treatment of osteoporosis	PMP, ≤80 yrs, BMD -2.5 SD/history of fractures	PLACEBO, RLX060, RLX120
GGGP	Treatment of osteoporosis	PMP, Low BMD,	PLACEBO, RLX060, RLX150
GGHD	Uterine safety and prevention of osteoporosis	Early PMP,	PLACEBO, RLX060, RLX150, HRT
GGHF	Histomorphometry	Healthy PMP,	PLACEBO, RLX150, HRT
GGHG	Uterine safety	Healthy PMP	PLACEBO, RLX060, RLX150, PRM625
GGHW	Tumor marker	Primary breast cancer, PMP, <80 yrs, surgery scheduled	PLACEBO, RLX060, RLX600
JOAA	Tumor response	Stage IV metastatic breast cancer	RLX300

Abbreviations: RLX = raloxifene HCl dose (mg/day); PMP = postmenopausal; BMD = bone mineral density; PRM625 = Premarin (conjugated equine estrogens) 0.625 mg/day; HRT = hormone replacement therapy (combined progestin/estrogens administered in a cyclic or continuous combined manner); SD = standard deviation.

Study	Primary Objective	Study Population (Women)	Therapy	Blinding	Study Duration in Months	Mean Age	Years PMP
Short-Term and/or Uncontrolled Studies:							
GGGB	Bone metabolism	251 Healthy PMP,	PLACEBO, RLX200, RLX600, PRM625	DB	2[a]	53	3
GGGC	Dose response	167 Healthy PMP	PLACEBO, RLX010, RLX060, RLX200	DB	2[a]	53	3
GGGE	Adrenal function	46 Healthy PMP,	PLACEBO, RLX200, PRM625	DB	2[a]	55	5
GGGJ	Reprod. endocrine function	33 Healthy PreMP,	RLX100, RLX200, RLX400	DB	1-2[a]	34	NA
GGHI	Histomorphometry	17 Healthy PMP,	RLX150	Open	6[b]	61	8
Long-Term Controlled Studies:							
GGGF	Prevention of osteoporosis	601 Healthy PMP,	PLACEBO, RLX030, RLX060, RLX150	DB	24[b]	55	5
GGGG	Prevention of osteoporosis	544 Healthy PMP	PLACEBO, RLX030, RLX060, RLX150	DB	24[b]	54	5
GGGH	Prevention of osteoporosis	619 Healthy PMP, hysterectomized	PLACEBO, RLX060, RLX150, PRM625	DB	24[b]	53	6
GGGM	Histomorphometry	51 Healthy PMP,	RLX060, PRM625	DB	6[b]	64	18
GGGN	Treatment of osteoporosis	143 PMP, Low BMD, ≥1 vertebral fracture	PLACEBO, RLX060, RLX120	DB	12[b]	68	22
GGGR	Calcium kinetics	35 Healthy PMP	RLX060, HRT, No Treatment	Open	6[a]	55	4
GGGY	Cardiovascular surrogates	390 Healthy PMP,	PLACEBO, RLX060, RLX120, HRT	DB	6[a]	59	10
GGGZ	Uterine safety	136 Healthy PMP,	RLX150, HRT	DB	12[b]	56	4

Abbreviations: RLX = raloxifene HCl dose (mg/day); PMP = postmenopausal; PreMP = premenopausal; BMD = bone mineral density; PRM625 = Premarin (conjugated equine estrogens) 0.625 mg/day; HRT = hormone replacement therapy (combined progestin/estrogens administered in a cyclic or continuous combined manner); DB = double blind.

[a] Completed study.

[b] Ongoing study.

Patient Demographics

Characteristics of patients assigned to placebo, raloxifene, estrogen, or HRT for all raloxifene clinical efficacy/safety studies unblinded to the sponsor are summarized in the table below. Of the 3458 female patients, 93.9% were Caucasian and 93.4% were less than 65 years of age, with a mean age of 55.28 years.

Variable	PLACEBO (N=707)	RALOX (N=2104)	EST (N=263)	HRT (N=384)	Total (N=3458)
GENDER					
No. Patients	707	2104	263	384	3458
Female	707 (100)	2104 (100)	263 (100)	384 (100)	3458 (100)
ORIGIN					
No. Patients	707	2104	263	384	3458
African Descent	11 (1.6)	33 (1.6)	6 (2.3)	6 (1.6)	56 (1.6)
Western Asian	2 (0.3)	10 (0.5)	0	0	12 (0.3)
Caucasian	663 (93.8)	1966 (93.4)	252 (95.8)	365 (95.1)	3246 (93.9)
East/Southeast A	9 (1.3)	21 (1.0)	1 (0.4)	4 (1.0)	35 (1.0)
Hispanic	17 (2.4)	60 (2.9)	3 (0.8)	3 (0.8)	82 (2.4)
Other	5 (0.7)	14 (0.7)	2 (0.8)	6 (1.6)	27 (0.8)
AGE					
No. Patients	707	2104	263	384	3458
Mean	55.63	55.14	54.32	56.05	55.28
Median	55.05	54.94	54.01	55.60	55.03
Standard Dev.	5.83	6.11	5.96	5.17	5.96
Minimum					
Maximum					
AGE					
No. Patients	707	2104	263	384	3458
<65	650 (91.9)	1968 (93.5)	250 (95.1)	361 (94.0)	3229 (93.4)
>=65	57 (8.1)	136 (6.5)	13 (4.9)	23 (6.0)	229 (6.6)

Extent of Exposure

The following tables provide data on the extent of exposure to raloxifene

Study Type/ Study Design	≤2 months	>2 months, ≤6 months	>6 months, ≤12 months	>12 months, ≤24 months	>24 months	Total
Clinical Efficacy/Safety Studies						
Primary Safety Database:						
Placebo-Controlled Database	352	204	212	721	233	1722
Estrogen-Controlled Database	157	44	32	185	55	473
HRT-Controlled Database	37	120	312	13	0	482
Subtotal[a]:	371	240	455	734	233	2033
Secondary Safety Database:						
Studies with Varying Populations/Designs	35	6	19	2	0	62
Japanese Studies	83	29	0	34	0	146
Subtotal: Clinical Efficacy/Safety Studies	489	275	474	770	233	2241
Clinical Pharmacology Studies[b]						
Basic Pharmacokinetics and Drug Disposition	54					54
Formulation Bioavailability/ Bioequivalence	252					252
Special Populations	45 (28)[c]					17
Drug Interaction and Probe Studies	55 (14)[c]					41
Subtotal: Clinical Pharmacology Studies	364					364
TOTAL	851 (32.7%)	276 (10.6%)	474 (18.2%)	771 (29.6%)	233 (8.9%)	2605

a Subtotal counts include only unique patients.

b Some patients participated in more than one clinical pharmacology trial, and are counted more than once.

c The number in parentheses represents patients previously counted in the Basic Pharmacokinetics/Drug Disposition or Formulation Bioavailability/Bioequivalence group.

Raloxifene HCl Dosage	≤2 months	>2 months ≤6 months	>6 months ≤12 months	>12 months ≤24 months	>24 months	Total (%)	Patient Years
10 mg	42	0	0	0	0	42 (2.07)	6
30 and 50 mg	59	23	18	175	54	329 (16.18)	470
60 mg	55	110	289	278	95	827 (40.58)	976
100, 120, and 150 mg	50	106	163	281	84	684 (32.32)	832
>150 mg	200	7	4	2	0	213 (8.85)	36
Total	406	246	474	736	233	2095	2320

5. Clinical Studies

PREVENTION OF OSTEOPOROSIS TRIALS

5.1 Study H3S-MC-GGGF

A Long-Term Comparison of Raloxifene Hydrochloride and Placebo in the Prevention of Osteoporosis in Postmenopausal Women 24-Month Interim Analysis

Enrollment started 3/14/94 and the last 24-month subject visit was 9/13/96.

Objectives: The primary objective was to establish the effect of long-term therapy (at least 3 years) with raloxifene, compared with placebo, on lumbar spine and total hip BMD in healthy, postmenopausal women. Secondary objectives included a comparison of the effects of raloxifene compared to placebo on:

- biochemical markers of bone metabolism
- serum lipid levels
- incidence of vertebral deformities (fractures) - after three years of study

Design: This is a multicenter (11 sites in eight European Countries), double-blind, placebo-controlled, block-randomized study with report of 24-month interim data. Subjects were randomized to one of four groups: raloxifene 30mg qd, 60mg qd, 150mg qd, or placebo. All groups are receiving supplemental calcium (any preparation that provides 400 to 600mg/day of elemental calcium). Following the 36-month core period, patients will continue in an additional 24-month double-blind extension period. Study medications were to be discontinued immediately in the event of an illness or condition which led to prolonged immobilization. Subjects who were to undergo surgery were to discontinue study medication approx. 72 hours prior to admittance to the hospital and should not have restarted the medication until they returned to their usual level of activity. If a subject demonstrated an accelerated loss of BMD >6% in one year and/or >10% in two years, the investigator may have decided, in consultation with the sponsor, to withdraw the subject from the study. In the event of any early withdrawal or discontinuation, the patient was to be seen as soon as possible by the investigator and all procedures required at the last visit were to have been performed, if appropriate in the opinion of the investigator or sponsor.

Protocol

Population: The study population consisted of postmenopausal women (estradiol ≤ 73 pmol/L or ≤ 20 pg/ml), years of age who became menopausal years before beginning the study. Women also had lumbar spine BMD measurements (average of L-1 through L-4) in the range of 2.0 standard deviations (SD) above mean peak lumbar spine BMD for premenopausal women (T-score) to 2.5 SD below. Exclusion criteria included: history of estrogen-dependent carcinoma (i.e., breast and endometrium), history of recent venous thrombotic event (VTE) including cerebral vascular accident (subjects with remote history of deep venous thrombosis not likely to recur may have enrolled), current use of phenytion, gabapentin, hypolipidemics, vitamin D (except in multivitamins), use within 6-months of starting study of androgen, calcitonin, systemic steroids, estrogen (other than topical estrogen), and progestin, ever use of bisphosphonate or systemic fluoride (other than dental), and subjects experiencing significant postmenopausal symptoms at the beginning of the study.

Endpoints: The following efficacy measures were obtained:

- lumbar spine and total hip BMD at baseline and every 6 months

- total body and forearm BMD in a subset of subjects
- serum osteocalcin, total and bone-specific Alk Phos, and urinary type I collagen fragment C-telopeptide at baseline and every 3 months
- total cholesterol (TC), low-density (LDL-C), high-density (HDL-C), and triglycerides (TG) at baseline and every 3 months
- lateral radiographs of the lower thoracic and lumbar spine at baseline and after three years of treatment

Statistical Analyses: Both intent-to-treat (LOCF) and completers populations were evaluated. The LOCF population was used as the basis for statistical inference. For the primary efficacy variables, the least-square means were used to test each pairwise comparison at the 0.029 two-sided level of significance. For the secondary efficacy variables, least-square means were used to test each pairwise comparison at the 0.05 level of significance. The changes in lumbar spine and total hip BMD were assessed by comparing the slopes of the regression of BMD versus time on study medication.

Results

Patient Disposition: A total of 601 patients were randomized to one of four groups: 150 to placebo, 152 to 30mg, 152 to 60mg, and 147 to 150mg. The rates of early discontinuation were as follows: 21% placebo, 25% 30mg, 22% 60mg, and 32% 150mg. The majority of the discontinuations (14%) occurred during the first 6 months of the trial and were coded as adverse events. There were no statistically significant differences among the groups for the rates of discontinuation due to adverse events.

Patient Demographics: The baseline demographic characteristics (rounded off means) are shown in the following table.

Variable	Placebo	30mg	60mg	150mg	p-value
Age (yrs)	55	55	55	55	0.06
Caucasian	100%	99%	98%	98%	0.4
BMI (kg/m^2)	25	26	26	26	0.6
Current Smoker	29%	28%	29%	31%	0.9
ETOH >3drinks/wk	27%	37%	25%	26%	0.05
Years PMP	4.5	5.0	5.2	4.6	0.004
Fam hx Osteop	20%	20%	17%	14%	0.7
Thiazide Use	11%	14%	15%	16%	0.9
Normal Baseline Mammogram	65%	64%	75%	68%	0.16
L1-L4 BMD (g/cm^2)	0.94	0.93	0.94	0.94	0.9
Vertebral Fx	19%	18%	17%	26%	0.2

Although some of the above characteristics were statistically significantly different among the groups, the differences are not likely to be of clinical relevance (e.g., age, which when rounded off are the same). The increased incidence of consumption of >3 alcoholic drinks per week in the 30mg group would only diminish efficacy of this dose, and is therefore of less concern from a regulatory perspective. Most importantly, the baseline spinal BMDs, the prevalence of vertebral deformities, and the distribution of T-scores (data not

shown), were not significantly different among groups.

Primary Efficacy Endpoint Outcomes

Unless otherwise indicated, all efficacy results are from the LOCF database. In general, the results from the LOCF analyses were not significantly different from the completers analyses.

Mean Percent Change in BMD

Lumbar Spine: The mean baseline values for LS BMD were similar among the groups. By 6 months post-randomization there were statistically significant increases in LS BMD in the three raloxifene groups and a significant reduction in the placebo group. In general, the reduction in BMD in the placebo group and the increases in BMDs in the raloxifene groups continued to Month 24. The mean percent changes from baseline to Month 24 are shown in the following table.

LUMBAR SPINE BMD

Treatment Group	Mean % Change in BMD Baseline to Month 24	Within Group P	Placebo Comparison P
Placebo n=135	-0.80%	0.003	
30mg n=139	1.3%	<0.001	<0.001
60mg n=133	1.6%	<0.001	<0.001
150mg n=125	2.2%	<0.001	<0.001

Although the mean percent change in LS BMD was statistically significantly greater in the 150mg vs the 30mg group, there were no significant differences between the 150mg and 60mg doses. Of interest, the linear trend test was statistically significant at $p<0.001$.

Total Hip: The mean baseline values for total hip BMD were similar for the four groups. By 12 months post-randomization there were statistically significant increases in BMD for the three raloxifene groups and a significant reduction in BMD in the placebo group. Following an additional 12 months of treatment there was a further reduction in BMD in the placebo patients and continued increases in the three drug-treated groups. The mean percent changes in total hip BMD from baseline to Month 24 are shown in the table below.

TOTAL HIP BMD

Treatment Group	Mean % Change in BMD Baseline to Month 24	Within Group P	Placebo Comparison P
Placebo n=135	-0.9%	0.006	
30mg n=139	1.0%	<0.001	<0.001
60mg n=133	1.6%	<0.001	<0.001
150mg n=125	1.5%	<0.001	<0.001

There were no statistically significant differences between the drug-treated groups; however, the linear trend test was significant at $p<0.001$.

Slope of Regression of BMD vs Time-on-Study

Lumbar Spine: Mean annualized slope values are shown in the table below.

LUMBAR SPINE BMD		
Treatment Group	**Mean Annualized Slope**	**Placebo Comparison P**
Placebo n=135	-0.0068	
30mg n=139	0.0033	<0.001
60mg n=133	0.0057	<0.001
150mg n=125	0.0074	<0.001

The change in the slope in the 150mg group was not statistically significantly different compared to the change in the 60mg group.

Total Hip: The mean annualized slope values are shown in the following table.

TOTAL HIP BMD		
Treatment Group	**Mean Annualized Slope**	**Placebo Comparison P**
Placebo n=135	-0.0056	
30mg n=139	0.0022	<0.001
60mg n=133	0.0047	<0.001
150mg n=125	0.0040	<0.001

Similar to the findings for lumbar spine, there were no significant differences between the 150mg and 60mg doses for the changes in slopes.

Secondary Efficacy Endpoint Outcomes (LOCF)

In general, there were significant relative increases in BMD at the secondary sites for the three raloxifene doses compared to placebo. The table below provides the mean percent changes in BMD from baseline to endpoint for the various secondary efficacy endpoint variables.

Variable	Placebo	30mg	60mg	150mg
Femoral Neck				
baseline	0.75	0.74	0.75	0.75
% change from baseline	-1.339a	0.554b	1.155ab	1.479ab
Trochanter				
baseline	0.66	0.65	0.65	0.65
% change from baseline	-0.623	2.00ab	2.076ab	2.202ab
Intertrochanter				
baseline	1.029	1.030	1.024	1.017

Variable	Placebo	30mg	60mg	150mg
% change from baseline	-0.69	0.956ab	1.755ab	1.383ab
Ward's Triangle				
baseline	0.603	0.590	0.588	0.592
% change from baseline	-0.353	2.441ab	3.665ab	2.983ab
Total Body				
baseline	1.047	1.021	1.022	1.028
% change from baseline	-0.549a	1.245ab	1.419ab	1.860ab
Radial Ultradistal				
baseline	0.343	0.337	0.334	0.339
% change from baseline	-2.295a	-1.383a	0.261b	-1.051
Radial Distal				
baseline	0.431	0.430	0.430	0.437
% change from baseline	-2.015a	-1.765a	-1.469a	-2.146a

a=Within group $p<0.029$; b=Between group vs placebo $p<0.029$

The direction of the drug-associated changes in BMD at the femoral neck, trochanter, intertrochanter, Ward's triangle, and in the total body were the same as those seen with the lumbar spine and the total hip. At all secondary sites, the placebo group sustained reductions in mean BMD. At all sites (except at the radial bone) the drug-treated effects were significantly greater compared with placebo. There were no significant drug effects noted at the distal or ultradistal radial sites. There do not appear to be meaningful differences in BMD between the 60mg and 150mg doses at most of the secondary sites.

Changes in Markers of Bone Metabolism

Serum levels of osteocalcin and bone-specific Alk Phos were measured to assess bone formation and urinary C-telopeptide levels were measured to assess bone resorption. These results were not normally distributed and therefore the sponsor has presented median values rather than means; this is appropriate.

For all markers of bone metabolism, the changes seen with all doses of raloxifene were significantly greater than the changes noted with placebo. With respect to the 60mg dose, osteocalcin levels plateued at 12 months and then rose slightly towards the 24 month time period; Alk Phos levels reached a nadir at 18 months and then rose slightly towards 24 months; and C-telopeptide levels plateued at 12 months, increased at 18 months, and then declined slightly by 24 months. The actual median percentage changes from baseline to endpoint for the bone markers are shown in the table below.

MEDIAN PERCENTAGE CHANGES IN MARKERS OF BONE METABOLISM				
Variable	**Placebo**	**30mg**	**60mg**	**150mg**
Osteocalcin (Ug/L)	-9.4%a	-23.2%ab	-23.1%ab	-28.8%ab
BS-Alk Phos (Ug/L)	-9.7%a	-17.4%ab	-15.0%ab	-21.5%ab
C-telopeptide/Creatinine (Ug/mmol)	-15.1%a	-35.8%ab	-34.0%ab	-40.3%ab

a=within group $p<0.05$; b=comparison with placebo $p<0.05$

It should be noted that the ratio of urine calcium to creatinine in the placebo group was significantly increased at 24 months ($p=0.017$), but there were no significant changes in the raloxifene groups.

Changes in Serum Lipid Levels

The baseline levels of TC, LDL-C, HDL-C, and TG were similar for the four groups. As shown in the table below, raloxifene had modest TC and LDL-C lowering effects when compared to placebo Median levels of HDL-C decreased a small amount and to a similar extent in all groups. And median levels of TG did not change appreciable in any of the groups.

MEDIAN PERCENTAGE CHANGES IN SERUM LIPIDS				
Variable	**Placebo**	**30mg**	**60mg**	**150mg**
TC (mmol/L)	-1%	-5%ab	-6%ab	-10%ab
LDL-C (mmol/L)	-1%	-6%ab	-10%ab	-14%ab
HDL-C (mmol/L)	-5%a	-3%a	-4%	-5%a
TG (mmol/L)	0%	0%	3%	0%

a=within group $p<0.05$; b=comparison with placebo $p<0.05$

The changes from baseline to Month 24 in the median levels of TC and LDL-C were not statistically significantly different between the 60mg and 150mg doses.

Pharmacokinetic Data

Plasma levels of raloxifene and total raloxifene in hydrolyzed plasma (TRHP) were measured in a subset of patients following 3, 6, 12, 18, and 24 months of therapy. Both raloxifene and TRHP levels were highly variable within (coefficients of variation 52% and 43%, respectively) and between individuals

).

SAFETY OUTCOMES

Adverse Events

Deaths: There were no deaths reported to the sponsor as of 9/16/96.

Serious Adverse Events: A total of 59 patients experienced a serious adverse event. The incidence rates among the groups were not significantly different (8%-12%, $p=0.5$). Surgical procedure was the most commonly reported serious adverse event: 9%, 7%, 6%, and 5%, in placebo, 30mg, 60mg, and 150mg,

respectively. Of interest, two placebo and two 30mg subjects were diagnosed with breast carcinoma during the trial. One placebo and two 60mg subjects developed pneumonia during the study.

Discontinuations Due to an Adverse Event: A total of 88 patients discontinued treatment during the first 24 months because of an adverse event. Thirteen percent of the placebo, 16% of 30mg, 12% of 60mg, and 18% of 150mg subjects discontinued because of an adverse event (p=0.5). The most common reason for discontinuation was vasodilatation: 4 placebo, 5 30mg, 3 60mg, and 7 150mg subjects dropped out of the study for this reason. Discontinuations for other reasons were infrequent, and in general, not serious.

Treatment-Emergent Adverse Events: Vasodilatation was by far the most commonly reported treatment-emergent adverse event, with over 20% of subjects in each group reporting this AE. The incidence was slightly higher in the 60mg and 150mg doses compared to placebo; although the differences were not statistically significant. Weight gain was reported by 7% of placebo patients and 15% of 60mg patients.

Vital Signs

When compared to placebo, there were no significant changes in any of the vital signs in the raloxifene-treated groups. It may merit some thought that the drug-treated groups had a greater reduction in mean height at endpoint, when compared with the placebo group; although the differences were not statistically significantly different.

Clinical Chemistries

The following table provides the clinical chemistry variables that changed by a statistically significant degree in the raloxifene groups compared with placebo.

MEAN CHANGES IN CLINICAL CHEMISTRY VARIABLES

Variable	Placebo	30mg	60mg	150mg
Calcium (mmol/L)				
baseline	2.2	2.2	2.2	2.2
change from baseline	0.02a	-0.02ab	-0.03ab	-0.04ab
Phosphorus (mmol/L)				
baseline	1.2	1.3	1.2	1.2
change from baseline	-0.02	-0.04a	-0.05a	-0.07ab
Alk Phos (U/L)				
baseline	69	69	68	68
change from baseline	-1	-8ab	-7ab	-10ab
Total Protein (g/L)				
baseline	71	71	71	71
change from baseline	-1.0a	-1.5a	-2.1ab	-2.2ab
Albumin (g/L)				
baseline	41	40	41	41

MEAN CHANGES IN CLINICAL CHEMISTRY VARIABLES

Variable	Placebo	30mg	60mg	150mg
change from baseline	-0.4	-1.3ab	-1.9ab	-1.8ab
Platelets (GI/L)				
baseline	264	265	266	268
change from baseline	-10.6a	-21.7ab	-25.9ab	-25.1ab

a=within group $p<0.05$; b=comparison with placebo $p<0.05$

The baseline levels of the above variables were similar for the four groups. There were small, but statistically significant reductions, in mean serum calcium levels in the raloxifene-treated groups compared with the placebo-treated group. More importantly, there were significantly more subjects in the raloxifene groups compared to the placebo group who had at least one calcium level below the lower limit of normal, and there was a significant trend with increasing doses of raloxifene ($p=0.008$). Mean serum phosphorus levels were reduced by a small degree in the raloxifene groups relative to placebo; with the changes in the 150mg group reaching statistical significance. However, from a clinical perspective, there were only 3 subjects (one from each raloxifene group) who had at least one phosphorus measurement below the lower limit of normal. As expected from the changes in bone-specific Alk Phos, the levels of serum total Alk Phos were reduced in the raloxifene groups compared to placebo. These changes do not merit concern from a safety standpoint and simply reflect the pharmacological action of the drug on bone resorption. There were relative reductions in the levels of total protein and albumin in the raloxifene groups compared with the changes in the placebo group. The magnitude of the changes is not likely to be of clinical significance. The only significant hematology parameter that was altered following raloxifene treatment was platelet count. Mean reductions of approximately occurred following treatment with all doses of raloxifene; these changes were statistically significant compared with placebo. Four subjects (two in the 30mg and two in the 60mg groups) had at least one platelet count below the lower limit of normal. The effect of raloxifene on platelets will be addressed in greater detail in the overview of safety. There were no significant changes in urinary chemistry variables following treatment with raloxifene.

Sponsor's Conclusions

This 24-month interim analysis demonstrates that therapy with raloxifene attenuates bone loss and lowers serum cholesterol without stimulation of the uterine endometrium in early postmenopausal women.

Medical Officer's Conclusions

The two-year interim data from this study demonstrate that the 30mg, 60mg, and 150mg once-daily doses of raloxifene inhibit both bone formation and resportion and maintain BMD at the lumbar spine and hip over a two-year period. Unlike other skeletal sites, raloxifene did not spare radial bone loss. Although the absolute values for the changes in spinal and hip BMD increased with increasing doses of raloxifene, the 30mg dose was not statistically significantly greater than the 60mg dose, which in turn was not statistically significantly different from the 150mg dose. Raloxifene exhibited a clearly favorable effect on the lipid profile. In a near dose-dependent manner, the drug reduced the levels of TC by and LDL-C by It had no effect on levels of HDL-C and TG, however.

Raloxifene was fairly well tolerated, with vasodilatation being the most commonly reported adverse event. There were small, non-clinically significant reductions in the plasma levels of calcium, phosphorous, total protein, and albumin in the raloxifene-treated groups. The mean value for platelet count was reduced by

5.2 Study H3S-MC-GGGG

A Long-Term Comparison of Raloxifene Hydrochloride and Placebo in the Prevention of Osteoporosis in Postmenopausal Women

Enrollment started 3/7/94 and the last 24-month subject visit was 8/23/96.

Objectives: The primary objective was to establish the effect of long-term therapy (at least 3 years) with raloxifene, compared with placebo, on lumbar spine and total hip BMD in healthy, postmenopausal women. Secondary objectives included a comparison of the effects of raloxifene compared to placebo on:

- biochemical markers of bone metabolism
- serum lipid levels
- incidence of vetebral deformaties (fractures) - after three years of treatment

Design: This is a multicenter (nine sites in North America), double-blind, placebo-controlled, block-randomized study with report of 24-month interim data. Subjects were randomized to one of four groups: raloxifene 30mg qd, 60mg qd, 150mg qd, or placebo. All groups are receiving supplemental calcium (any preparation that provides 400 to 600mg/day of elemental calcium). Following the 36-month core period, patients will continue in an additional 24-month double-blind extension period. Study medications were to be discontinued immediately in the event of an illness or condition which led to prolonged immobilization. Subjects who were to undergo surgery were to discontinue study medication approx. 72 hours prior to admittance to the hospital and should not have restarted the medication until they returned to their usual level of activity. If a subject demonstrated an accelerated loss of BMD >6% in one year and/or >10% in two years, the investigator may have decided, in consultation with the sponsor, to withdraw the subject from the study. In the event of any early withdrawal or discontinuation, the patient was to be seen as soon as possible by the investigator and all procedures required at the last visit were to have been performed, if appropriate in the opinion of the investigator or sponsor. A protocol ammendment was made on Nov. 25, 1996 to extend the study to five years.

Protocol

Population: The study population consisted of postmenopausal women (estradiol ≤ 73 pmol/L or ≤ 20 pg/ml), years of age who became menopausal before beginning the study. Women also had lumbar spine BMD measurements (average of L-1 through L-4) in the range of 2.0 standard deviations (SD) above mean peak lumbar spine BMD for premenopausal women (T-score) to 2.5 SD below. Exclusion criteria included: history of estrogen-dependent carcinoma (i.e., breast and endometrium), history of recent venous thrombotic event (VTE) including cerebral vascular accident (subjects with remote history of deep venous thrombosis not likely to recur may have enrolled), current use of phenytion, gabapentin, hypolipidemics, vitamin D (except in mulitvitamins), use within 6-months of starting study of androgen, calcitonin, systemic steriods, estrogen (other than topical estrogen), and progestin, ever use of bisphosphonate or systemic fluoride (other than dental), subjects experiencing significant postmenopausal symptoms at the beginning of the study, subjects with any endocrine disorder requiring medication (except thyroid replacement), subjects with acute or chronic liver disease (bilirubin >2.0mg/dl, ALT>100U/L, or Alk Phos>300U/L), subjects with serum creatinine >2.0mg/dl, and subjects with abnormal uterine bleeding.

Endpoints: The following efficacy measures were obtained:

- lumbar spine and total hip BMD at baseline and every 6 months
- total body and forearm BMD in a subset of subects at baseline and Month 24
- serum osteocalcin, total and bone-specific Alk Phos, and urinary type I collagen fragment C-telopeptide

at baseline and every 3 months
- total cholesterol (TC), low-density (LDL-C), high-density (HDL-C), and triglycerides (TG) at baseline and every 3 months
- lateral radiographs of the lower thoracic and lumbar spine at baseline and after three years of treatment

Statistical Analyses: Both intent-to-treat (LOCF) and completers populations were evaluated. The LOCF population was used as the basis for statistical inference. For the primary efficacy variables, the least-square means were used to test each pairwise comparison at the 0.029 two-sided level of significance. For the secondary efficacy variables, least-square means were used to test each pairwise comparison at the 0.05 level of significance. The changes in lumbar spine and total hip BMD were assessed by comparing the slopes of the regression of BMD versus time on study medication.

Results

Patient Disposition: A total of 544 subjects were randomized to one of four groups: 136 to placebo, 136 to 30mg, 134 to 60mg, and 138 to 150mg. The percentage of patients in each group who discontinued early were as follows: placebo 27%, 30mg 30%, 60mg 33%, and 150mg 41% (p=0.06). A time to early study discontinuation analysis indicated a significant difference among the groups, with the higher raloxifene doses having higher discontinuation rates. Adverse events were the most common reason for early discontinuation; and the rates were similar among the four groups. Lost-to-follow-up was the reason for discontinuation for 1.5% of placebo, 7.4% of 30mg, and 5.2% of 60mg, and 5.8% 150mg (p=0.15).

Patient Demographics: Baseline demographic characteristics are shown in the following table.

PATIENT DEMOGRAPHIC CHARACTERISTICS

Variable	Placebo	30mg	60mg	150mg	p-value
Age (yrs)	54	54	54	54	0.1
Caucasian	86%	81%	87%	86%	0.8
BMI (kg/m^2)	27	27	27	26	0.5
Current Smoker	18%	23%	17%	205	0.6
ETOH >3drinks/wk	10%	11%	10%	11%	0.9
Years PMP	4.5	4.5	4.7	4.7	0.5
Fam hx Osteop	23%	27%	27%	25%	0.9
Thiazide Use	10%	7%	8%	7%	0.8
Normal Baseline Mammogram	85%	81%	75%	78%	0.2
L1-L4 BMD (g/cm^2)	0.96	0.95	0.95	0.95	0.9
Vertebral Fx	11%	9%	14%	13%	0.5

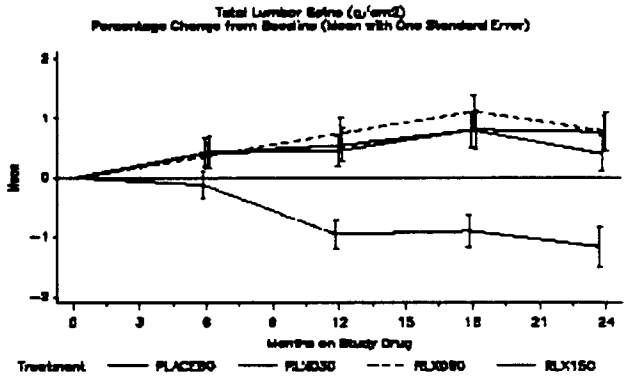
None of the above characteristics were significantly different among the groups. In addition, the distribution of T-scores for LS BMD were not significantly different among groups at baseline.

Primary Efficacy Endpoint Outcomes

Unless otherwise indicated, all efficacy results are from the LOCF database. Compliance did not appear to differ significantly among the groups, nor did calcium intake. Very few subjects had missing BMD measurements and the rates were not significantly different among the groups.

Mean Percent Change in BMD

Lumber Spine: The mean baseline LS BMD values were similar for the four groups (approx. 0.95 g/cm^2). At Month 12, but not Month 6, there was a significant reduction in BMD in the placebo group and significant increases in BMD in the three raloxifene doses. As shown in the figure below, the drug-treated patients had progressive increases in BMD over the first 18 months of the study, with small decreases from Month 18 to 24.



The mean percent changes in LS BMD at Month 24 are shown in the table below. All raloxifene doses were associated with increases in LS BMD and these differences were statistically significantly different compared to the decrease in BMD observed in the placebo group. The mean percent changes in LS BMD among the three raloxifene doses were not statistically significantly different at Month 24; yet, the linear trend test was significant at p<0.001.

LUMBAR SPINE BMD

Treatment Group	Mean % Change in BMD (Baseline to Month 24)	Within Group P	Placebo Comparison P
Placebo n=124	-1.2%	<0.001	
30mg n=119	0.40%	0.2	<0.001
60mg n=118	0.78%	0.004	<0.001
150mg n=119	0.76%	0.03	<0.001

Total Hip: The mean baseline hip BMDs were similar for the groups (approx. 0.85 g/cm^2). By six months significant differences in BMD were noted between all doses of raloxifene and placebo. The magnitude of these differences increased with time, such that by Month 24 the mean BMD in the placebo group decreased from baseline by -0.8% and the mean BMD in the 60mg dose increased by 1.2% (p<0.001) (table below).

TOTAL HIP BMD			
Treatment Group	**Mean % Change in BMD (Baseline to Month 24)**	**Within Group P**	**Placebo Comparison P**
Placebo n=123	-1.76%	0.01	
30mg n=119	1.0%	0.001	<0.001
60mg n=118	1.2%	<0.001	<0.001
150mg n=119	1.6%	<0.001	<0.001

The differences in the mean percent increases in BMD at Month 24 were not statistically significantly different among the three raloxifene doses; although the test for linear trend was significant at $p<0.001$.

Slope of Regression of BMD vs Time-on-Study

Lumber Spine: The mean annualized slope values for lumbar spine are shown below.

LUMBAR SPINE BMD		
Treatment Group	**Mean Annualized Slope**	**Placebo Comparison P**
Placebo n=124	-0.0063	
30mg n=119	0.0019	<0.001
60mg n=118	0.0049	<0.001
150mg n=119	0.0041	<0.001

None of the slope values for the raloxifene doses were significantly different.

Total Hip: The mean annualized slope values for total hip are shown in the following table.

TOTAL HIP BMD		
Treatment Group	**Mean Annualized Slope**	**Placebo Comparison P**
Placebo n=124	-0.0044	
30mg n=119	0.0022	<0.001
60mg n=118	0.0040	<0.001
150mg n=119	0.0062	<0.001

None of the slope values for the raloxifene doses were significantly different.

Secondary Efficacy Endpoint Outcomes

Variable	Placebo	30mg	60mg	150mg
Femoral Neck				
baseline	0.73	0.73	0.74	0.73
% change from baseline	-1.06a	0.51b	1.08ab	1.43ab
Trochanter				
baseline	0.62	0.63	0.63	0.63
% change from baseline	-0.24	1.74ab	1.92ab	2.33ab
Intertrochanter				
baseline	1.01	1.02	1.02	1.01
% change from baseline	-0.94a	0.80ab	1.34ab	1.41ab
Ward's Triangle				
baseline	0.58	0.59	0.60	0.58
% change from baseline	-2.19a	0.12b	0.88b	2.21ab
Total Body				
baseline	1.05	1.06	1.06	1.06
% change from baseline	-0.92a	0.06b	0.39b	-0.19
Radial Ultradistal				
baseline	0.43	0.42	0.42	0.43
% change from baseline	-2.41a	-1.57a	-2.42a	-2.25a
Radial Distal				
baseline	0.65	0.65	0.65	0.66
% change from baseline	-1.94a	-1.06a	-0.95a	-1.16a

There were no significant drug effects on total body BMD or distal and ultradistal radius BMD. In the raloxifene-treated group, the individual skeletal sites that comprise the total hip BMD measurement all sustained relative increases in BMD when compared to the respective changes in the placebo group.

Changes in Markers of Bone Metabolism

The changes in the median values for the markers of bone metabolism from baseline to endpoint are shown below. Baseline values for all parameters were similar for the four groups. There were significant reductions in levels of osteocalcin in all groups with significantly greater reductions in the raloxifene groups compared with placebo. These values reached a nadir at approximately 9 months and remained stable thereafter. Levels of bone-specific Alk Phos decreased from baseline to Month 24 only in the 150mg dose. In all other groups, including placebo, Alk Phos measurements increased during the trial; the increase in the 60mg group was significantly less compared with placebo. Levels of C-telopeptide were the same at baseline in all groups.

Treatment with both drug and placebo was associated with reductions in C-telopeptide levels; but the reductions in the raloxifene groups were significantly greater than placebo. C-telopeptide values reached a nadir early in the trial, approx. 3 months, and remained at that level for the remaining 21 months.

MEDIAN PERCENTAGE CHANGES IN MARKERS OF BONE METABOLISM

Variable	Placebo	30mg	60mg	150mg
Osteocalcin (Ug/L)	-19.7%a	-33.9%ab	-31.7%ab	-38.4%ab
BS-Alk Phos (Ug/L)	11.1%a	7.7%a	0.9%b	-12.2%b
C-telopeptide/Creatinine (Ug/mmol)	-9.1%	-33.6%ab	-29.7%ab	-32.8%ab

a=within group p<0.05; b=comparison with placebo <0.05

Changes in Serum Lipid Levels

Baseline levels of lipids were similar for the four groups. The changes in lipids from baseline to endpoint are shown in the table below. There were small relative improvements in the levels of TC and LDL-C in the raloxifene groups compared with placebo. Levels of HDL-C decreased by a small extent in all groups, with no significant differences noted among groups. The levels of TG did not change in any of the groups.

MEDIAN PERCENTAGE CHANGES IN SERUM LIPIDS

Variable	Placebo	30mg	60mg	150mg
TC (mmol/L)	-0.5%	-3.3%ab	-3.2%ab	-5.4%ab
LDL-C (mmol/L)	1.6%a	-4.3%b	-4.1%b	-7.3%ab
HDL-C (mmol/L)	-3.9%a	-3.5%a	-2.6%	-1.4%
TG (mmol/L)	0.05	1.3%	1.5%	0.0%

a=within group p<0.05; b=comparison with placebo p<0.05

SAFETY OUTCOMES

Adverse Events

Deaths: There were two deaths reported in this interim analysis.

One patient was a 49-year-old Caucasian female who died from hepatic failure. This patient was randomized to 30mg qd of raloxifene. The sponsor's summary of her records indicates that she admitted, after the trial began, to chronic alcohol ingestion and to being homeless. Her MCV at enrollment (6/6/94) was elevated at as was her GGT these abnormalities are consistent with, among other things, excessive alcohol intake. She was diagnosed with squamous cell cancer of the head and neck on 1/9/95 and experienced a subsequent depression. On 1/17/95 she was taken to an emergency room in a confused and agitated state. Upon admission to the hospital she was diagnosed with hepatic failure - with an acetaminophen level of and a positive hepatitis A antibody (IgM).

Given the patient's history of heavy alcohol ingestion, and the investigator's statement that the patient

discontinued her raloxifene two months prior to admission to the hospital with hepatic failure, it is unlikely that the drug was related to her death.

The second patient who died during this trial was a 55-year-old Caucasian female who died from an auto accident after 456 days on study. The sponsor states that they have had limited success obtaining information from the investigator regarding any antecedent events to the accident (e.g., syncope, chest pain). However, the patient did not report any cardiovascular adverse events during the trial. The limited data preclude making an educated assessment of drug-event causality.

Serious Adverse Events: The percentages of patients in each group with at least one serious adverse event were similar (8%-10%). The most common COSTART term was surgical procedure: 6% of patients in the 60mg group and 6.6% in the placebo group. A review of each case did not reveal any particular trend or pattern for a specific surgical procedure. The events ranged form appendectomy to removal of a lipoma. Most of the events listed were rare with one or two patients in a group affected, and there were no statistically significant differences among groups in the incidence rates for individual serious adverse events.

Discontinuation Due to an Adverse Event: The most common adverse event that was associated with early withdrawal was vasodilatation: 2.2% of placebo, 0% 30mg, 1.5% 60mg, and 3.6% 150mg (p=0.16). Of interest, two raloxifene patients (30mg and 150mg) withdrew because of endometrial cancer, and one raloxifene patient (60mg) withdrew because of abnormal liver function tests.

Treatment-Emergent Adverse Events: The following table provides the adverse events that were associated with an overall p value ≤ 0.20 and where the frequency that was greater in the 60mg compared to the placebo group.

TREATMENT-EMERGENT ADVERSE EVENTS

Event	Placebo	30mg	60mg	150mg	p value
Vasodilatation	12.5%	10.3%	22.4%	18.1%	0.03
Arthralgia	12.5%	11.0%	14.2%	5.8%	0.14
Myalgia	5.1%	13.2%	9.7%	11.6%	0.13
Arthritis	4.4%	9.6%	6.0%	2.2%	0.06
Rash	3.7%	7.4%	6.0%	2.2%	0.19
Contact Derm	0.0%	2.2%	0.7%	3.6%	0.09

The time-to-event curves for vasodilatation indicate that the percent of patients reporting this AE remains fairly constant after 13 months of therapy; whereas, the placebo rate becomes steady after approximately 6-9 months of treatment. Of importance, none of the above adverse events appear serious in nature.

There were no significant differences among the groups in the reported severity of Aes.

The following is a list of medications that were used by greater percentage of patients in the 60mg vs the placebo group and the overall p value was ≤ 0.20.

Rolaids 3.7% vs 0%, p=0.03
Penicillin 3.7% vs 1.5%, p=0.14
Paracetamol 29% vs 24%, p=0.04

Nambumetone 4.5% vs 2.2%, p=0.19

Vital Signs

The baseline values for pulse, systolic, and diastolic blood pressure were comparable for the four groups. The mean changes from baseline to endpoint for all vital signs were very small (not clinically significant) and similar among the four groups. While not statistically significantly different, the drug-treated groups had greater reduction in mean height than did the placebo group.

Clinical Chemistries

The following table provides the clinical chemistry variables that changed by a statistically significant degree in the raloxifene groups compared with placebo.

MEAN CHANGES IN CLINICAL CHEMISTRY VARIABLES

Variable	Placebo	30mg	60mg	150mg
Calcium (mmol/L)				
baseline	2.3	2.3	2.2	2.3
change from baseline	0.03	0.003b	-0.01b	-0.01b
Phosphorus (mmol/L)				
baseline	1.3	1.3	1.3	1.3
change from baseline	-0.004	-0.01	-0.02	-0.05ab
Alk Phos (U/L)				
baseline	77	76	73	73
change from baseline	-2	-9ab	-8ab	-10ab
Total Protein (g/L)				
baseline	71	72	71	71
change from baseline	-0.1	-2.0ab	-1.3ab	-1.5ab
Albumin (g/L)				
baseline	42	41	41	41
change from baseline	-0.2	-1.6ab	-1.3ab	-1.5ab
CPK (U/L)				
baseline	83	84	81	81
change from baseline	7.0a	-2.0b	-3.0ab	-6.0ab
Uric Acid (umol/L)				
baseline	274	276	283	283
change from baseline	5	12a	11a	15ab

As seen in the previous trial - GGGF - there were small mean reductions from baseline to endpoint in serum values for calcium, phosphorus, Alk Phos, total protein, albumin, and CPK in the 60mg group vs placebo. There appeared to be a dose-related trend for phosphorus and CPK, but not for the other analytes. In general, one would not consider these mean changes of clinical significance. The categorical analyses of high and low values did not indicate that significantly more raloxifene-treated subjects compared to placebo had low values for calcium, phosphorus, Alk Phos, total protein, albumin, or CPK. There were however, significantly more 60mg vs. placebo subjects who had at least one high AST value during the trial (5.6% vs 0.8%, p=0.03). No dose-related trend was apparent. Similarly, although the changes in the mean values were not different, more 60mg vs. placebo subjects had at least one high ALT value during the trial (5.6% vs 1.5%, p=0.07); again, no dose-related trend was apparent. Unlike trial GGGF, the reduction in platelet counts in the raloxifene groups were not statistically significantly different when compared with placebo.

The sponsor identified six raloxifene subjects who developed significantly elevated LFTs during the trial. A brief summary of these cases is provided below.

Subject 001-1377 (raloxifene HCl 60 mg) experienced a moderate increase in ALT accompanied by smaller increases in AST , GGT and alkaline phosphatase) at Visit 6 (12-month visit). AST and ALT levels had returned to within normal limits by Visit 7 and remained at the upper end of normal through 24 months, while GGT levels increased further to at 24 months. The subject denied alcohol use at baseline, and no further comments were made about alcohol intake during the study. The laboratory abnormalities were determined by the investigator to be clinically significant at Visits 6 through 8. An abdominal ultrasonogram performed prior to Visit 10 reportedly was normal. No diagnosis was made. Notably the subject used acetaminophen and ibuprofen as needed after Visit 4 and also had a Hepatitis B vaccine prior to Visit 5. In the absence of a clear etiology, a causal relationship with raloxifene therapy cannot be excluded in this case.

Subject 003-464 (raloxifene HCl 60 mg) experienced a small increase in transaminase levels prior to randomization: AST from , ALT from suggesting an underlying liver abnormality. Transaminase concentrations fluctuated after baseline, but remained below 100 U/L . Levels returned to normal at Visit 9 (AST ALT increased again at Visit 10 (AST ALT , and fell again at Visit 11 (AST ALT . Other liver-derived analytes did not change significantly during therapy. The subject had a history of cholecystectomy and was obese(BMI at baseline. She denied alcohol use. Two antibiotics (cefaclor andciprofloxocin) were used briefly prior to Visits 6 and 7, respectively, and may have contributed to the increases in transaminase levels. No diagnosis was made. In the absence of a clear etiology, a causal relationship with raloxifene therapy cannot be excluded in this case. Subject 003-502 (raloxifene HCl 30 mg) experienced a marked increase in AST , ALT , GGT alkaline phosphatase (and total bilirubin) at the 18 month visit. Each of these analytes was normal prior to that time and had returned to normal by Visit 10. This subject was diagnosed with cholelithiasis (presumably causing cholestatic jaundice) and underwent cholecystectomy after Visit 10.

Subject 003-371 (raloxifene HCl 30 mg) experienced a moderate increase (approximately 4-fold over baseline) in transaminase concentrations at Visit 7, with peak values for AST) and ALT noted at Visit 9 and slightly lower values at Visit 10. GGT and total bilirubin levels also increased over the same time period, with peak levels of at Visit 9. The subject had denied alcohol use at baseline, but upon notification of the abnormal test results, admitted that alcohol intake had increased (extent not specified). Possibly also related to the abnormality was underlying mixed connective tissue disease, diagnosed as a pre-existing condition after randomization, and obesity (BMI increased from . While alcohol alone can cause the laboratory abnormalities noted in this case, a relationship with raloxifene therapy cannot be excluded with certainty.

Subject 004-2934 (raloxifene HCl 30 mg) experienced gradual increases in AST and ALT with peak values of ,respectively at Visit 7 (15-month visit). Other liver-derived analytes did not increase concomitantly. Transaminase concentrations returned to within normal limits by Visit 9 (21-month visit). The subject did not drink alcohol, and no diagnosis was made explaining the transaminase increase. Notably, the subject started several medications shortly prior to the transaminase increase noted at Visit 7: loratidine, terfenadine/pseudoephedrine, clemastine/phenylpropanolamine, rimantidine, cefaclor, losartan, and famotidine. The medications were not all used concomitantly; however, it is possible that one or more of these medications was causally related to the transaminase elevation. Nevertheless, a relationship to raloxifene therapy cannot be excluded with certainty in this case.

Subject 007-2538 (raloxifene HCl 60 mg) experienced an abrupt increase in AST) and ALT concentrations noted at the 18-month visit, with a smaller (1.5-fold) increase in GGT. Liver-derived analytes were all normal prior to that time. Briefly, the subject was asymptomatic and no etiology of the elevated liver transaminase concentrations was readily apparent. A liver ultrasonogram examination was reportedly normal. Raloxifene was discontinued, and transaminase concentrations were checked approximately 2 weeks later. Levels had increased further to , respectively, for AST and ALT. The subject never restarted raloxifene. Approximately 6 months later, her liver tests had returned to normal range. The temporal pattern of transaminase increase argues against a causal relationship to raloxifene therapy, since transaminases increased initially after 18 months of therapy and further significantly increased 2 weeks after raloxifene discontinuation. Nevertheless, such a relationship cannot be excluded with certainty.

Sponsor's Conclusions

In summary, raloxifene provided as 30, 60, or 150mg once daily for 24 months was safe, very well tolerated, and effective in preventing bone loss associated with postmenopausal estrogen deficiency in generally healthy women. Based on these results and because of its ease of use - once daily monotherapy without regard to meals and without the need for gynecological surveillance -raloxifene appears to be an important alternative to estrogens for the prevention of postmenopausal osteoporosis. Whether raloxifene will also prove effective in preventing other disorders associated with estrogen deficiency, such as cardiovascular disease, remains to be seen; however, the extension of this osteoporosis prevention study through five years will continue to provide valuable data on the chronic effects of raloxifene in multiple target organ systems.

Medical Officer's Conclusions

In this study of primarily middle-aged Caucasian women, 30mg, 60mg, and 150mg once-daily doses of raloxifene were superior to placebo in attenuating bone loss, although the absolute increases from baseline to Month 24 in lumbar spine BMD were less than 0.8% in the active-treatment groups. For unknown reasons, in all three raloxifene groups, increases in lumbar spine BMD peaked at the 18 month time point and then declined by Month 24. It does not appear that early withdrawal of patients explains this finding. Continued study of these patients will show whether this relative decline in BMD persists with continued treatment. Of note, the changes in lumbar spine BMD were not significantly different among the three raloxifene groups. In general, raloxifene treatment had beneficial effects on BMD measured at other skeletal sites. Like study GGGF, all patients in this study had reductions in radial BMD. The reductions in the levels of osteocalcin and C-telopeptide are consistent with raloxifene's inhibition of bone resorption and formation. Active treatment was associated with statistically significant, but small, reductions in the levels of TC and LDL-C, whereas the mean levels of HDL-C and TG remained fairly stable in the placebo and raloxifene groups.

Aside from an increased incidence of vasodilatation in the raloxifene 60mg and 150mg groups, the drug was well tolerated. As noted in the previous trial, there were minor changes in the plasma levels of calcium, total protein, and albumin in the raloxifene-treated groups. There were no significant reductions noted in platelet count in the raloxifene-treated subjects.

5.3 Study H3S-MC-GGGH

A Long-Term Comparison of Raloxifene HCl, Placebo, and Premarin® in the Prevention of Osteoporosis in Postmenopausal, Hysterectomized Women

Enrollment started 3/25/94 and the last 24-month patient visit was 8/7/96.

Objectives: The primary objective was to establish the effect of long-term therapy with raloxifene on lumbar spine and hip BMD in healthy, postmenopausal, hysterectomized women. The primary comparisons are between raloxifene and placebo and between an unopposed estrogen (Premarin) and placebo. Secondary objectives included a comparison of the effects of raloxifene compared with placebo or Premarin on:

- biochemical markers of bone metabolism
- serum lipid levels
- the incidence of vetebral fractures after three years of treatment

Design: This is a multicenter, multinational, double-blind, placebo-controlled, block-randomized study with report of 24-month interim data. Subjects were randomized to one of four treatment groups: placebo, raloxifene 60mg qd, raloxifene 150mg qd, or Premarin 0.625 mg qd. All groups are receiving supplemental calcium (any preparation that provides 400 to 600mg/day of elemental calcium). Following the 36-month core period, patients will continue in an additional 24-month double-blind extension period. Study medications were to be discontinued immediately in the event of an illness or condition which led to prolonged immobilization. Subjects who were to undergo surgery were to discontinue study medication approx. 72 hours prior to admittance to the hospital and should not have restarted the medication until they returned to their usual level of activity. If a subject demonstrated an accelerated loss of BMD >6% in one year and/or >10% in two years, the investigator may have decided, in consultation with the sponsor, to withdraw the subject from the study. In the event of any early withdrawal or discontinuation, the patient was to be seen as soon as possible by the investigator and all procedures required at the last visit were to have been performed, if appropriate in the opinion of the investigator or sponsor. After a subject completes the 36-month core portion of the study, she may elect to continue into a 24-month extension phases.

Protocol

Population: The study population consisted of postmenopausal women (estradiol ≤ 73 pmol/L or ≤ 20 pg/ml and FSH ≥ 40IU/L), with a history of having had a hysterectomy no more than 15 years before beginning the study and aged Women also had lumbar spine BMD measurements (average of L-1 through L-4) in the range of 2.0 standard deviations (SD) above mean peak lumbar spine BMD for premenopausal women (T-score) to 2.5 SD below. Exclusion criteria included: women who did not qualify for therapy according to the prescribing information for Premarin, history of estrogen-dependent carcinoma (i.e., breast and endometrium), history of recent venous thrombotic event (VTE) including cerebral vascular accident (subjects with remote history of deep venous thrombosis not likely to recur may have enrolled), current use of phenytion, gabapentin, hypolipidemics, vitamin D (except in mulitvitamins), use within 6-months of starting study of androgen, calcitonin, systemic steriods, estrogen (other than topical estrogen), and progestin, ever use of bisphosphonate or systemic fluoride (other than dental), subjects experiencing significant postmenopausal symptoms at the beginning of the study, subjects with any endocrine disorder requiring medication (except thyroid replacement), subjects with acute or chronic liver disease (bilirubin >2.0mg/dl, ALT>100U/L, or Alk Phos>300U/L), and subjects with serum creatinine >2.0mg/dl.

Endpoints: The following efficacy measures were obtained:

- lumbar spine and total hip BMD at baseline and every 6 months

- total body and forearm BMD in a subset of subjects at baseline and Month 24
- serum osteocalcin, total and bone-specific Alk Phos, and urinary type I collagen fragment C-telopeptide at baseline and every 3 months
- total cholesterol (TC), low-density (LDL-C), high-density (HDL-C), triglycerides (TG), and apolipoproteins A1 and B at baseline and every 3 months
- lateral radiographs of the lower thoracic and lumbar spine at baseline and after three years of treatment
- cost effectiveness at selected English-speaking sites

Statistical Analyses: Both intent-to-treat (LOCF) and completers populations were evaluated. The LOCF population was used as the basis for statistical inference. For the primary efficacy variables, the least-square means were used to test each pairwise comparison at the 0.029 two-sided level of significance. For the secondary efficacy variables, least-square means were used to test each pairwise comparison at the 0.05 level of significance. The changes in lumbar spine and total hip BMD were assessed by comparing the slopes of the regression of BMD verus time on study medication.

Results

Patient Disposition: A total of 619 patients were randomized: 152 to placebo, 152 to 60mg, 157 to 150mg, and 158 to Premarin. The rates of early discontinuation were as follows: placebo 32%, 60mg 30%, 150mg 28%, and Premarin 25% (p=0.6). The most common reason for early withdrawal was adverse event and the rates across groups were similar (approx. 13-16%).

Patient Demographics: Aside from abnormalities in the baseline breast exam (approx. twice as many abnormalities were reported for subjects assigned to Premarin (12%) compared to the other groups), the baseline demographic characteristics were similar for the four groups (table below). The distribution of T-scores was similar for the four groups, with the majority of patients having baseline T-scores in the range of -

Variable	Placebo	60mg	150mg	Premarin	p-value
Age (yrs)	53	53	53	53	0.9
Caucasian	96%	96%	95%	96%	0.7
BMI (kg/m^2)	28	27	27	27	0.8
Current Smoker	20%	19%	20%	22%	0.9
ETOH >3drinks/wk	26%	24%	24%	21%	0.8
Years PMP	6	6	6	7	0.3
Fam hx Osteop	18%	19%	19%	18%	1.0
Thiazide Use	10%	13%	11%	11%	0.8
Normal Baseline Mammogram	78%	76%	81%	74%	0.5
Years PHyst	9	9	9	9	0.5
L1-L4 BMD (g/cm^2)	0.98	0.97	0.97	0.97	0.6
Vertebral Fx	10%	15%	16%	17%	0.3

Primary Efficacy Endpoint Outcomes

Unless otherwise indicated, all efficacy results are from the LOCF database. In general, the results from the LOCF and completers analyses yielded similar results.

Mean Percent Change in BMD

Lumbar Spine: The baseline values for LS BMD were similar for the four groups. After six months of treatment with placebo there was a mean percent reduction in LS BMD of 0.4% (p=0.07); whereas six months of treatment with 60mg of raloxifene was associated with a mean percent increase in BMD of 0.8% (p=0.002), and the mean percent BMD increased by 0.6% in the 150mg group (p=0.01). After six months of treatment with Premarin, the mean percent BMD increased by 2% (p<0.001). Surprisingly, the mean percent changes in BMD in the two raloxifene groups decreased with continued treatment, such that by Month 24 the mean percent change in BMD in the 30mg group was a nonsignificant 0.2% and only 0.5% in the 150mg group (p=0.1). However, these changes were significant when compared with the reduction noted in the placebo group (p<0.001). The 4% mean increase in LS BMD from baseline to Month 24 in the Premarin group was clearly superior to placebo (p<0.001) and to both raloxifene doses (p<0.001).

Total Hip: The baseline values for total hip BMD were not significantly different among the groups. In the placebo group there was a steady decline in the mean percent BMD, such that at Month 24 the mean change from baseline was -0.5% (p=0.06). In both raloxifene groups the mean percent increase in BMD peaked at Month 18 and then declined by Month 24. The mean percent increases in BMD in the 60mg and 150mg groups at Month 24 were 0.8% (p=0.002) and 0.5% (p=0.04), respectively. When compared with placebo, the changes in BMD observed in the raloxifene groups were statistically significant. The greatest percent increase in total hip BMD was seen with Premarin therapy: 2.4% increase at Month 24 (p<0.001). This increase was significant when compared to the change in the placebo group (p<0.001) and when compared to the changes in both raloxifene groups (p<0.001). The changes in hip BMD in the two raloxifene groups were not significantly different from one another.

Slope of Regression of BMD vs Time-on-Study

Lumbar Spine: The mean annualized slope values are shown in the following table.

LUMBAR SPINE BMD

Treatment Group	Mean Annualized Slope	Placebo Comparison P
Placebo n=130	-0.0108	
60mg n=131	-0.0009	<0.001
150mg n=136	0.0012	<0.001
Premarin n=137	0.0172	<0.001

APPEARS THIS WAY ON ORIGINAL

The change in slope values for the two raloxifene dose were not significantly different. It is of interest to recognize that the slope is negative for the 60mg raloxifene dose; this is a result of the decline in the mean percent BMD from Month 6 to Months 12, 18, and 24.

Total Hip: The mean annualized slope values are shown in the table below.

TOTAL HIP BMD		
Treatment Group	**Mean Annualized Slope**	**Placebo Comparison P**
Placebo n=130	-0.0030	
60mg n=130	0.0024	0.002
150mg n=134	0.0012	0.02
Premarin n=136	0.0098	<0.001

Unlike LS BMD, the slope was positive for total hip BMD in the 60mg group. Similar to the LS analysis, the two raloxifene doses were not significantly different.

Secondary Efficacy Endpoint Outcomes

The table below provides the mean percent changes in BMD at secondary sites (baseline to endpoint). The baseline BMD values were not significantly different among the groups. The patterns of change in BMD at the secondary sites in the four groups were similar to those noted in the lumbar spine. The placebo group had a steady decline in BMD throughout the 24 months. The BMD values in the raloxifene groups peaked at 12 or 18 months and then declined at Month 24. In contrast, in the Premarin group, BMD at all sites except Ward's triage, increased steadily throughout the 24 months. From a statistical standpoint, both raloxifene doses outperformed placebo ($p<0.05$) and Premarin outperformed both placebo and raloxifene at all secondary sites.

MEAN PERCENT CHANGE IN BMD (g/cm^2)(Baseline to Endpoint)				
Variable	**Placebo**	**60mg**	**150mg**	**Premarin**
Femoral Neck				
baseline	0.75	0.76	0.75	0.74
% change from baseline	-1.32a	0.30bc	0.41bc	1.50ab
Trochanter				
baseline	0.66	0.66	0.67	0.66
% change from baseline	-0.68	0.62bc	1.23abc	3.25ab
Intertrochanter				
baseline	1.05	1.06	1.07	1.05
% change from baseline	-0.45	0.86abc	0.36c	2.28ab
Ward's Triangle				
baseline	0.61	0.61	0.60	0.59
% change from baseline	-3.17a	0.52b	0.04bc	2.01ab

a=p≤ 0.029 within group comparison, b=p≤ 0.029 vs placebo, c=p≤ 0.029 vs Premarin

Changes in Markers of Bone Metabolism

Serum levels of osteocalcin and bone-specific Alk Phos were measured to assess bone formation and urinary C-telopeptide levels were measured to assess bone resporption. These results were not normally distributed and therefore the sponsor has presented median values rather than means.

The table below provides the median percentage change in the markers of bone metabolism (baseline to endpoint). The baseline values for all three parameters were similar in the four groups.

MEDIAN PERCENTAGE CHANGES IN MARKERS OF BONE METABOLISM

Variable	Placebo	60mg	150mg	Premarin
Osteocalcin (Ug/L)	-17.0%a	-29.2%abc	-33.5%abc	-49.3%ab
BS-Alk Phos (Ug/L)	-4.5%	-11.2%bc	-13.8%bc	-44.8%ab
C-telopeptide/Creatinine (Ug/mmol)	5.5%a	-2.4%c	-28.4%abc	-58.9%ab

a=p≤ 0.029 within group comparison, b=p≤ 0.029 vs placebo, c=p≤ 0.029 vs Premarin

These findings are similar to the BMD results and suggest that raloxifene reduces bone resorption and formation to a greater extent than placebo; although, to a lesser extent than Premarin. In general, the two raloxifene doses had similar effects on the above bone markers.

Changes in Serum Lipid Levels

The baseline values for TC, LDL-C, HDL-C, and TG were similar in the four groups. Compared with placebo, both doses of raloxifene significantly lowered levels of TC, LDL-C, and Apo B. Compared with Premarin, the raloxifene groups had significantly greater reductions in levels of TC and similar degrees of lowering of LDL-C levels. Levels of HDL-C decreased in the placebo and raloxifene groups; whereas, they increased in the Premarin group. Apolipoprotein A1 levels did not change in the placebo group and increased in the raloxifene and Premarin groups. The increases in the raloxifene groups were significant when compared to placebo, but significantly less than the change in the Premarin group. Levels of TG decreased in the placebo group and increased in the raloxifene and Premarin groups. The increase was greatest in the Premarin group with lower dose-related increases in the raloxifene groups. The median percentage changes in lipid levels (baseline to endpoint) are presented in the following table.

MEDIAN PERCENTAGE CHANGES IN SERUM LIPIDS

Variable	Placebo	60mg	150mg	Premarin
TC (mmol/L)	-0.85%	-4.1%abc	-7.7%abc	-2.2%
LDL-C (mmol/L)	1.3%	-8.2%ab	-11.6%	-10.4%ab
HDL-C (mmol/L)	-4.2%a	-2.7%c	-3.2%ac	6.3%ab
TG (mmol/L)	-3.8%	5.1%ac	14.6%abc	25.7%ab
Apo A1 (g/L)	0.05	-3.5%abc	-5.8%abc	16.7%ab
Apo B (g/L)	3.7%a	-2.3%abc	-5.5%abc	1.2%

a=p≤ 0.029 within group comparison, b=p≤ 0.029 vs placebo, c=p≤ 0.029 vs Premarin

Changes in Markers of Hemostatic Activation and Fibrinolysis

As part of addendum H3S-MC-GGGH(a)(5), six markers of hemostasis/fibrinolysis were assessed at investigative site 241 throughout the first 24 months of study (N = 56). The following plasma analytes were determined at baseline, 6, 12, and 24 months: fibrinogen, prothrombin fragment 1.2 (F1+2), thrombin-antithrombin III complex (TAT), plasmin-alpha- 2 antiplasmin complex (PAP), tissue plasminogen activator antigen (tPA), and plasminogen activator inhibitor-1 antigen (PAI-1). Briefly, the results were as follows (all inferences from median percentage change from baseline, ITT analysis):

· Fibrinogen: Significant decreases in fibrinogen were observed for all active therapies by 12 months and were sustained through 24 months in the following order: Premarin (-9.09%) (p=0.002), raloxifene HCL 150 mg (-17.1%) (p<0.001), and raloxifene HCl 60 mg (-17.9%) (p<0.001). Each active therapy was significantly different from placebo (p=0.035), but not from each other, at endpoint.
· F1+2: Both raloxifene HCl 150 mg and Premarin caused significant increases of 32% and 37% from baseline, respectively, by 12 months (p=0.008), while levels did not change with raloxifene HCl 60 mg therapy. Levels in each group had decreased by 24 months and no group was significantly different from no change (ie, baseline value) at endpoint.
· TAT: There were no statistically significant changes from baseline through endpoint within or between therapy groups.
· PAP: Statistically significant reductions in PAP of 12% and 19% from baseline to endpoint were observed in the raloxifene HCl 60-mg and 150-mg groups, respectively (p=0.025). The raloxifene HCl 150-mg group was significantly different from placebo at endpoint (p=0.029) with no other between-group differences noted.
· tPA: Premarin significantly reduced tPA antigen by 6 months and further reduced the level through endpoint, resulting in a decrease from baseline to endpoint of 22% (p=0.010). Premarin was significantly different from each of the other groups at endpoint (p£0.015). tPA antigen did not change significantly with raloxifene therapy.
· PAI-1: An increase in PAI-1 antigen from baseline was noted at 6 (31%) through 24 months (59%) in the placebo group (p=0.047). In contrast, PAI-1 antigen decreased significantly with Premarin therapy by 6 months (43%) and was sustained through 24 months (41%) (p<0.050). PAI-1 did not change significantly with raloxifene therapy. Premarin was significantly different from each of the other groups at endpoint (p<0.024).

SAFETY OUTCOMES

Adverse Events

Deaths: As of 8/7/96, one patient randomized to the 150mg group died as a result of a car accident.

Serious Adverse Events: From a statistical standpoint there were no significant (p<0.05) group differences in the incidence of serious adverse events. The most commonly reported serious adverse event was surgical procedure: 3.9% placebo, 8.6% 60mg, 9.6% 150mg, and 10.1% Premarin (p=0.18). Of interest, there were four cases of either breast carcinoma or neoplasm: one in the 150mg group and three in the Premarin group. Two cases of DVT were reported: one in the 60mg and one in the 150mg groups.

Discontinuation Due to an Adverse Event: Approximately of the patient discontinued early because of an adverse event. There were no significant differences in the rates of discontinuation among the groups (p=0.9). The most common adverse event associated with early withdrawal was vasodilatation: 2.6% placebo, 2.6% 60mg, 3.2% 150mg, and 0% Premarin (p=0.2). Weight gain was the second most common: 1.3% placebo, 0.7% 60mg, 0.6% 150mg, and 1.9% Premarin (p=0.7). Three subjects discontinued because of LFT abnormalities: one in 60mg and two in 150mg. One patient in the 60mg group withdrew early because of liver damage.

Treatment-Emergent Adverse Events: The following adverse events occurred with a greater frequency in the 60mg vs the placebo group and the overall p value (four-way comparison) was ≤ 0.20: Vasodilatation, accidental injury, breast pain, leg cramps, flatulence, laryngitis, and sleep disorder. A comprehensive discussion of treatment-emergent adverse events is provided in the overall summary of safety.

Concomitant Medications: The following is a list of medications used more often by patients in the 60mg group compared to the placebo patients:

Paracetamol 31% vs 19%, p=0.08
Atenolol 5.9% vs 0.7%, p=0.02
Magnesium/aluminum hydroxide 3.9% vs 0.0%, p=0.002

Vital Signs

Mean body weight increased by approximately 1.0 kg in the two raloxifene groups ((p<0.05), but did not increase significantly in the placebo or Premarin groups. The only statistically significant difference in blood pressure was noted in the 150mg group: systolic blood pressure increased by 2.2 mmHg (p<0.05 vs placebo).

Clinical Chemistries

The following table provides the clinical chemistry variables that changes by a statistically significant degree in the raloxifene groups compared with placebo. Not shown are the small changes in the mean levels of RBCs, Hb, and Hct observed in both raloxifene groups as well as in the Premarin group. The reductions in these parameters were very small and of the same magnitude in the raloxifene and Premarin groups.

MEAN CHANGES IN CLINICAL CHEMISTRY VARIABLES

Variable	Placebo	60mg	150mg	Premarin
Calcium (mmol/L)				
change from baseline	0.03a	-0.01b	-0.01b	-0.01b
Phosphorus (mmol/L)				
change from baseline	0.01	-0.05abc	-0.07ab	-0.10ab
Total Protein (g/L)				
change from baseline	-0.22	-1.97ab	-2.10ab	-1.46ab
Albumin (g/L)				
change from baseline	-0.48	-1.52abc	-2.1ab	-2.18ab
Uric Acid (umol/L)				
change from baseline	5.2	14.0ac	4.9	-2.8

a=p≤ 0.05 within group comparison, b=p≤ 0.05 vs placebo, c=p≤ 0.05 vs Premarin

Significantly more subjects in the Premarin group had a phosphorus level below normal at any time during the trial compared to placebo or raloxifene.

The following is a summary of the cases who developed abnormal LFTs during the trial.

Subject 600-2105 (raloxifene HCl 60-mg group) had slightly abnormal serum transaminase concentrations at baseline and experienced marked increases by 3 months. She eventually discontinued early due to the increase in these analytes. Although a drug relationship could not be excluded with certainty due to the absence of an identified etiology for hypertransaminasemia, the onset of abnormalities prior to randomization and the lack of improvement more than 2 months after stopping raloxifene argue against a causal relationship in this case.

Subject 964-0487 (raloxifene HCl 150-mg group) was noted to have normal serum transaminase concentrations at baseline and elevated concentrations by 3 months. She discontinued early shortly afterward due to the increase in these analytes. A drug relationship could not be excluded in this case.

Subject 017-3344 (raloxifene HCl 60-mg group) was noted to have abnormal transaminase concentrations at Visit 1 (AST,) and Visit 2 (AST, ; ALT) and frankly elevated concentrations by 3 months. Transaminase concentrations further increased by the 6-month visit (AST, ALT,) and by the 9-month visit were considered clinically significant by the investigator, although the subject remained asymptomatic. Transaminase concentrations remained elevated and the subject was asked to stop raloxifene after Visit 9 (21-month visit). On repeat testing following a 4-week drug "holiday," AST and ALT . Levels reportedly declined even further following continuation of the drug "holiday" through 12 weeks . The subject restarted raloxifene soon afterward. Transaminase levels again increased near peak highs. Study drug was again stopped and tests repeated 7 weeks later; levels had decreased again: AST and ALT A causal relationship to drug is almost certain in this case.

Sponsor's Conclusions

In summary, raloxifene therapy provided as 60 or 150 mg once daily for 24 months was safe, well-tolerated, and effective in preventing bone loss associated with postmenopausal estrogen deficiency in healthy women without a uterus. Based on these results and because of its ease of use-once daily monotherapy without regard to meals- raloxifene appears to be an important alternative to estrogens for the prevention of postmenopausal osteoporosis. Whether raloxifene will also prove to be effective for preventing other disorders associated with estrogen deficiency, such as cardiovascular disease, remains to be seen; however, the extension of this osteoporosis prevention study through 5 years will continue to provide valuable data on the chronic effects of raloxifene in multiple target organ systems.

Medical Officer's Conclusions

This study provides comparative data on the efficacy of raloxifene and unopposed estrogen (0.625mg Premarin). In terms of changes in lumbar spine and hip BMD, treatment with Premarin was far superior to both doses of raloxifene and placebo, while both doses of raloxifene were better than placebo. Of some concern is the downward slope of the line depicting the change in lumbar spine BMD in the 60mg group at the 24 month time point. Premarin treatment was associated with significant increases in the mean levels of HDL-C, Apo A1, and TG when compared with both doses of raloxifene and placebo. The ratios of TC/HDL-C and LDL-C/HDL-C improved by a significantly greater degree following treatment with Premarin as compared with raloxifene and placebo treatment. Regarding coagulation-related parameters, Premarin, in comparison with raloxifene, significantly decreased the levels of tPA and PAI-1, whereas there were no significant differences between Premarin and raloxifene in the changes in fibrinogen, F1+2, TAT, or PAP. These results indicate that, when compared with placebo, raloxifene favorably effects the lipoprotein lipid profile; although not to the same extent as Premarin..

As the sponsor has pointed out, in general, Premarin and raloxifene induced similar reductions in the levels of serum calcium, phosphorus, total protein, and albumin. The magnitude of these changes are not likely to be of

clinical significance.

5.4 Histomorphology Study

Study GGGM

Raloxifene Hydrochloride versus Estrogen: Histomorphologic Effects in Bone in Postmenopausal Women

Objective: To determine the histomorphologic effects of short-term (six months) therapy with raloxifene on the iliac crest in postmenopausal women. The primary histomorphologic effects evaluated include activation frequency and bone formation rate referent to bone volume.

Methods: This is an ongoing Phase 2, single-center, double-blind, randomized study. The study consists of five phases: a screening phase, a 24-week double-blind therapy phase, a six- to 10-week therapy follow-up phase, an optional 18-month open-label extension phase, and a 2-week extension follow-up phase. This report includes data and analyses for visits one through nine (screening, double-blind therapy, and follow-up therapy phases) only. A total of 79 subjects were screened and 51 subjects were randomly assigned to one of two double-blind therapy groups (60-mg dose of raloxifene HCl or 0.625-mg dose of Premarin). Subjects were treated daily for 24 weeks during double-blind therapy.

Inclusion criteria included: Women with their last menstrual period at least five years before beginning the study and women with lumbar spine BMD measurements in the range of 1 standard deviation above mean peak lumbar spine BMD for premenopausal women to three SD below. Exclusion criteria included subjects with a dietary calcium intake less than 500mg/day or greater than 1500 mg/day, subjects with known or a suspected history of breast cancer, subjects with vetebral fractures as determined by recent height loss and symptoms, and subjects with hip fractures within 1 year of beginning the study (refer to prevention protocols for additional exclusion criteria).

Iliac crest bone biopsies were performed at Visits 1 and 6. The bone biopsies were performed using a 2.5mm Jamshidi needle following double-tetracycline labeling. The bone biopsies were obtained from the anterior superior iliac crest. Specimens were ethanol fixed and then dehydrated in progressive ethanol washes, embedded in methyl methacrylate and sectioned at 5 micron and 10 micron thicknesses. Sections were stained with toluidine blue, and static parameters were measured using a Zeiss Videoplan image analysis system.

Results: Fifty-one subjects were randomly assigned to therapy: 25 to 60mg qd of raloxifene and 26 to 0.625mg qd of Premarin. During the six-month double-blind period eight subjects discontinued early: seven in the Premarin group and one in the raloxifene group; seven were due to an adverse event. The baseline demographic features of the two groups were reasonably well matched. All of the patients were Caucasian, the mean age was ≈64 years, and the average number of years postmenopausal was ≈17. Twenty-two subjects had evaluable bone biopsy data.

The changes from baseline to endpoint in some key dynamic indices are shown in the following table.

Test	Therapy	n	Baseline	Change (p-value[a])	p-value[b]
Bone formation rate/bone volume (%/year)	Raloxifene	11	33.2	-2.96 (0.7)	0.05
	Premarin	8	58.4	-31.26 (0.04)	

Test	Therapy	n	Baseline	Change (p-value[a])	p-value[b]
Activation frequency (per year)	Raloxifene	10	0.58	-0.08 (0.6)	0.05
	Premarin	8	1.06	-0.63 (0.03)	
Mineralization lag time (days)	Raloxifene	11	16.8	3.8 (0.5)	0.4
	Premarin	8	15.8	12.0 (0.1)	
Mineral appositional rate (micron/day)	Raloxifene	11	0.59	-0.01 (0.8)	0.1
	Premarin	8	0.63	-0.11 (0.04)	

a= Within-group p-value, b=Between-group p-value (ANOVA)

The direction of the changes in the above indices were similar in the raloxifene and Premarin groups, while the magnitude of the changes were greater in the Premarin vs. the raloxifene group. The differences between the groups were not statistically significant, however (after adjustment for baseline differences in bone formation rate/bone volume and activation frequency were made, the differences between groups were no longer significant; ANCOVA p-values of 0.4 and 0.5 for bone formation and activation frequency, respectively). Wall thickness increased by approximately 2.3 microns in both groups and the increase was of borderline significance in the raloxifene group (p=0.09), but not in the Premarin group (p=0.3). The sponsor reported that there was no evidence of osteomalacia, marrow fibrosis, cellular toxicity, or woven bone seen in any of the samples.

Discussion: Limited conclusions can be made from the results of this interim report. The period of study was relatively short, the number of subjects exposed to raloxifene was small, and there was no placebo arm. Nevertheless, limitations aside, the data presented do not signal that raloxifene has a detrimental effect on bone histomorphometry. Results from the ongoing study, GGHF, will provide needed information about the effects of the raloxifene on bone histromorphometry in comparison with placebo.

5.5 Cardiovascular Study

Study H3S-MC-GGGY

Comparison of Raloxifene Hydrochloride, Hormone Replacement Therapy, and Placebo in Healthy, Postmenopausal Women: Assessment of Serum Lipids and Coagulation Parameters

Objectives: The primary objectives of this study were to assess the effect of raloxifene, compared with placebo, on serum lipids and coagulation parameters in healthy postmenopausal women and to establish the overall safety of raloxifene administration in these women.

Design: This was a Phase 2, multicenter, double-blind, controlled, randomly assigned, parallel study. A total of 390 subjects were randomly assigned to one of four therapy groups: raloxifene HCl 60 mg/day, raloxifene HCl 120 mg/day, HRT (0.625 mg of Premarin ® and 2.5 mg of Provera ® given in a continuous combined fashion), or placebo. Subjects were treated daily for 6 months in each therapy group.

Protocol

Population: The study population consisted of postmenopausal women aged Subjects had to have had their last menstrual period at least one year before beginning the study. Postmenopausal status was verified by FSH level ≥ 30IU/L and serum estradiol ≤ 40 pg/mL. The following exclusion criteria were used to screen participants: Women who did not qualify for therapy according to the prescribing information for Premarin and Provera. Women with known, suspected, or history of carcinoma of the breast or estrogen-dependent neoplasia (eg, endometrial carcinoma), unless it was an in situ lesion of the uterus that had been cured by removal of the diseased organ. Women with history of any cancer within the previous 5 years, except for excised superficial lesions (eg, basal cell carcinoma or squamouscell carcinoma of the skin). Women with abnormal uterine bleeding of an unknown etiology. Women with a history of deep venous thrombosis, thromboembolic disorders, or cerebral vascular accident. Women with acute coronary disease (eg, acute myocardial infarction) or unstable angina occurring less than 1 year before beginning the study. Current systemic treatment with any of the following medications at the beginning of the study: Hypolipidemics or Warfarin. Treatment with any of the following medications more recently than 3 months before beginning the study: Androgen, Corticosteroids (systemic), Estrogen, Progestin. Women experiencing intolerable postmenopausal symptoms at the beginning of the study. Women who had diabetes mellitus or other endocrine disorders requiring pharmacological therapy except for thyroid replacement (see below). Women who were not biochemically euthyroid (thyroid-stimulating hormone [TSH] within the normal range) or who had changes in replacement therapy in the 3 months before the start of the study. Women with acute or chronic liver disease (bilirubin >34 μmol/L or >2.0 mg/dL, alanine transaminase [ALT] >100 U/L, or alkaline phosphatase >300 U/L). Women who had impaired kidney function (serum creatinine >180 μmol/L or >1.5 mg/dL). Women who consumed an excess of alcohol or abused drugs. (An excess of alcohol was defined as more than four of any one of the following or a combination of more than four of the following per day: 1 oz of distilled spirits, 12 oz of beer or wine cooler, or 4 oz of wine.). Women experiencing more than 15% fluctuation in weight during the preceding 2 years. Women with a body mass index (BMI) value <18 or >31 kg/m 2. Women who, in the opinion of the investigator, were poor medical or psychiatric risks for therapy with an investigational drug. And women who had participated in any other raloxifene clinical trial.

Endpoints: Serum lipids and coagulation markers were measured at baseline and at the end of each 3-month visit interval. Measurements were obtained following a 12-hour fast. Blood for lipids was obtained on 3 days during a 7-day period and blood for coagulation markers was obtained on 2 of those 3 days at each visit . All clinical efficacy laboratory tests were performed by a central laboratory. Serum lipids included total cholesterol, HDL-C, LDL-C, very low-density lipoprotein cholesterol (VLDL-C), triglycerides, HDL-C2 , high density lipoprotein cholesterol3 (HDL-C3) , Lp(a), and apolipoproteins A1 and B. Coagulation markers included F1+2 , fibrinopeptide A (FPA), fibrinogen, and plasminogen-activator inhibitor 1 (PAI-1). In an addendum, one investigative site measured endothelium-dependent vasodilatation in response to reactive hyperemia and endothelium-independent vasodilatation in response to sublingual nitroglycerin at baseline and Month 3. Brachial artery reactivity was assessed using high-resolution ultrasonography.

Laboratory Methodology

At each of the therapy visits, serum lipids were collected on 3 days during the 7-day visit period and coagulation markers were collected on 2 of those 3 days. The three serum lipid samples were pooled, resulting in one serum lipid measurement for each visit. The mean of the two coagulation markers measurements was calculated and used as the single measurement.

Lipids: Sample Collection: For all lipid analyses, three fasting serum specimens were drawn within a 7-day period of time at Visits 2, 3, and 4. Non-fasting specimens were excluded. The serum was separated and frozen at -70°C until assayed. The samples were put in the refrigerator to thaw the night before testing. The tubes were checked visually by trained technologists for lipemia, hemolysis, and samples with inadequate volume (less than 500 ml). All suitable serum samples from the same visit were then pooled to minimize the effects of day-to-day variation. Samples with inadequate volume and samples that had any visual lipemia were excluded from the pool. The following lipid analyses were conducted using pooled serum by a central laboratory. Total Cholesterol: Total cholesterol was quantitated using an enzymatic reaction with cholesterol esterase and cholesterol oxidase on the The intra-assay precision was ; inter-assay precision ranged from CV. HDL-C (Including Subfractions): Total HDL-C and HDL-C subclasses (HDL-C2 and HDL-C3) were quantitated using to bind VLDL-C and LDL-C to form an insoluble complex that was sedimented by low speed centrifugation at 4°C. The supernatant solution containing total HDL was assayed for cholesterol. The supernatant was then treated with additional to precipitate HDL-C2 which was removed by centrifugation. HDL-C3 was quantitated as cholesterol in the supernatant. HDL-C2 was calculated as the difference between total HDL and HDL-C3 . The intra-assay precision for HDL-C was /; inter-assay precision ranged The intra-assay precision for HDL-C3 cholesterol was and inter-assay precision ranged from LDL-C: LDL-C was calculated using the Friedewald equation (below). Since the LDL-C value was a calculated value, there is no inter- or intra-assay data available. *LDL-C = (Total cholesterol) - (HDL-C) - (Triglycerides x 0.20)* VLDL-C: of lipoproteins by ultracentrifugation is based upon the principle of lipoprotein separation based upon their differing hydrated densities. After centrifugation, VLDL-C and were in the upper layer of the tube. With a minimum 12-hour fast, were eliminated and the upper layer was VLDL-C. The tube was sliced and the bottom layer was assayed for cholesterol. The result (HDL-C plus LDL-C) was then subtracted from the total cholesterol to yield the VLDL-C. Since the VLDL-C value was calculated, there is no inter- or intra-assay data available. Typical intra-assay precision for the bottom fraction was typical inter-assay precision was Lipoprotein a: Lp(a) was quantitated by an The assay was performed on the . Typical intra-assay precision for typical inter-assay precision was Apolipoproteins A1 and B: Apolipoproteins A1 and B were quantitated using rate nephelometry. Apolipoprotein A1 or B antibody was added to the subject specimen and the intensity of light as it was

scattered by particles in the suspension was measured. The increase in light scatter resulting from the antigen-antibody reaction was converted to a peak rate signal that was a function of the Apolipoprotein A1 or B concentration in the specimen. Typical intra-assay precision for Apolipoprotein A1 , typical inter-assay precision was Typical intra-assay precision for apolipoproteins B was typical inter-assay precision was

Coagulation Factors: Sample Collection: Two samples for coagulation factors were collected within the same week as the lipid samples. Unlike the lipid samples, the two aliquots were NOT pooled; each sample was assayed. Prothrombin Fragment 1 and 2: F1+2 was quantitated using an After incubation with labeled antibody, a was added. After further incubation and the addition of stopping solution, samples were measured . The concentration of subject samples was read from a which was performed using the standards included in the test kit. Typical intra-assay precision ranged from typical inter-assay precision ranged from . Fibrinopeptide A: FPA was quantitated using a modified procedure based on a competitive technique. The FPA contained in the standard and test sample was first allowed to bind to a known amount of rabbit anti-FPA antibody. An aliquot of this mixture was then transferred to a solid support that had been previously coated with pure synthetic FPA, so the antibody sites that remain unoccupied during the first phase were allowed to bind to synthetic FPA. Finally, a substrate was added and the color change produced was inversely proportional to the concentration of FPA in the samples. Typical intra-assay precision for this assay ranged from , inter-assay precision ranged from . Plasminogen Activator Inhibitor 1: PAI-1 activity was quantitated using a two-stage, In stage one, a fixed amount of tissue plasminogen activator (tPA) was added to the plasma sample and allowed to react with the PAI-1 present. Then the sample was acidified to destroy alpha-2-antiplasmin and other plasmin inhibitors which would interfere with the assay, and the sample was subsequently diluted. In stage two, the residual tPA activity was measured by adding the sample to a The residual tPA activity in the sample catalyzed the conversion of plasminogen to plasmin, which hydrolyzed the The amount of color developed was proportional to the amount of tPA activity in the sample. The PAI-1 content of the sample was then identified as the difference between the amount of tPA added and the amount of tPA found. Typical intra-assay precision for PAI-1 ranged from typical inter-assay precision ranged from . Fibrinogen: Fibrinogen was quantitated on an

, to measure clotting time based on the principle as a clot forms. passing through a plasma sample was monitored by a The enzyme thrombin converted the soluble plasma protein fibrinogen into its insoluble polymer, fibrin. Fibrinogen was quantitated by measuring the clotting time of dilute plasma to which excess thrombin was added. The clotting time obtained was then compared with that of a standardized fibrinogen preparation. Typical intra-assay precision for fibrinogen ranged from typical inter-assay precision ranged from

Endothelial-Dependent Vasodilatation and Endothelial-Independent Vasodilatation: Studies were done in a temperature-controlled vascular research laboratory as previously published. All subjects were placed in a supine position. Vascular reactivity was studied in a conduit vessel, the brachial artery. An imaging study of the brachial artery was done using a that was equipped with a 7.5 MHZ . Baseline images of the brachial artery were obtained proximal to the antecubital fossa. Imaging of the artery was done longitudinally, allowing clear visualization of the posterior wall intima-lumen interface and the anterior wall media-adventitial interface. Endothelium-dependent vasodilatation was assessed by measuring the change in the caliber of the brachial artery during reactive hyperemia, a maneuver that increased flow through the conduit segment being studied (flow-mediated vasodilatation). To create this stimulus, a cuff placed on the upper arm was inflated to

supra systolic pressure for 5 minutes, thereby occluding flow to the forearm. This resulted in dilatation of downstream forearm resistance vessels. After cuff deflation, reactive hyperemia occurred as brachial artery blood flow increased to accommodate the dilated resistance vessels. Imaging of the brachial artery was continually done for the 5-minute period after cuff deflation until basal conditions were re-established. Then sublingual nitroglycerin (at a dose of 0.4 mg) was administered to assess endothelium-independent vasodilatation. The artery was studied for an additional 5 minutes. Blood pressure and heart rate were monitored continuously throughout the procedure using a All images were recorded on Super VHS videotape for subsequent analysis, transferred to CD-ROM, and analyzed on a computer equipped with a video frame grabber. The recorded images were analyzed by an investigator blinded to therapy assignment. Previous studies have shown that the peak diameter change during reactive hyperemia occurs approximately 1 minute after cuff deflation and 3 minutes after nitroglycerin administration. These time points were used in the current study. Images corresponding to the end of the T-wave on a simultaneous electrocardiographs were selected. Image analysis was then done using proprietary analysis software that measures the distance between user-defined regions of interest. Arterial walls were defined by tracing lines along the intima and media of the proximal and anterior arterial walls. Ten to 20 paired measurements were made along a 10-mm length and averaged. Three separate images were used to determine arterial diameter. Measurements were reported in millimeters using calibration factors derived from real-time ultrasonography. In the investigator's laboratory, the technique has a variability of 0.0 + 0.1 mm.

The methods employed to measure lipids and coagulation parameters are well established and technically sound.

Statistical Analyses: The assumption of normality of the distributions for residuals of actual values, change from baseline and percentage change from baseline were checked using the Shapiro-Wilk test. The homogeneity of variances were verified using Bartlett's and Levene's test. All the primary efficacy variables were significantly non-normally distributed and some of the variables had heterogeneity of variances. For each variable, from among a group of potential transformations, the most appropriate transformation was chosen, which resulted in homogeneity of variances (and if possible normality).The primary analysis was the change from baseline (Visit 2) to endpoint, according to the ITT principle. In addition, analyses were conducted at Visits 3 and 4 for the change-from-baseline values. The four therapy groups were compared using an ANOVA model with therapy and investigator as fixed effects in the model. Initially, a term for therapy-by-investigator interaction was included and tested for statistical significance at the 0.10 level of significance. If it was not statistically significant, it was deleted from the model. The overall therapy comparisons were performed at the two-sided 0.05 level of significance. The statistical significance of each pairwise comparison was dependent on the statistical significance of the overall therapy comparison (Fisher's protected least significant difference rule). Although there were four therapy groups, the primary comparisons were paired comparisons between each dose of raloxifene and the placebo therapy group. Consequently, no adjustments for multiple comparisons were performed.

Results

Patient Disposition: Three hundred ninety patients were randomized to treatment: 98 to placebo, 95 to 60mg, 101 to 120mg, and 96 to HRT. Approximately 17% of the patients discontinued early. The most common reason for early discontinuation was adverse event. Seven placebo, six 60mg, seven 120mg, and 19 HRT subjects dropped from the study because of an adverse event (p=0.003).

Patient Demographics: The baseline demographic characteristics (racial origin, age, height, and weight) of the subjects at study entry were not statistically significantly different among the four therapy groups. The mean age at study entry was 58.97 years. Most of the subjects were Caucasian (88.7%). The therapy groups were comparable at baseline with respect to smoking habits, alcohol consumption, and family history of

cardiovascular disease. Of the 390 randomly assigned subjects, 81% were non-smokers or quit smoking within 6 months of randomization, 23.3% consumed more than 3 drinks daily (moderate to heavy drinkers) and 55.4% had a family history of cardiovascular disease (first generation, second generation, or both). Years postmenopausal were significantly different among the therapy groups (p=0.031), with the HRT group having a greater number of years postmenopause: placebo-9.72 years, raloxifene HCl 60 mg/day-10.91 years, raloxifene HCl 120 mg/day-9.84 years, and HRT-12.59 years. These differences should not materially affect the results. Subjects had similar baseline systolic and diastolic blood pressures and the baseline dietary intake of macro nutrients were not significantly different among groups.

Primary Efficacy Endpoint Outcomes

Serum Lipids (see table below)

Because the values for the lipids were heavily skewed, the medians will be reported rather than the means.

TC: The baseline values for TC were not significantly different among groups: approximately 5.9 mmol/L. All three active-treatment groups had significant within group reductions in TC levels. Compared with placebo, all three active-treatment groups had significant reductions in the levels of TC, although the differences between HRT and the two raloxifene groups were not significantly different.

HDL-C: The baseline HDL-C levels were similar among the groups: approx. 1.38 mmol/L. Only the HRT and 120mg groups had significant within group increases in levels of HDL-C. The HRT group had the greatest percentage increase in HDL-C levels, and this increase was significantly greater than the change observed in the placebo, 60mg, and 120mg groups. The median changes in HDL-C were not significantly different between the placebo and raloxifene groups.

LDL-C: The baseline levels of LDL-C were comparable among groups: approx. 3.9 mmol/L. At endpoint, there were significant within group reductions in LDL-C in the HRT and raloxifene groups. While the changes from baseline to endpoint were not significantly different between the HRT and raloxifene groups, all three groups did have significant reductions in LDL-C when compared with placebo.

TG: The baseline concentrations of TG were similar among the groups: approx. 1.29 mmol/L. At endpoint, there was a significant within group increase in TG levels in the HRT group, but no significant changes in the placebo or raloxifene groups. The increase in the HRT group was significantly greater than the changes observed in the placebo and raloxifene groups.

MEDIAN PERCENTAGE CHANGES IN SERUM LIPIDS (baseline to endpoint)

Variable	Placebo	60mg	120mg	HRT
TC (mmol/L)	0.9	-6.6ab	-6.7ab	-4.4ab
LDL-C (mmol/L)	1.0	-10.9ab	-11.4ab	-12.7ab
HDL-C (mmol/L)	0.9	0.7c	3.9ac	10.6ab
TG (mmol/L)	-0.3	-4.1c	-0.5c	20.0ab
LDL/HDL	-0.5	-10.4abc	-13.3abc	-20.9ab

a=within group p<0.05, b=comparison with placebo p<0.05, c=comparison with HRT p<0.05

The table below provides the median percentage changes in secondary lipid parameters.

MEDIAN PERCENTAGE CHANGES IN SERUM LIPIDS (baseline to endpoint)

Variable	Placebo	60mg	120mg	HRT
VLDL (mmol/L)	0.0	-5.2	-7.7	0.6
HDL-C2 (mmol/L)	0.0	15.4ac	16.7a	33.3ab
HDL-C3 (mmol/L)	0.0	-2.5bc	0.0	2.7
Lp(a) (g/L)	3.3	-4.1ab	-4.3b	-16.3ab
Apo A1 (mmol/L)	-0.01	0.04c	0.07abc	0.18ab
Apo B (mmol/L)	-0.23	-8.8abc	-8.6ab	-3.6

a=within group $p<0.05$, b=comparison with placebo $p<0.05$, c=comparison with HRT $p<0.05$

Compared with placebo, the 60mg dose of raloxifene significantly reduced the levels of Apo B, Lp(a), and HDL-C_3. The major differences between HRT and raloxifene were the significant increases in the levels of HDL-C_2, HDL-C_3, and Apo A1 in the HRT group.

Coagulation Markers:

MEDIAN PERCENTAGE CHANGES IN FIBRINOLYSIS PARAMETERS
(baseline to endpoint)

Variable	Placebo	60mg	120mg	HRT
F_{1+2} (nmol/L)	-2.7	2.4	1.4	16.0a
FPA(ng/ml)	13.3a	8.8	8.8	16.1a
Fibrinogen (g/L)	-2.1	-12.2abc	-13.5abc	-2.8
PAI-1 (u/mL)	-9.5	-2.1c	-2.4c	-29.0ab

a=within group $p<0.05$, b=comparison with placebo $p<0.05$, c=comparison with HRT $p<0.05$

F_{1+2}: The baseline levels were similar among groups. The only significant difference in the percentage change from baseline to endpoint was a within-group increase in the HRT group.

FPA: The baseline levels were comparable among groups. There were significant within-group increases in the levels of FPA in the placebo and HRT groups, but not in the raloxifene groups. There were no significant between-group differences.

Fibrinogen: The baseline values were not significantly different among groups. The levels of fibrinogen decreased significantly in the two raloxifene groups. And these reductions were significant in comparison to the changes noted in the placebo and HRT groups.

PAI-1: The baseline concentrations were similar for the four groups. There was a significant within-group reduction in PAI-1 levels in the HRT group and this reduction was significant when compared with the changes in the placebo and raloxifene groups.

Endothelial-Dependent and Independent Vasodilatation: Brachial artery diameter was measured before and after administration of nitroglycerin and reactive hyperemia. In no case were there significant between group changes in these parameters of vasodilatation.

SAFETY OUTCOMES

There were no deaths reported. Of note, six HRT subjects discontinued the study because of vaginal bleeding; no subjects in the placebo or raloxifene groups withdrew for this reason.

A full safety review of this study is included in the overview of safety section.

Medical Officer's Conclusions

The results of this study confirm those from the prevention trials, and demonstrate that raloxifene has a favorable effect on the lipoprotein lipid profile. To the extent that one can draw conclusion from this relatively small study, in comparison with raloxifene, HRT therapy produced a more favorable change in the lipid profile because of its ability to raise levels of HDL-C. Raloxifene did not significantly lower levels of PAI-1, as did HRT, but fibrinogen was reduced following treatment with raloxifene. Whether raloxifene's favorable effect on the lipid profile will translate into a reduction in the risk for cardiovascular disease remains to be seen.

APPEARS THIS WAY
ON ORIGINAL

6.0 Overview of Efficacy

Three studies were conducted to examine raloxifene's effect on BMD in relatively early post-menopausal women. Studies GGGF and GGGG were nearly identical in design - comparing placebo vs raloxifene 30mg, 60mg, and 150mg once-daily doses- while study GGGH compared placebo with Premarin and raloxifene 60mg and 150mg once-daily doses.

As expected, the placebo-treated (calcium) women had progressive reductions in BMD at the lumbar spine and hip in the range over a two-year period. In contrast, raloxifene-treated patients had small, but significant increases in lumbar spine and hip BMD, with placebo-subtracted differences of approximately 2% at the lumbar spine and at the hip. Of note, raloxifene did not have a positive effect on radial bone.

Roughly of the women in these trials were osteopenic at baseline Following two-years of treatment, approximately 8% of the osteopenic women in the placebo group developed osteoporosis defined as a T-score below -2.5; whereas approximately 3% of raloxifene-treated subjects met the BMD criteria for osteoporosis (p=0.01). In another categorical analysis of pooled data from studies GGGF and GGGG, 68% of patients treated with 60mg of raloxifene had a maintenance or an increase in LS BMD during two years of treatment vs. 37% of subjects receiving placebo (p<0.01).

There is some evidence from these trials that raloxifene increases BMD in a dose-related manner. Therefore, the 150mg dose may offer greater efficacy than the 60mg dose in terms of the prevention of osteoporosis (fracture reduction). Yet, this Reviewer supports the sponsor's current proposal to market the 60mg once-daily dose for the prevention of osteoporosis, in part, because of an interim analysis from the treatment study GGGK, which indicates that the high dose of raloxifene is associated with a significantly higher rate of mortality than the 60mg dose [relative risk = 2.6, (1.3, 5.0)]. A re-assessment of the most appropriate dose for the prevention of postmenopausal osteoporosis should be done when fracture data and a complete safety database become available.

That the 60mg dose of raloxifene attenuates bone loss in early post-menopausal women is not debatable. It remains to be seen, however, whether the relative increase in BMD seen in the patients who received two years of raloxifene is maintained with longer-term treatment; and more importantly, will raloxifene reduce the risk for osteoporotic fracture?

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The following table summarized the main two-year efficacy findings from the three prevention trials.

OVERVIEW OF EFFICACY (MEAN PERCENT CHANGES FROM BASELINE TO ENDPOINT)

Tx Group	%ΔLSBMD•	%ΔHipBMD•	%ΔOsteocal	%ΔTelopep	%ΔTC	%ΔLDL	%ΔHDL	%ΔTG
GGGF								
Placebo	-0.8	-0.9	-9.4	-15.1	-1	-1	-5	0
30mg	1.3	1.0	-23.2	-35.8	-5	-6	-3	0
60mg	1.6	1.6	-23.1	-34.0	-6	-10	-4	3
150mg	2.2	1.5	-28.8	-40.3	-10	-14	-5	0
[illegible]								
[illegible]	-1.2	-1.8	-19.7	-9.1	-0.5	2	-4	0.1
[illegible]	0.4	1.0	-33.9	-33.6	-3	-4	-4	1
[illegible]	0.8	1.2	-31.7	-29.7	-3	-4	-3	2
[illegible]	0.8	1.6	-38.4	-32.8	-5	-7	-1	0
[illegible]								
[illegible]	-1.6	-0.5	-17.0	5.5	-0.9	1	-4	-4
[illegible]	0.2	0.8	-29.2	-2.4	-4	-8	-3	5
[illegible]	0.5	0.5	-33.5	-28.4	-8	-12	-3	15
[illegible]	3.8	2.4	-49.3	-58.9	-2	-10	6	26

•Baseline to Month 24

Raloxifene's ability to maintain bone mineral density over a two-year period is due to its inhibition of bone resorption and formation - as shown by the reduction in the levels of C-telopeptide and osteocalcin.

Regarding lipoprotein lipid metabolism, data from the three prevention studies and study GGGY, provide consistent evidence that raloxifene produces modest reductions in the levels of total and LDL cholesterol and has little to no effect on the levels of TG and HDL-C.

7.0 Overview of Safety

As of 16 October 1996, 49 raloxifene clinical studies had been initiated in 27 countries, pursuant to its potential use in osteoporosis. Among the 49 studies, 31 were clinical efficacy/safety studies, and 18 were clinical pharmacology studies. Of the 31 clinical efficacy and safety studies, 15 were completed, 15 were ongoing, and 1 was discontinued (due to lack of enrollment). Of the 15 ongoing studies, a total of 8 were still blinded to the sponsor (hereafter, these studies are referred to as triple-blind studies). All studies except 6 clinical pharmacology studies included only women.

As of the study cutoff dates, a total of 2605 patients had received at least one dose of raloxifene. An additional estimated 5548 patients had received raloxifene in 7 of the 8 triple-blind studies (sponsor remains blinded to treatment).

The sponsor has categorized the safety data into two sets: primary and secondary. The primary dataset is comprised of 12 studies of varying design: placebo-controlled, estrogen-controlled, and hormone replacement therapy (HRT)-controlled studies. Three studies —GGGB, GGGC, and GGGE — are 2-month studies; while the other studies are at least 6 months in duration. The sponsor has chosen to pool the safety data from the three short-term studies separately from the six-month studies. This is an acceptable approach. The secondary database includes studies of diverse patient populations and designs (e.g., Japanese studies).

Extent of Exposure

A totalof 12,505 patients were assigned to a treatment, and 12,495 patients were exposed to a study drug. Of the 12,505 patients, 8486 were still blinded to the sponsor and were assumed to have taken at least one dose of any study drug. In all the other studies, a total of 4009 patients were exposed to study drug, including 17 patients lost to follow-up (no further contact was able to be obtained after the patient received study medication). These 17 patients were assumed to have taken at least one dose and were included in the count of exposed patients.

Excluding the ongoing studies that the sponsor remains blinded to, a total of 2605 patients comprising the primary and secondary databases have been exposed to raloxifene. The majority (47.8%) of these patient were exposed for a duration of 6-24 months, with 8.9% exposed for greater than 24 months. An additional 364 patients have been exposed to raloxifene for less than two months in clinical pharmacology studies.

Exposure by Dose

Excluding the Japanese studies, approximately 41% of patients were exposed to 60mg of raloxifene, with 32% exposed to either 100mg, 120mg, or 150mg of raloxifene. Just over 9% of patients were exposed to doses greater than 150mg. A total of 706 patients have been exposed to placebo (excluding Japanese studies), 262 to estrogen, and 380 to HRT.

Patient Demographics

For the clinical efficacy and safety studies that are unblinded to the sponsor as of the cuttoff dates above, all patients were female. The majority (>90%) were Caucasian, with a mean age of 55 years Approximately 6% of the patients were 65 years of age or older.

General Comments about Calculations for Special Safety Issues

Clinical laboratory tests were assayed by a central laboratory except for studies GGGH, GGGX, and GGGY. Mammogram data were collected for studies GGGF, GGGG, GGGH, GGGN, and GGGX both at baseline and at least one postbaseline visit. Endometrial thickness was measured at baseline and at a six-month interval (GGGF, GGGG, and GGGM) or at a 12-month interval (GGGN, GGGX, and GGGZ).

Data from triple-blind studies (the sponsor is blinded) were included in the discussions for four specific safety variables: deaths, venous thromboembolism (VTE), breast cancer, and uterine cancer.

Deaths

All deaths reported to the sponsor by 6/20/97 were included in the calculations of estimated mortality rates. Any additional deaths reported between 6/20/97 and 8/15/97 were included in the analysis of relative risk (RR) comparing raloxifene treatment groups with placebo. For the various groupings of the placebo-controlled studies in the primary safety database and the secondary safety database, the estimated mortality rates were reported as crude mortality rate and mortality rate per 1000 patient years adjusted for the study drug exposure. Since the overwhelming majority of deaths occurred in Study GGGK, more analyses of mortality rates were performed using data from this study. The treatment group differences in crude mortality rates were compared using Pearson's Chi-square test. Relative risks (point estimates and 95% Mantel-Haenszel confidence intervals) were calculated comparing each raloxifene dose with placebo. In addition, for those patients who died, some demographics and baseline clinical characteristics (age at randomization, age at death, years postmenopausal, and lipids) were compared among treatment groups using an ANOVA with the term of treatment.

Breast Cancer

For the studies that had a baseline and at least one scheduled postbaseline mammogram, the frequency of patients with abnormal mammogram results at any time after baseline was summarized by treatment group for pooled studies or individual studies in the primary placebo-controlled, primary estrogen-controlled and HRT-controlled integrated databases, according to data availability. Treatment-emergent clinically relevant abnormal mammogram results were those that developed after a normal baseline or clinically nonrelevant abnormal baseline and were assessed by the investigator to be clinically relevant. In the patients who had at least 1 month of treatment, all the breast cancer cases reported to the sponsor as of 6/20/97 were included in the analyses. For the various groupings of the placebo-controlled studies in the primary safety database and the secondary safety database, the incidence rates of breast cancer were reported by treatment group as crude incidence rate and incidence rate per 1000 patient years adjusted for the study drug exposure as of 6/20/97. Relative risks (point estimates and Mantel-Haenszel 95% confidence intervals) were calculated comparing pooled raloxifene with placebo for every study grouping. The relative risk of treatment-emergent breast cancer for patients in the pooled raloxifene treatment group versus patients in the placebo treatment group was analyzed at three different timepoints, based upon the date on which breast cancer was diagnosed, by using Mantel-Haenszel 95% confidence interval. The first timepoint included all patients who were diagnosed with breast cancer at least 1 month after initiation of therapy. The second timepoint included all patients who were diagnosed with breast cancer at least 6 months after initiation of therapy, and the third timepoint included all patients diagnosed at least 12 months after initiation of therapy. For all the cases reported in the placebo-controlled studies, plots of cumulative incidence rates of breast cancer versus days after randomization to the diagnosis of the cancer were displayed by the pooled raloxifene and placebo treatment groups, respectively.

Venous Thromboembolic Events

All events relating to VTE reported to the sponsor by 6/20/97 were included in the analysis of VTE. All

statistical inferences were based on the relative risk of the frequency of incident events per randomized patient in the raloxifene group compared with the placebo group. The estimated incidence rates per 1000 patient years of exposure were also summarized. The incidence of VTE in the placebo group and pooled raloxifene group were described and analyzed for the various groupings of the placebo-controlled studies in the primary safety database and the secondary safety database. For each of the groups, the incidence rate of VTE in the pooled raloxifene treatment group and the placebo treatment group was estimated, and the estimated relative risk of raloxifene compared with placebo along with a 95% Mantel-Haenszel confidence interval was described. Similar analyses and descriptions were performed using subgroups of VTE such as pulmonary embolism, and VTE excluding retinal vein thrombosis. As the majority of VTE have occurred in Study GGGK, further analyses were performed using data from that study only. Incidence rates were described as a function of geographic factors and compared using a Pearson's Chi-squared test on the relative frequency of events across regions (Australia/Asia, Europe, Mediterranean, North America, Scandinavia, and South America). A similar analysis was performed excluding Australia/Asia, Mediterranean, and South America because of the small number of events in those regions. Kaplan-Meier curves were used to describe the time course of the onsetof VTE. Furthermore, a case-cohort analysis was performed to identify predictors of risk across all treatment groups. For each patient the response variable, VTE (Yes, No) was a binary variable, and in the analyses was assumed to follow a binomial distribution yj ~ bin (1, pj), where yj = 1 if the *j*th patient reports a VTE and 0 otherwise. pj is the probability of a VTE occurring for the *j*th patient. A generalized linear modeling technique (using PROC GENMOD) was utilized to relate the probabilities to the other continuous explanatoryvariables, the model being log(pj) = **x b** j T. The log-link function was used in place of logit-link because for rare events, such as venous thrombotic events, risk is approximately equal to the odds (pj ´(1- pj) @ pj). The estimated relative risk for two different levels of the risk factors from the above model was calculated by*exp* {(**x**1 - **x**2) T b }(where **x**1 and **x**2 are two different values of the risk factors. The approximate 95% confidence interval of the above estimated relative risk was given by *exp* {(**x**1 - **x**2)T b ± 1.96 Ö (**x**1 - **x**2) TVar(b) (**x**1 - **x**2). The individual continuous risk factors were tested for statistical significance using this binomial regression model. For the categorical risk factors the relative risk for two different levels of each of them was tested using a Pearson's Chi-square test. Finally, binary models using multiple categorized risk factors were fit in a stepwise manner to find the most parsimonious model to provide estimates of relative risk adjusted for other important factors. This overall model was also used to estimate population attributable risks of raloxifene therapy (absolute risks of VTE specifically attributable to therapy). Attributable risks were calculated for combinations of risk factors by subtracting the estimated incidence rate for placebo-treated patients from the estimated incidence rate for raloxifene-treated patients. Weighted averages of these incidence rates were used to estimate the attributable risk of raloxifene adjusted for other risk factors.

Overview of Placebo-Controlled Integrated Databases

This summary includes five studies that comprise the primary, placebo-controlled database, as shown in the table below. Three of the studies — GGGF, GGGG, and GGGH — comprise the primary efficacy studies for this NDA, One trial (GGGN) is an osteoporosis treatment study and study GGGY is a cardiovascular surrogate study. The data from these trials, along with reports of serious adverse events from study GGGK — an osteoporosis treatment trial of over 7000 older women randomized to placebo, raloxifene 60mg, or raloxifene 120mg — are the primary sources for this review of raloxifene's safety.

Study Design/Study	Primary Objective	Study Population	Treatments	Reporting Interval (Months)	Study Duration (Months)
Primary Placebo-Controlled Integrated Database					
GGGF	Prevention of osteoporosis	601 Healthy, PMP,	Placebo, RLX030, RLX060, RLX150	24	36[b]
GGGG	Prevention of osteoporosis	544 Healthy, PMP,	Placebo, RLX030, RLX060, RLX150	24	36[b]
GGGH	Prevention of osteoporosis	619 Healthy, PMP, hysterectomized,	Placebo, RLX060, RLX150, ERT	24	36[b]
GGGN	Treatment of osteoporosis	143 PMP, Low BMD, ≥1 vert. Fx	Placebo, RLX060, RLX120	12	24[c]
GGGY	Cardiovascular surrogates	390 Healthy, PMP, yrs	Placebo, RLX060, RLX120, HRT	6	6[a]

Patient Demographics

The groups were well matched for baseline characteristics. All the patients in the above listed studies were female. Approximately of these patients were Caucasian, with the next largest ethnic group being Hispanic (≈3%). The mean age was 56 years , the average number of years postmenopausal was seven, and the frequency of current smokers was approximately 22%. of the subjects were previous HRT users and approximately 1% had an unkown HRT history. The majority of the patients (62%) did not have a history of having a hysterectomy.

Patient Disposition

There were no significant differences in the categories of patient disposition among the different raloxifene dose and placebo groups. Approximately 13% of the patients discontinued treatment because of an adverse event and 0.2% because of death.

Patient Exposure

The total patient years of exposure to all doses of raloxifene was 2436 (945 for 60mg, the proposed dose for marketing). Of the 945 patients exposed to 60mg of raloxifene, 54% received this dose for over 24 months.

ADVERSE EVENTS

Deaths

Six deaths have been reported from the primary placebo-controlled integrated database: four raloxifene-treated and two placebo-treated subjects. Two raloxifene high-dose subjects died from accidental injury, one from the low dose group died from hepatic failure, and one from the 60mg group died from pneumonia.

Review of these cases, does not, in and of itself, raise serious concern about the role of raloxifene in these deaths. As the majority of reported deaths have occurred in the ongoing study GGGK, a more meaningful assessment of raloxifene and mortality will be presented later in this review.

Serious Adverse Events

Using the standard FDA definition of serious adverse event (SAE), there were no statistically significant differences in the incidence of SAEs between the placebo and raloxifene groups. The majority of patients (89%) did not report a SAE during the trials. The most commonly reported SAE was coded as surgical procedure, with an approximate incidence of 7.0% for the various groups. A review of the individual surgical procedures did not reveal any obvious differences among groups. The incidence rates for other SAEs were, in general, quite low (<1%).

Discontinuation Due to Adverse Event

There were no statistically significant differences in the incidence of dropouts for adverse events (AE) between the placebo and raloxifene groups. Approximately 12% of placebo- and 12% of raloxifene-treated subjects discontinued from study participation because of an adverse event. The two most common reasons for discontinuation were vasodilatation (2.2%, 1.7%, 1.7%, and 3.1% for placebo, 30mg, 60mg, and high dose, respectively) and weight gain (0.9%, 0.7%, 1.2%, and 0.8% for placebo, 30mg, 60mg, and high dose, respectively).

Incidence of Treatment-Emergent Adverse Events

Three events were reported by significantly (statistically significant, $p<0.05$, on both Cochran-Mantel-Haenszel (CMH) and Fisher's Exact tests) more raloxifene-treated patients compared to placebo-treated subjects: vasodilatation, leg cramps, and stomach ulcers. The following table provides the incidence rates for the treatment-emergent adverse events for placebo, low-dose raloxifene (<60mg), 60mg raloxifene, and high-dose raloxifene (>60mg) groups. Only those events were the incidence rate is higher in the raloxifene 60mg group compared to the placebo group and the overall p value on both the CMH and Fisher's exact tests were ≤ 0.20 are reported. The p value from the CMH trend test is also provided.

TREATMENT-EMERGENT ADVERSE EVENTS (All dose groups)

Event	Placebo n=584	Ralx low n=288	Ralx 60mg n=581	Ralx high n=590	CMH	Fisher's	Trend+
Vasodilatation	18%	17%	25%	28%	<0.001	<0.001	<0.001
Sinusitis	7%	12%	10%	10%	0.05	0.04	0.19
Leg Cramps	2%	3%	6%	5%	0.003	0.001	0.002
Peripheral Edema	2%	2%	3%	4%	0.09	0.06	0.02
Increased Appetite	0.3%	1%	2%	2%	0.13	0.09	0.04
Stomach Ulcer	0%	0.3%	0.7%	1%	0.02	0.02	0.002
Anemia	0%	1.0%	0.2%	0.8%	0.03	0.02	0.06
Fibroid Enlargement	0.5%	0.4%	2%	2%	0.07	0.12	0.08

+Trend test compares placebo, low-dose, 60mg, and high-dose
CMH = Cochran-Mantel-Haenszel

Some of the reported adverse events merit further comment, as provided below.

Vasodilatation

Vasodilatation or flushing — a non-serious adverse event — was the most commonly reported adverse event in both the placebo-and raloxifene-treated subjects. There is some evidence that the risk for developing vasodilatation is higher in the raloxifene 60mg and high-dose raloxifene groups when compared with the raloxifene 30mg dose. Also, the risk for developing raloxifene-related vasodilatation appears to be greatest during the first six months of treatment. Younger postmenopausal women as compared with older women can be expected to experience more symptoms classified as vasodilatation, irrespective of treatment with raloxifene.

Sinusitis

Sinusitis was reported by significantly more raloxifene-treated patients compared with placebo. There was no evidence of a dose-response relationship for this adverse event. Kaplan-Meirer curves for time to event indicate that the risk for developing sinusitis in the raloxifene-treated women was greater following six months of treatment. The statistical significance was altered somewhat, but not to a meaningful extent, after the actual terms originally mapped to "sinusitis" were remapped, to what may be considered by some, to be appropriate terms. For example, head cold and head congestion were remapped to rhinitis; sinus headache was remapped to headache; and throat congestion was remapped to pharyngitis. Because the sponsor did not find an association between treatment with raloxifene and use of antibiotics it was concluded that sinusitis is not an adverse drug reaction attributable to raloxifene. While this Reviewer agrees that there is no plausible mechanism to explain a causal relationship between this adverse event and raloxifene, I would not dismiss the finding altogether. In the end, sinusitis, or the related conditions reported in the trials, were not serious in nature. Including this information in the labeling will be sufficient from a regulatory perspective.

Leg Cramps

Leg cramps of mild to moderate severity were reported by 6% of raloxifene 60mg subjects compared with 2% of placebo subjects. There is no obvious mechanism to explain an association between raloxifene with the development of leg cramps. In two raloxifene-treated patients the physical exam raised suspicion for DVT. Both subjects had negative noninvasive vascular tests, however. The risk for developing leg cramps following treatment with raloxifene appears to be greater for Caucasian vs. non-Caucasians and increases after six months of treatment. Of note, 19 out of 79 patients who reported at least one episode of leg cramps were provided specific drug treatment: 11 quinine and 6 magnesium and/or calcium supplements. There was an equal distribution of drug-treatment among the four groups. Also of note, there did not appear to be a significant difference between raloxifene- and placebo-treated patients in the duration of the leg cramps.

Stomach Ulcers

An intriguing finding from the primary, placebo-controlled studies was a significant dose-related increase in the incidence of conditions coded under the COSTART term "stomach ulcers" in raloxifene- vs. placebo-treated patients. Stomach ulcers were reported by 1/288 low-dose raloxifene patients, 4/581 60mg raloxifene patients, 8/590 high-dose raloxifene subjects, and none of the 584 subjects randomized to placebo.

As the sponsor has pointed out, peptic ulcer disease is a disorder that includes esophageal ulcers, stomach ulcers, and duodenal ulcers. No subject in any treatment group was coded as developing an "esophageal ulcer". "Duodenal ulcer" was reported by 0.07% of raloxifene-treated patients and by 0.3% of placebo-assigned subjects. "Reactivated duodenal ulcer" was reported by one (0.07%) raloxifene subject. When these upper GI ulcers are combined with stomach ulcers, and the incidence rates are compared across groups, the p-value changes

Patients were diagnosed with "stomach ulcers" even though the vast majority did not have definitive diagnostic procedures (e.g., endoscopy). This does raise the issue of diagnostic accuracy, and without knowing the exact symptoms that the patients complained of (which are not available from the case report forms), one has to concede that some patients may not have had stomach ulcers *per se*. Nevertheless, the data indicate that more raloxifene-treated patients compared with placebo-treated subjects had complaints suggestive of upper GI irritation.

Of note, there were similar patterns of use across treatment groups of medications used to treat dyspepsia and ulcers (e.g., antacids, H2-blockers, proton pump inhibitors). Additionally, there was no evidence from

preclinical studies that the drug induced stomach pathology.

In the end, the magnitude of the increase in risk for "stomach ulcers" in the raloxifene- vs. the placebo-treated patients, as well as the dose-response relationship, imply that there is a causal relationship between treatment with raloxifene and the development of GI symptoms suggestive of a stomach ulcer. Because the absolute incidence rate for this adverse event was low (13/1459; 0.9%), the severity of events were reported as mild to moderate, and the data are interim, it should be sufficient to include the information in the product labeling and update the issue as more clinical data become available.

Severity of Adverse Events

This section is limited to the more commonly reported adverse events listed in the above tables. For vasodilatation, there were more raloxifene 60mg and high dose patients compared to placebo that were coded as moderate or severe. (e.g., moderate: placebo 7%, 60mg 10%, and high dose 11%). For sinusitis; moderate: placebo 3%, 60mg 4%, high dose 5%. For leg cramps, moderate: placebo 0.5%, 60mg 2%, high dose 2%. There were no significant differences between groups in the cases of minor, moderate, or severe back pain, or accidental injury.

Vital Signs, Body Weight, and Height

As shown below there were small, non-clinically and non-statistically significant differences among groups for the changes from baseline to endpoint in sitting diastolic and systolic blood pressure and pulse.

MEAN CHANGE IN BLOOD PRESSURE AND PULSE (baseline to endpoint)

Variable	Placebo n=561	Ralx low n=273	Ralx 60mg n=546	Ralx high n=563
Diastolic BP (mmHg)	-0.19	-0.54	-0.09	-0.18
Systolic BP (mmHg)	0.30	1.10	0.10	0.42
Pulse (bpm)	0.97	2.28	2.16	1.88

When one looks at the percentage of patients in each group who had a diastolic BP > 90 mmHg or systolic BP >160 mmHg, or a pulse rate > 100 bpm at any time after baseline, there were no significant differences among the groups. Similarly, there were no significant differences among the groups in the percentages of patients with at least one low BP or pulse reading.

When measured from baseline to endpoint, there were small increases in mean body weight in all groups; there were no significant differences among the groups however. All changes were less than 1.0 kg.

The percentages of patients in the placebo and raloxifene 60mg groups that gained 5%, 7%, and 10% of baseline body weight are shown below. The greater percentage of patients who gained 5% of baseline weight in the 60mg group compared with placebo was of borderline statistical significance and probably of little clinical importance.

PERCENT OF PATIENTS WITH WEIGHT GAIN ABOVE STATED THRESHOLD (Baseline to Endpoint)

Threshold	Placebo (n=562)	RLX 60mg (n=551)	p-value
At least 5% gain	18%	22%	0.08
At least 7% gain	11%	12%	0.4
At least 10% gain	5%	5%	0.8

An analysis of the relationship between dose and weight gain did not suggest that there was a correlation between increasing doses of raloxifene with an increased incidence of weight gain.

Laboratory Tests

Serum Chemistry

The table below illustrates the mean changes from baseline to endpoint in serum chemistry parameters for which there was a meaningful difference between drug and placebo and the p value was ≤ 0.05.

MEAN CHANGES IN SERUM CHEMISTRY PARAMETERS (baseline to endpoint)

Variable	Placebo n=565	Ralx low n=272	Ralx 60mg n=545	Ralx high n=563
Phos (mmol/L)	-0.01	-0.03 (0.04)	-0.05 (<0.001)	-0.08 (<0.001)
Calcium mmol/L	-0.01	-0.04 (0.005)	-0.06 (<0.001)	-0.07 (<0.001)
Uric Acid umol/L	-0.46	2.26 (0.6)	3.27 (0.2)	5.1 (0.03)
AST U/L	0.9	0.70 (0.8)	1.66 (0.2)	2.02 (0.04)
T. Prot g/L	-0.34	-0.73 (0.005)	-1.29 (<0.001)	-1.58 (<0.001)
Albumin g/L	-0.43	-0.81 (<0.001)	-1.39 (<0.001)	-1.68 (<0.001)

p values comparing drug to placebo are shown in parentheses

A greater percentage of patients treated with raloxifene experienced a low serum calcium at some point during the trials, as shown below. However, none of the study participants developed a serum calcium level (adjusted and unadjusted for serum albumin levels) that was 1.5x below the lower limit of normal. Additionally, none of the patients who had a low serum calcium level during the trial had a low level at the last visit. The overall picture with abnormalities in the above laboratory parameters is one of single, transient abnormalities.

Analyte	Placebo	Rlx low dose	Rlx 60mg	Rlx high dose	p-value
Low Ca^+	2.3%	5.9%	4.0%	5.6%	0.02

P value from Cochran-Mantel-Haenszel general association test

Hematology

There were changes in several of the hematology parameters following treatment with raloxifene, some of which were statistically significant, but the change in mean platelet count was the only one of potential clinical significance. The changes from baseline to endpoint in the mean platelet counts for placebo, low, 60mg, and high-dose raloxifene were: -13, -21, -20, and -17 GI/L, respectively (p values vs. placebo 0.15, 0.004, and 0.09, respectively). The were significantly more subjects in the drug-treated groups compared with placebo who had low platelet counts during the trials. The percentages for placebo, low, 60mg, and high-dose raloxifene were:

0.4%, 1.2%. 1.4%, and 0%, respectively (p value for placebo vs. 60mg =0.03).

The sponsor investigated the changes in platelet count to determine if any clinical manifestations of the decrease in platelet count had occurred. This investigation included a review of the deaths due to cerebral hemorrhage, intracerebral hemorrhage, intracerebral bleed, and subarachnoid hemorrhage found in the reporting databases. For these patients, the platelet count was evaluated. The lowest recorded platelet count was 176 x 10^9/L. In addition, a review of the platelet count results for all raloxifene-treated patients in the integrated primary safety database who reported a serious adverse event which was potentially related to low platelet count (ie, hemorrhage, intracranial hemorrhage, purpura, uterine hemorrhage, vitreous hemorrhage) was performed and the lowest recorded platelet count was 217 x 10^9/L. Of interest, raloxifene HCl 60 mg decreased platelet count in a magnitude similar to that reported following treatment with tamoxifen.

Urinalyses

Other than an increase in levels of urinary casts (0.8% vs 0%, 60mg vs placebo, p=0.05), there were no significant changes in urine chemistry values. The clinical significance of 0.8% of patients in the 60mg group having casts is unknown. However, given that there were no other overt urine abnormalities, the finding of casts is probably not clinically relevant.

SPECIAL SAFETY CONSIDERATIONS

Deaths from All Raloxifene Clinical Trials as of June 20, 1997

As of June 20, 1997 there have been 70 deaths reported to the sponsor. All but 14 deaths occurred in study GGGK. Twelve deaths were excluded from the analysis of crude mortality rate for various reasons including deaths occurred prior to randomization, death occurred in breast cancer population, and death occurred in a non-placebo controlled study.

Deaths Reported in Study GGGK as of August 15, 1997

In this ongoing study, there have been 61 deaths reported as of August 15, 1997. Four of the deaths occurred prior to randomization and are not included in the tables below.

An interim analysis of the relative risk for death in study GGGK indicates no significant difference between the 60mg and placebo groups: RR = 0.61 (0.29, 1.28). Of interest, the interim relative risk for death in the raloxifene 120mg group vs. the 60mg group is 2.55 (1.30, 4.98). These calculations were made with the assumption that exposure to study drug is the same in the two groups. It will be interesting to see if the increased relative risk for death in the 120mg vs. the 60mg group is still significant at the end of the trial.

Breast Cancer (see consult for Division of Oncological Drugs)

Any drug that is shown to reduce the risk for breast cancer will, without question, gain wide-spread attention and use by middle-aged and older women seeking to avoid a feared and relatively common disease. Moreover, an osteoporosis drug that can make a breast cancer risk reduction claim will have immediate appeal to women taking estrogen — a hormone that increases the risk for postmenopausal breast cancer by approximately 35% if taken for 5 years or more (Collaborative Group on Hormonal Factors in Breast Cancer).

The sponsor's *in vitro* and *in vivo* data indicate that higher doses of raloxifene inhibit estrogen-stimulated breast cancer cell growth. Based on these preclinical findings, it's reasonable to speculate that raloxifene might delay, or even prevent, the occurrence of primary breast cancer in postmenopausal women. To this end, the

sponsor has provided favorable interim data on the incidence of breast cancer in postmenopausal women participating in the ongoing phase 3 osteoporosis prevention and treatment trials.

Of the breast cancer data available at this time the most complete data base comes from the prevention studies, GGGF, GGGG, GGGH, and GGGY. Women in these studies had a "normal" mammogram that was done within one year of randomization and as of October 16, 1997 all patients who remained in the studies for two years have had their two-year mammogram performed, read, and the results reported to the sponsor. In this cohort of women, there have been nine breast cancer cases reported: 3/536 in placebo patients and 6/1364 in raloxifene-treated women; RR = 0.8 (0.20, 3.1). If one limits the cases to those diagnosed after 18 months of treatment (3/536 placebo and 3/1364), then the RR for breast cancer in the raloxifene- compared with placebo-treated women is 0.4 (0.08, 1.84).

While these preliminary data are encouraging, they are far from definitive. Limitations in study design aside, this Reviewer believes that responsible comments about raloxifene's effect on the risk for postmenopausal breast cancer cannot be made until the ongoing treatment and prevention trials are completed. Dialogue among the Division of Metabolic and Endocrine Drugs, the Division of Oncology Drugs, and the sponsor, continues to direct the review of the breast cancer data.

Uterine Cancer (see consult from the Division of Reproductive and Urological Drugs)

Data from the preclinical studies in mice and rats indicate that raloxifene has a weaker stimulatory effect on the endometrium than estradiol and tamoxifen. In randomized, placebo-controlled trials several parameters were used to evaluate raloxifene's effect on the endometrium. These included endometrial ultrasound, incidence of bleeding, and endometrial biopsy. Of these parameters the most useful from the standpoint of evaluating raloxifene's carcinogenic potential is endometrial biopsy, with an evaluation for hyperplasia. In study GGGZ, 67 subjects were randomized to 150mg once-daily of raloxifene and 69 to HRT. Twelve-month interim data are reported in this submission. None of the subjects that had evaluable biopsies at baseline and Month 12 developed hyperplasia. From these data one could conclude, with reasonable assurance, that raloxifene does not substantially increase (≈ 20%) the incidence of hyperplasia.

While looking at the incidence of endometrial hyperplasia may be useful in the assessment of a drug's potential to initiate or promote the development of endometrial cancer, it remains a surrogate endpoint and therefore has inherent limitations. Therefore, the greatest effort should be placed in the analysis of the endometrial cancer data itself. Any analysis of raloxifene treatment and cancer incidence must be considered preliminary at this time given the relatively short exposure to drug.

With these caveats in mind, Dr. Bruce Stadel's (Medical Officer and Epidemiologist from HFD-510) analysis of the endometrial cancer data follows. "In total, eleven cases of endometrial cancer were diagnosed in the eight phase 3 trials through 22 September 1997, of which seven were found in the largest trial -- the GGGK study -- which enrolled 7704 women, or 78% of the 9853 women enrolled in the eight phase 3 trials as a whole. I will focus on the seven cases in the GGGK study, since the other four cases are dispersed across three of the remaining seven trials.

The GGGK study began in November 1994 and is scheduled for completion in August 1999. The treatment duration is scheduled for three years with a one year extension; the last patient to complete 2-years of treatment did so in August of 97. There are three arms -- placebo, raloxifene 60 mg per day, and raloxifene 120 mg per day. Of the 7704 women randomized to the three arms, 5957 had intact uteri at baseline, or 1986 per arm. Since the study has not been unblinded, this is the only denominator available for analyzing rates of endometrial cancer.

Collaborative Group on Hormonal Factors in Breast Cancer. The Lancet. 1997 350;Oct 11

The rates of endometrial cancer are 4/1986 for placebo, 1/1986 for raloxifene 60 mg per day, and 2/1986 for raloxifene 120 mg per day. Combining the two raloxifene doses, the relative risk for raloxifene compared to placebo is 3/3972 / 4/1986 = 0.38, 95% confidence interval 0.08 - 1.67. The above finding is consistent with the finding on page 94 in volume 1 of the 14 October 1997 draft briefing document that Lilly sent in for the 19-20 November 1997 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. There, the relative risk for raloxifene compared to placebo is 0.64, 95% confidence interval 0.14 - 2.18, based on data obtained through 20 June 1997."

Therefore, based in large part on interim data from study GGGK, when compared with placebo, relatively short-term exposure to raloxifene does not appear to increase the risk for endometrial cancer.

Venous Thrombotic Events (VTE)

For the purposes of this discussion VTE is defined as follows: (1) any acute venous thrombosis (clot) involving a deep peripheral vein (commonly known as deep vein thrombosis (DVT); (2) acute pulmonary embolism (PE); (3) other acute serious vein thromboses, including mesenteric and intracerebral vein thromboses (of these, only retinal vein thrombosis (RVT) was actually reported). Excluded from this analysis are superficial vein thromboses and arterial thromboses. It is unlikely that a meaningful number of VTE went undetected by the sponsor. To identify the VTE cases, the sponsor searched their DEN database twice using a total of 63 event terms. A review of the event terms indicates that they were comprehensive and would pick-up most of the cases of VTE.

As of 6/20/97 the sponsor has identified 56 cases of VTE; the majority being DVTs.

For DVT, the majority of the cases were diagnosed by noninvasive methods - mostly duplex scanning and doppler flow studies. These two techniques, are for the most part, accurate in the diagnosis of proximal vein thromboses. Duplex scanning may lack sensitivity compared with doppler studies in the detection of isolated calf thromboses; yet, a very small percentage of clots originating below the knee will embolize to the lungs, and consequently, calf thromboses do not represent a serious health threat. Most of the cases of PE were diagnosed by the use of two noninvasive methods: duplex scanning of the lower extremities along with V/Q scanning. The use of two noninvasive techniques to diagnose PE is a commonly accepted approach that has a high positive predictive value when conducted in the presence of a high pre-test probability for disease. The clinical diagnosis of acute DVT can be complicated in a patient with a history of previous DVT as symptoms for acute thrombosis can mimic those of post-thrombotic syndrome. This is not a great concern when reviewing the raloxifene data because only seven patients diagnosed with an on-study DVT had a previous diagnosis of lower extremity thrombosis. Two of these seven patients had the on-study DVT diagnosed by venogram and the remaining five received a diagnosis by duplex scanning.

The majority of the VTE cases were identified in the ongoing, triple-blind study GGGK. Study GGGK is a large three-year treatment trial with reporting of interim data of serious adverse events. Because the study is still blinded (except for the serious adverse events) calculations of the incidence rates for VTE are based on the assumption of equal exposure distributions across treatment groups. This assumption may, or may not, be accurate, only time will tell.

The table below provides the relative risk estimates for VTE, VTE except retinal vein thrombosis (RVT), and PE. The risks are presented for the 60mg dose of raloxifene as well as for all doses of raloxifene combined. The results are also provided for all placebo-controlled studies combined, for the placebo-controlled prevention studies, for the placebo-controlled treatment studies, and for study GGGK alone.

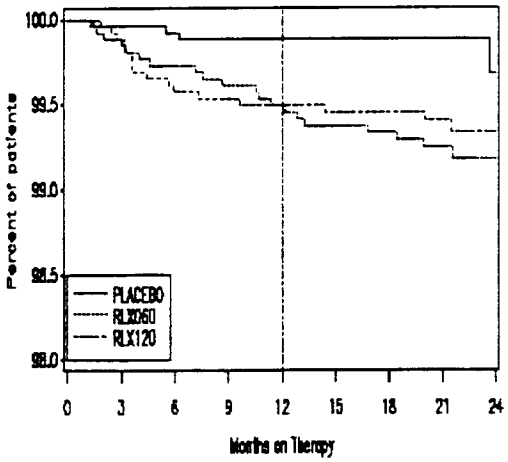
	PLACEBO		RLX 60 MG			RLX ALL DOSES		
	# Events	Estimated Exposure (years)	# Events	Estimated Exposure (years)	RR (95%CI)	# Events	Estimated Exposure (years)	RR (95%CI)
Overall[a]		N=3195		N=3192			N=6681	
All VTE	7	6150	24	6123	**3.4 (1.6,8)**	44	12879	**3.0 (1.4,6.4)**
VTE (-RVT)	5	6150	22	6123	**4.4(1.8,11)**	42	12879	**4.0 (1.7,9.4)**
PE	4	6150	9	6123	**2.3(0.7,7)**	15	12879	**1.8 (0.6,5.3)**
Prevention[b]		N=536		N=533			N=1364	
All VTE	1	1070	4	1045	**4.0(0.5,30)**	5	2723	**2.0 (0.2,16)**
VTE (-RVT)	0	1070	4	1045	**NE**	5	2723	**NE**
PE	0	1070	2	1045	**NE**	2	2723	**NE**
Treatment[c]		N=2659		N=2659			N=5317	
All VTE	6	5079	20	5078	**3.3(1.4,8)**	39	10156	**3.3 (1.5,7.3)**
VTE (-RVT)	5	5079	18	5078	**3.6(1.4,9)**	37	10156	**3.7 (1.6,8.8)**
PE	4	5079	7	5078	**1.8(0.5,6)**	13	10156	**1.6 (0.5,4.9)**
GGGK		N=2568		N=2568			N=5136	
All VTE	5	4962	20	4962	**4.0(1.7,10)**	38	9925	**3.8 (1.6,9.0)**
VTE (-RVT)	5	4962	18	4962	**3.6(1.4,9)**	36	9925	**3.6 (1.5,8.6)**
PE	4	4962	7	4962	**1.8(0.5,6)**	13	9925	**1.6 (0.5,4.9)**

a=GGGF,H,G,K,N,P,andY b=GGGF,H,G,andY c=GGGK,N,andP NE=inestimable -RVT=except retinal vein thrombosis

Four patients in Study GGGK had a previous history of VTE. When these patients are removed from the analyses — as is appropriate given that the drug will be contraindicated in women with a pre-existing history of VTE — the relative risk estimate are slightly reduced.

The sponsor claims that there is no evidence for a dose-related increase in the incidence of VTE. The data shown in table ISS.6.15 — estimated annual incidence rate per 1000 — support the sponsor's assertion.

The risk for VTE is greatest during the first three to four months of exposure, as shown in the below figure depicting the VTE incidence as a function of exposure to drug in study GGGK [relative risk for VTE during the first four months of treatment is 6.7 (1.2, 39) in raloxifene- vs. placebo-treated women].



It merits mention that the sponsor identified the incidence of idiopathic VTE (cases without identifiable risk factors). The major risk factors were considered antecedent major surgery, prolonged immobilization, or local or major trauma (all within 6 months prior to event), prior VTE, or known coagulopathy (including preexisting conditions not diagnosed until after the event). Minor risk factors were as follows: hypertension (HTN) requiring pharmacological treatment, BMI 30 kg/m^2, history of varicose veins or superficial thrombophlebitis, bilateral oophorectomy, or current tobacco smoking. Since risk factors for retinal vein thrombosis are not as well established as for DVT and PE, all cases of retinal vein thrombosis (RVT) were considered idiopathic. Cases were classified as idiopathic (no risk factors or RVT), nonidiopathic (major risk factor(s) present), or potentially idiopathic (minor risk factor(s) only). Of the 51 total reported VTE cases, seven (14%) were idiopathic (ie, had no known risk factors). Thus, excluding the four RVT cases, there were only three (6.3%) idiopathic cases of DVT or PE. If potentially idiopathic cases (ie, those with at least one known risk factor) were also considered as "idiopathic", then 16 (31%) of the 51 total cases or 12 (25%) of the 47 non-RVT cases were idiopathic. Thus, the majority of reported VTE cases had at least one major risk factor prior to the event.

While major surgery, prolonged immobilization, and local or major trauma certainly increase the immediate risk for VTE, it's questionable whether the risk is appreciably increased by one of these events if they predate the thrombotic episode by as much as four to six months. Nevertheless, the relative risk for idiopathic VTE (DVT and PE only) for all doses of raloxifene vs. placebo was 2.8 (0.6, 13). This estimate is not statistically significant and the magnitude of the estimated risk is not sizably greater than the risk for all (nonidiopathic and idiopathic) VTEs.

In an effort to identify risk factors for VTE in raloxifene-treated subjects the sponsor is conducting an ongoing nested case-control study in study GGGK. Although the results of this analysis will not be available for some time, the sponsor did perform a case-cohort analysis of baseline risk factors for VTE in study GGGK. A binomial regression model using a log-link function was used to determine which continuous baseline factors were statistically significantly associated with development of VTE. Similarly, a chi-square test was used to identify categorical factors associated with VTE risk. The following baseline factors were investigated:

- Age, weight, BMI, years postmenopause
- Systolic blood pressure, diastolic blood pressure, pulse
- LDL-C, HDL-C, hemoglobin A1C, apolipoprotein A1, apolipoprotein B
- Bone-specific alkaline phosphatase, osteocalcin, urine CrossLaps: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 myocardial infarction ([MI] yes/no), prior percutaneous transluminal coronary angioplasty ([PTCA] yes/no), prior stroke (yes/no), and prior coronary bypass graft (yes/no).

Following identification and categorization of potential VTE risk factors, a multivariate model incorporating treatment was used to determine the impact of these factors on treatment-associated VTE risk. Following a stepwise procedure, the most parsimonious model identified age, weight, prior MI, and treatment as independent VTE risk factors

The following baseline characteristics were significantly different between the cases randomized to 60mg and placebo vs the unaffected cohort.

BASELINE FACTOR	CASES (n=24)	UNAFFECTED COHORT (n=5085)
Age (yrs)	70.9	66.5
Weight (kg)	70.4	63.7
BMI (kg/m2)	27.1	25.2
Systolic BP (mmHg)	146	133
Diastolic BP (mmHg)	84.8	78.4
Prior use of thiazides (% yes)	39.1	12.0
Prior MI (% yes)	12.5	2.0

Information does not include data from four-month safety udpdate (10/8/97)

In a multivariate regression model, only age, weight, prior MI, and treatment with raloxifene were identified as independent risk factors for VTE. The magnitude of the risks associated with these variables are provided in the following table.

RISK FACTOR	ALL VTE CASES RELATIVE RISK (95%CI)
Treatment (raloxifene vs placebo)	4.0 (1.6, 10)
Prior MI (yes vs no)	5.0 (2, 12)
Age (above 71 yrs vs below)	2.1 (1.1, 3.8)
Weight (above 70 kg vs below)	3.1 (1.7, 5.5)

These interim data support the finding that raloxifene, at a daily dose of 60 mg, significantly increases the risk for VTE. Additional identifiable risk factors include previous MI, age above 71 years, and body weight above 70kg. If these risk factors are verified as independent predictors of VTE in the ongoing case-control study, this information will be valuable to prescribing physician when assessing the risk vs. benefit profile of raloxifene.

For obvious reasons, the identification of potential risk factors for VTE in the raloxifene-treated populations will be limited by the characteristics of the enrolled patients. In general, patients with concomitant illness and medication were excluded from the raloxifene trials. As an additional safety measure, those conditions that have been identified as risk factors for VTE from the published literature — e.g., heart failure, history of malignancy, lower-limb arteriopathy— should be mentioned in raloxifene's labeling.

The use of estrogen replacement therapy by postmenopausal women increases the risk for deep venous

thrombosis and pulmonary embolism by approximately 3 fold. Like raloxifene, the first six months or so of treatment are associated with the greatest risk.

Of note, there was only one VTE event in the placebo group and five in the raloxifene groups during the conduct of the prevention studies: relative risk = 2.0 (0.2, 17). This estimate — in a population of women with a mean age of approximately 55 years — must be viewed as very preliminary due to the low overall incidence rates for VTE events. At present the most reliable estimates for the risk for VTE come from study GGGK — a trial of women with a mean age of over 65 years.

Hepatic Function

Transaminase Levels

In general, patients were considered to have elevated levels of AST, ALT, or GGT if they had an increase 2x the upper limit of normal during the trial. In the primary placebo-controlled database, there were no significant differences between raloxifene- and placebo-treated patients in the percentage of patients with elevated levels of ALT, AST, and GGT, and the overall incidence rates were low. Fourteen subjects developed an elevated AST 1.5x the upper limit of normal during these trials: two receiving placebo and 12 receiving raloxifene (4 patients each in raloxifene low dose, 60mg, and the high-dose groups, p=0.3). The highest value observed was 311 U/L in a patient randomized to the 60 mg dose. In four raloxifene 60mg patients and one placebo patient, the elevated levels of AST did not return to within normal limits during the trial. In four raloxifene-treated patients the elevated AST levels spontaneously returned to within normal limits during the trial. In one placebo patient and four raloxifene patients the AST levels returned to within normal limits following a specific intervention, in most cases drug withdrawal.

The absolute risk for developing a mildly elevated AST level (1.5x ULN) was approximately 0.4% in the placebo group and 0.9% in the raloxifene group — relative risk 2.5 (0.6, 11) in raloxifene- vs. placebo-treated patients.

In the ongoing study GGGK, one patient out of 7704 has withdrawn because of abnormal liver function tests.

Hepatic and Biliary Abnormalities

In the primary placebo-controlled studies there were no significant differences among groups in the incidence of cholelithiasis, cholecystitis, fatty liver, or liver damage. Of note, one patient died as a result of acute liver failure. This patient was randomized to 30mg/day of raloxifene. She received a diagnosis of head and neck cancer after enrolling in the raloxifene trial, and the sponsor states that the patient admitted to heavy use of alcohol and acetaminophen, again after she was enrolled in the trial. The patient reportedly stopped taking the study medication two months prior to her death. Her workup at the time of admission to the hospital for liver failure revealed a positive hepatitis A IgM antibody and an acetaminophen blood level of 25 ug/ml. All things considered, it's reasonable to assume that alcohol, acetaminophen, and hepatitis A were the culprits in this case of acute liver failure (Schiodt).

In study GGGK one patient died as a result of hepatic cancer. This patient was randomized to the 120mg raloxifene arm. Study medication was started on June 15, 1995 at which time she had an elevated Alk Phos level (174 U/L). She died in November of 1995.

One patient in GGGK has discontinued because of hepatomegaly. This patient, who was reportedly obese and diabetic (NIDDM), was randomized to 60mg of raloxifene qd. She was diagnosed as having a tender enlarged liver and was discontinued from the study. No additional relevant information about this patient's condition (other than the fact that she has not had a liver biopsy) is available as of 10/15/97. The sponsor has committed to sending follow-up information as it becomes available.

Schiodt FV, Rochling FA, Casey DL, et al. Acetaminophen toxicity in an urban county hostpital. New Engl J Med. 1997; 337:1112

While the above data are not alarming, they do raise the possibility that raloxifene will be associated with some degree of hypertransaminasemia after introduction into the market place.

Central Nervous System

There is a growing body of literature on estrogens and cognitive function. There is evidence, although not universal, that estrogen enhances verbal memory and may be a useful preventive agent against Alzheimer's disease. The most prominent adverse event noted with raloxifene was vasodilatation, or flushing. That raloxifene increases this adverse event and estrogen decreases it suggests that raloxifene has estrogen antagonistic activity at the pituitary/hypothalmus. Does raloxifene act as an estrogen antagonist in other parts of the brain? If so, what consequences might this have?

In the one study in this NDA that specifically examined the cognitive effects —assessed from a computerized psychometric battery designed by the Memory Assessment Clinic — of raloxifene compared with placebo in women with established osteoporosis, no statistically significant differences were noted between groups for subjects that completed the 12-month study. Additionally, there were no obvious differences between raloxifene- and placebo-treated patients in the incidence of patient reported, cognitive-related adverse events (e.g., depression, anxiety, confusion). One may surmise, from these limited data, that raloxifene is probably not associated with large alterations in cognitive function. Yet, as with most drugs, experience in a larger, more heterogenous population is required to detect small or subtle drug-induced changes. If the drug is approved for the prevention of osteoporosis, tens of thousands of women, if not more, will be exposed to this compound for long periods of time. It would behoove the sponsor to continue to examine the impact, if any, that raloxifene has on cognitive function in postmenopausal women.

8.0 Discussion

It's estimated that more than 30% of women between the ages have osteoporosis —or low BMD. The incidence climbs to nearly 70% for women over the age of 80 years (Kanis and Melton). While low bone density is the hallmark of osteoporosis, fractures of the spine, hip, and wrist account for the morbidity and mortality of this disease. Therefore, effective interventions - be they the treatment or prevention of osteoporosis - should be defined by their ability to reduce the risk for fractures.

Raloxifene is the first selective estrogen receptor modulator to seek an indication for the prevention of osteoporosis. In support of this indication, the sponsor has provided two-year interim data from three trials involving over 1500 postmenopausal women, many of whom were osteopenic (T-score -1 to -2.5) at baseline. In studies GGGF and GGGG, subjects were randomized to one of four arms: placebo, or raloxifene 30mg, 60mg or 150mg once daily, while in study GGGH patients were randomized to either placebo, raloxifene 60mg or 150mg, or Premarin 0.625mg once daily. All subjects were instructed to take 400-600mg/day of supplemental calcium.

After two years of treatment, the placebo-treated women in all three studies lost BMD at the lumbar spine and hip , whereas the raloxifene-treated subjects had small but statistically significant increases in lumbar spine and hip BMD ($p<0.03$ all raloxifene doses vs. placebo). In study GGGH, women treated with Premarin had mean increases in lumbar spine and hip BMD of 3.8% and 2.4%, respectively ($p<0.03$ vs. placebo and raloxifene). The fact that total body BMD increased in raloxifene-treated women relative to placebo-treated subjects, indicates that the raloxifene-induced increases in lumbar spine and hip BMD did not occur at the expense of bone density at other skeletal sites.

The sponsor's proposal to market the 60mg dose of raloxifene seems reasonable since the dose-response curve relating dose to BMD is relatively flat between the 60 mg and 150mg doses. Moreover, the incidence of some adverse events is higher with the 150mg dose. And parenthetically, interim data from study GGGK, a large treatment trial, indicate that total mortality is significantly higher in the 120mg vs. 60mg raloxifene group [RR 2.28, (1.8, 3.45)]. Given that all data are interim at this time, the most appropriate dose for the prevention of postmenopausal osteoporosis should be re-evaluated after all studies have been completed and fracture data are available.

The phase 3 data provide evidence that, when compared with placebo, the 60mg dose of raloxifene produces modest reductions in the levels of TC, LDL-C, Apo B, and Lp(a) and has a neutral effect on the levels of HDL-C and TG. The notable difference between treatment with raloxifene and HRT was the ability of the latter to significantly increase the concentrations of HDL-C, TG, and Apo A1, and significantly lower the levels of Lp(a). Regarding parameters of coagulation, compared with placebo and HRT therapy, treatment with raloxifene was associated with a modest reduction in the levels of fibrinogen, a risk factor for coronary heart disease in women (Kannel WB). Plasminogen activator inhibitor-1, another fibrinolytic parameter that may increase the risk for cardiovascular disease (Cortellaro), decreased significantly in the HRT group when compared with the changes seen following treatment with placebo or raloxifene. Some observational data suggest that HRT reduces the risk for heart disease (Chae); it's reasonable to speculate, based on the changes in surrogate endpoints, that raloxifene will also impact favorably upon the risk for cardiovascular disease.

Kanis JA, Melton LJ, Christiansen C, et al. The diagnosis of osteoporosis. J Bone Miner Res. 1994;9:1137

Melton LJ. How many women have osteoporosis now? J Bone and Miner Res. 1995:10:175

Kannel WB, Wolf PA, Castelli WP, et al. Fibrinogen and risk for cardiovascular disease. The Framingham Study. JAMA. 1987;258:1186

Cortellaro M, Cofranscesco E, Boschelli C, et al. Increased fibrin turnover and high PAI-1 activity as predictors of ischemic events in atherosclerotic patients. A case-control study. The PLAT Group. Arteriscler Thromb. 1993;10:1412

Chae CU, Pidker PA, Manson JE. Postmenopausal hormone replacement and cardiovascular disease. Thrombosis and Hemostasis. 1997;78:770

Thus far, the most serious adverse event causally linked to raloxifene treatment is venous thromboembolism, principally DVT. The absolute risk for DVT and pulmonary embolism in placebo-treated women is approximately 1 case/1000 persons/year. Against this background rate, the relative risk for thromboembolic events during the first four months of treatment with raloxifene is 6.7 (1.2, 39). This risk declines substantially with longer-term exposure [relative risk during months 4-12 of treatment is 1.8 (0.6, 5.3)]. Unlike estrogen, the relationship between raloxifene and thromboembolism does not appear to be dose related.

Two major concerns with estrogen replacement therapy are breast and endometrial cancer. To date, the data indicate that raloxifene is not associated with an increased risk for either one of these diseases. However, precise estimates of raloxifene's effect on these risks must await longer-term study.

To conclude, raloxifene maintained BMD in relatively early postmenopausal women during two years of treatment. It's unknown, however, whether this preservation of BMD will persist with longer-term therapy and ultimately reduce the risk for osteoporotic fracture.

RECOMMENDATION

The data provided in this NDA demonstrate that, over a two-year period, the 60mg dose of raloxifene increased BMD at the lumbar spine and hip by about 2% relative to placebo. This difference was statistically significant. The critical issue remains one of clinical significance. Will this relative improvement in BMD persist with continued treatment and ultimately reduce the risk for osteoporotic fracture — the meaningful endpoint for patients taking this drug to prevent osteoporosis?

Of concern is the fact that, in studies GGGG and GGGH, the lines depicting the mean change in lumbar spine BMD in the groups randomized to 60mg per day of raloxifene are trending down at the 2-year time point. It would be of great value to have the third year data in order to ensure that the relative efficacy of the drug is not diminishing with continued treatment.

In sum, this Reviewer believes it would be prudent to delay approving raloxifene for the prevention of osteoporosis until the Division receives additional data. Within the next six to eight months 2-year fracture data from the osteoporosis treatment trial, GGGK, will be available. Within the next 12 months 3-year BMD and vertebral fracture data from the three prevention trials will be available. I believe that provision of any one of the following (shown in order of preference) would support the approval of raloxifene for the prevention of osteoporosis:

1. Three-year pooled vertebral fracture data from the three prevention trials showing at least a trend in favor of raloxifene vs. placebo.

2. Two-year vertebral fracture data from GGGK showing at least a trend in favor of raloxifene vs. placebo.

3. Three-year lumbar spine and hip BMD data from the prevention trials demonstrating the absence of a negative slope for the lines depicting the percentage change in BMD vs. time in the raloxifene 60mg groups.

11/19/97

Eric Colman, M.D.

Gloria Troendle
11-24-97

cc: Orig NDA
Division file
HFD-510- Hedin/Troendle/Sobel

APPEARS THIS WAY
ON ORIGINAL

AUG 6 1997

Medical Officer Consult

Review: NDA 20-815, EVISTA™ (Raloxifene Hydrochloride)

HFD-510 Contact: Eric Colman, M.D.

Submission Received (HFD-150): July 29, 1997
Reviewing Medical Officer: Karen Johnson, M.D.
Review completed: August 6, 1997

Background: An NDA for raloxifene submitted to HFD-510 by Eli Lilly on June 8, 1997, was filed and given a priority review status. Raloxifene is a selective estrogen receptor modulator (SERM) that Lilly plans to market with an indication for osteoporosis prevention. Based on *in vitro*, preclinial, and limited clinical trial data, the sponsor also claims that this drug reduces the risk for breast cancer. HFD-510 has requested an opinion as to whether the methodology employed in the phase 3 osteoporosis trials was rigorous enough to support a claim that raloxifene reduces the risk for breast cancer. Information provided by HFD-150 with this consult request included one page from the NDA that provides the proposed text for the portion of the raloxifene label entitled "Effects on the Breast" (which claims a statistically significant reduction in breast cancer incidence with raloxifene treatment). Also provided were nine pages from a section (6.3. Breast) of the sponsor's Integrated Summary of Safety.

Reviewer Comments: The data provided appear to be grossly insufficient to support a claim that raloxifene reduces breast cancer risk. Despite the summary nature of the information provided, it is unlikely that more information will improve the acceptability of the methodology or the credibility of the data used by the sponsor to conclude that raloxifene reduces the risk for breast cancer. It is stated in Section 6.3.2 that the analysis of raloxifene's impact on breast cancer risk is based on 28 cases of breast cancer. The sponsor indicates that 13 cases were "pre-existing" at the time of study entry. We know of no rationale to support treatment of "pre-existing" breast cancer with raloxifene or placebo for a period of months or years until the breast cancer comes to subsequent clinical attention. Given the fundamental difference in the population of individuals with "pre-existing" breast cancer compared to individuals who would enter a study with no clinical or radiographic evidence of breast cancer, only the 15 non-pre-existing cases could be considered in evaluating the effects of raloxifene on the subsequent development of breast cancer.

Experience based on as few as 15 cases is inadequate to justify a claim of breast cancer risk or incidence reduction, because it is unlikely that this number of events is sufficient for the reliable detection of a difference between treatment groups. According to Dr. Colman, not all of the raloxifene studies included in the meta-analysis were designed to have a baseline mammogram at entry. Studies lacking a baseline mammogram should be considered inadequate to contribute to an analysis of breast cancer prevention. Excluding such studies would reduce the sample size and probably the number of cases in the analysis. As a point of reference, it should be noted that the NSABP Breast Cancer Prevention Trial with tamoxifen was designed with the anticipation that there would be at least 180 breast cancer events in only the 8,000 person placebo-control arm.

There are many other questions that could not be answered by review of the summary information provided in the consult package. The answers to these questions would bring to light additional information that could further weigh against the sponsor's claim that raloxifene reduces breast cancer risk. The following questions are examples of the kind of review questions that would need to be answered to fully address the claim that raloxifene prevents breast cancer:

1. <u>OBJECTIVES/ENDPOINTS FOR BREAST CANCER PREVENTION PROTOCOLS</u>. The demonstration of breast cancer prevention should be documented prospectively, in a trial or trials specifically designed for this purpose. Study protocols should specify that patients/subjects will be monitored for the development of breast cancer and that breast cancer incidence is a primary endpoint. Without these measures, the studies could be flawed by a detection bias. For the raloxifene studies,

what procedures, in place from the beginning of each trial, were designed to monitor patient status with respect to the breast cancer endpoint? Was a baseline mammogram and clinical breast exam with no evidence of breast malignancy required before a participant could enter the raloxifene trials? Was an annual mammogram scheduled as part of the follow-up? Were follow-up breast physical exams part of the protocol and if so how frequently were they performed? What was the level of compliance with these protocol procedures?

2. ADDITIONAL QUESTIONS RELATED TO DETECTION BIAS. Evidence should be provided that differential ascertainment of cases or other factors did not cause bias. Was there a difference between the raloxifene vs. the control arms in the kind of breast cancer cases being detected? The stages and the histologies of all the breast cancer cases that were diagnosed in the course of the studies would have to be reviewed and compared according to study arm.
3. ADEQUACY OF THE RANDOMIZATION. Data should be provided that confirms the adequacy of the randomization. When the patient population receiving raloxifene is compared with the placebo population, the two groups at baseline should have been similar with respect to breast cancer risk factors. As part of the clinical data collection, were the variables needed to perform an estimate of breast cancer risk collected? (for the Gail model - number of breast biopsies, age of menarche, age at first live birth, number up to 2 of first degree relatives with a breast cancer history, etc.)
4. PLAUSIBILITY OF RESULTS. If the patient population participating in the osteoporosis trials are not representative of the general population, information should be provided that adequately describes the study population. Are the rates of breast cancer incidence in the placebo population consistent with the rate that would have been expected or predicted on the basis of the known characteristics of the group and the female population from which they were drawn?

Recommendations:

1. Although it is understood that the sponsor is not seeking a formal indication that raloxifene reduces breast cancer risk, the acceptance of such a claim anywhere in the label is, in reality, equivalent to granting approval for marketing raloxifene for the indication of breast cancer prevention. Normally, breast cancer prevention claims are reviewed by the Division of Oncology Drug Products (DODP) and discussed before the Oncologic Drugs Advisory Committee. Consequently, HFD-150 recommends that the sponsor request a meeting with DODP to facilitate the future development of raloxifene for the breast cancer prevention indication.
2. In conveying this information to the sponsor, the following language is suggested:

   In reviewing the proposed label for raloxifene as an agent that is indicated for the prevention of osteoporosis, it is not acceptable to include language elsewhere in the label that "there was a statistically significant reduction in the frequency of newly diagnosed breast cancer in raloxifene-treated women compared with placebo". Acceptance of this claim would effectively provide the sponsor with a second indication for raloxifene without review by the Division of Oncology Drug Products or the Oncologic Drugs Advisory Committee. Consequently, it is recommended that the sponsor request a meeting with the Division of Oncology Drug Products to discuss the breast cancer prevention claim and the data that support it.
3. Information from the conclusions and points 1 to 4 should also be conveyed to the sponsor.

MD 8/6/97

Karen Johnson, M.D., Ph.D.

APPEARS THIS WAY
ON ORIGINAL

Julie Beitz MD 8/6/97

Julie Beitz, M.D.

cc: orig. NDA
HFD-150/Division File
HFD-150/J. Beitz
HFD-150/K. Johnson
HFD-150/D. Pease
HFD-101/R. Temple
HFD-510/ S. Sobel
HFD-102/J. Bilstad
HFD-150/ Consult file

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION
HFD-580

Subject:
Request from HFD-510 for comments concerning the endometrial effects of Evista (raloxifene) submitted with **NDA 20-815**
Date the consultation was received by this reviewer:
August 29, 1997
Date this review was completed:
October 1, 1997

Purpose of this consultation

The medical officer in HFD-510 responsible for reviewing NDA 20-815 asked this Division for an opinion whether the drug, Evista (raloxifene), under review in HFD-510 for prevention of osteoporosis, **"has been appropriately evaluated with respect to its effect on the endometrium and risk for endometrial cancer".**

Raloxifene is a selective estrogen receptor modulator reputed to have a positive effect on bone, but an anti-estrogen effect on breast. It is of special concern to rule out adverse effects of the drug on the endometrium as seem with another anti-estrogen, tamoxifen; this is the purpose of the portion of the sponsor's NDA sent to this Division for review.

Material reviewed

HFD-510 provided pages 158-179 of the Integrated Summary of Safety of the NDA submission for review. Insofar as this material failed to include sufficient information (such as identification of all the drugs used in the studies, and their doses) to permit review, protocols for most of the studies discussed in the presentation and a definition of the "*gynecological surveillance algorithm*", employed in a minority of subjects, were also obtained. Further information was obtained by attending a 510 staff meeting on October 1, 1997.

Statements in italics are quotations from the documents provided.

Summary of the protocols reviewed

Summaries of the 6 protocols that the sponsor states are relevant to the uterine findings are presented below. The degree to which the studies were designed to monitor uterine effects is noted.

Protocol GGGB

This was an 8 week comparison of the effects of raloxifene 200 mg, raloxifene 600 mg, Premarin 0.625 mg, and placebo in 160 "*healthy premenopausal women...on mineral homeostasis and bone mineral metabolism*". This study was done in the USA.

The effect of the drug on the uterus was a secondary objective of this study.

Protocols GGGF and **GGGG**

These were 2 similar up-to-5 year comparisons of 3 doses of raloxifene vs placebo, each in "*approximately 480..healthy, postmenopausal women*", both conducted primarily to ascertain effects "*on lumbar spine and hip bone mineral density*". The study design for both of these studies is provided in **Attachment 1**. GGGF was conducted in Europe and GGGG was conducted in North America.

The effect of the drug on the uterus was a secondary objective of these studies.

Protocol GGGM

This was an up-to-114 week study of 1 dose of raloxifene compared with Premarin (followed by Provera) in up-to-96 "*healthy, postmenopausal women*" to obtain "*baseline-to-endpoint changes in each therapy group..with respect to histomorphologic measurements of the iliac crest*". The study design is provided in **Attachment 2**. The study was conducted in the USA.

The effect of the drug on the uterus was not a stated objective of this study.

Protocol GGGN

This was an up-to-3 year comparison of 2 doses of raloxifene with placebo in at least 138 "*postmenopausal, osteoporotic women with vertebral fractures*" to determine "*rates of change in total body bone mineral, lumbar spine, and proximal femur bone mineral density, and to establish a dose response relationship*". The study design is provided in **Attachment 3**. The study was conducted in the USA.

The effect of the drug on the uterus was a secondary objective of this study.

Protocol GGGX

This was an up-to-2 year comparison of one dose of raloxifene with cyclic Premarin-containing HRT in "*at least 340..healthy, postmenopausal women*" to ascertain "*subject preferences*". The study design is provided in **Attachment 4**. The study was conducted "*worldwide*".

The effect of the drug on the uterus was not a stated objective of this study.

Protocol GGGZ

This was an at-least-2 year study comparing one dose of raloxifene with continuous Premarin-containing HRT in 100 postmenopausal women to ascertain the effect on the uterus. The study design is provided in **Attachment 5**. The study was conducted in Canada.

The effect of the drug on the uterus was a primary objective of this study.

Discussion of the uterine findings

The sponsor's presentation concerns the effect of the subject drug on the endometrium in the following categories:

1. "***Endometrial thickness***"

Findings from protocols with data deemed related to this issue are presented by means of a series of comparisons provided in Tables ISS.6.35. through ISS.6.41. Two outcomes are discussed: "*mean change in endometrial thickness from baseline to endpoint*" and the "*percentage of patients who developed a thick endometrium*". (A thick endometrium is defined as 5 mm thick or greater.)

1.1. Tables 6.35 and 6.38 display findings from protocols GGGF, GGGG, and GGGN, and compare 3 doses of raloxifene with placebo with 200 or more subjects in each of 4 cells.

These tables demonstrate that none of the raloxifene doses were distinguishable from placebo in terms of the

2 outcomes under consideration.

1.2. Tables 6.36 and 6.39 display findings from protocol GGGM, comparing 1 dose of raloxifene with estrogen, with less than 20 subjects in each of 2 cells.

These tables demonstrate that estrogen has a greater effect than raloxifene on the 2 outcomes under consideration.

1.3. Tables 6.37 and 6.40 display findings from protocol GGGZ (Table 6.40 also includes data from GGGX), comparing 1 dose of raloxifene with HRT, with over 40 subjects in each of 2 cells.

These tables demonstrate that HRT and raloxifene have the same effect on the 2 outcomes under consideration.

Conclusion: One may agree with the sponsor that "*(f)ollowing a maximum of 2 years treatment, no significant difference was observed from baseline to endpoint in the percentage of patients that developed notable increases in endometrial thickness between raloxifene and placebo*".

2. "***Vaginal bleeding***"

This issue was less effectively studied than endometrial thickness because, as stated by the sponsor, "*the investigation of patients with vaginal bleeding was left to the discretion of the clinician in the majority of cases*", with the result that many subjects were not followed as assiduously as would be desired. Furthermore, the sponsor provides no definition of "*vaginal bleeding*", which, apparently, included "*vaginal spotting*". (See **Comments**.)

2.1. Study GGGZ (the only one specifically designed to study effects on the uterus) was a comparison of 1 dose of raloxifene with HRT. It demonstrated "*vaginal bleeding or spotting*" in %7.6 (5 of 66) of women on raloxifene and 63.8% (44 of 66) of women on HRT.

2.2. Table 6.42. displays data from studies GGGF, GGGG, GGGN, and GGGY (the protocol of which was not obtained), and demonstrates that subjects on 3 different doses of raloxifene had significantly less bleeding that subjects on placebo. Each of 4 cells displays 230 or more subjects.

2.3. Table 6.43. displays data from study and demonstrates that subjects on 1 dose of raloxifene had significantly less bleeding that subjects on estrogen. Each of 2 cells displays 19 or more subjects.

2.4. Table 6.44. displays data from studies GGGR (the protocol of which was also not obtained), GGGX, GGGY, and GGGZ, and demonstrates that subjects on 2 different doses of raloxifene had significantly less bleeding that subjects on HRT. There were 75 subjects on HRT and 138 and 274 on each of 2 doses of raloxifene.

Conclusion: Despite the deficiencies in this presentation, it is seems correct to agree with the sponsor's claim that "*the incidence of vaginal bleeding during raloxifene treatment is rare and indistinguishable from placebo*".

3. "***Endometrial biopsies***"

3.1. "***WHO/Blaustein Endometrial Biopsy Mapping***"

Again, this issue was examined in a less robust fashion than desired because biopsies were often "*left to the discretion of the clinician*", and the "*gynecological surveillance algorithm*" was applied in a minority of subjects. (The number of subjects to whom the algorithm was applied is not provided.)

Patients in 3 studies (GGGB, GGGM, and GGGZ) were subject to entry and exit biopsies with the following results:

3.1.1 Study GGGB, with 208 subjects for 8 weeks: Percent with proliferative endometrium at the endpoint:

placebo	21 %
raloxifene	4.6%
estrogen	85 %

3.1.2. Study GGGM, with only 10 endpoint biopsies after 6 months treatment, was too small to be of significance.

3.1.3. Study GGGZ, with 84 patients for 12 months: Percent with proliferative endometrium at the endpoint:

raloxifene	2.2%
HRT	36.1%

Conclusion: Despite the deficiencies in this presentation, one may agree with the sponsor these biopsy studies support the "*endometrial neutrality of raloxifene*".

3.2. "***Estrogen Effect Grade***"

The sponsor states that an "*estrogen effect grade*" (defined as a "*scoring system based on standard glandular and stromal morphologic criteria..used to quantitate estrogen-induced effects in postmenopausal endometrium* (sic!)" was also employed in GGGB and GGGZ. Unfortunately, insufficient details of this system and its application are provided to allow proper evaluation. Furthermore no results are provided other than p values.

Conclusion: More information must be provided if these findings are to be evaluated.

3.3. "***Uterine surveillance***"

Using the "*uterine surveillance algorithm*" to monitor episodes of vaginal bleeding and cases of thickened endometrium, the following data were obtained:

3.3.1. In study GGGX 413 subjects were randomly assigned to raloxifene or HRT:

8 subjects on raloxifene had increased endometrial thickness; 4 were biopsied at endpoint with the following results:

- proliferative endometrium: 4
- polyp: 1
- atrophic endometrium: 1

35 subjects on HRT had increased endometrial thickness; 13 were biopsied at endpoint with the following results:

- proliferative endometrium: 10
- polyp: 1
- endometrial hyperplasia: 1
- surface endometrium only: 1

3.3.2. In studies GGGF and GGGG, a total of 92 subjects were biopsied "*because of endometrial thickness changes or vaginal bleeding deemed clinically significant by the investigator*".

Subjects whose biopsies showed "*proliferative changes, polyps, or malignancy*" were distributed as follows:

placebo: 5 of 21 (23.8%)
raloxifene "*low dose*": 2 of 14 (14.3%)
raloxifene 60 mg: 2 of 22 (9.0%)
raloxifene "*high dose*": 3 of 23 (13.0%)

Conclusion: Insufficient details, such as a more precise definition of "*uterine surveillance*" and the doses of the drug used, are presented to allow evaluation of these findings.

4. "***Uterine carcinoma***"

In all, despite screening, 9 cases of uterine carcinoma were reported to the sponsor in "*all raloxifene clinical studies*": 8 on the subject drug and 1 on placebo; apparently there were none on estrogen alone or HRT. The 8 drug-associated cases were reviewed by an "*Adjudication Review Board*" (composition not provided), apparently blindly, and were all deemed by the Board to be due to a "*pre-existing abnormality*".

Attachment 7 displays the details provided of the 8 cases of uterine cancer. It seems correct to agree that most of the cases may be due to a "*pre-existing abnormality*". Two cases (**GGGF**-300-1574 and **GGGG**-006-3651), however, do not seem to be clearly due to a "*pre-existing abnormality*". It's' also troubling to note that there appears to be discordance between Table ISS.6.45., which displays 3 cancer cases on raloxifene from study GGGK, whereas Table ISS.6.46. displays only 1 case.

Conclusion: See Recommendation #3.

Comments

In attempting to answer the question posed in the consultation, it must be said that these studies, primarily designed to study the effect of the drug on osteoporosis, are compromised by that fact that, except for Protocol GGGZ, they were not designed primarily to study effects on the endometrium. The rigor of the findings is further weakened by the fact that for the majority of subjects, "*the investigation of patients with vaginal bleeding was left to the discretion of the clinician in the majority of cases*" with the result that the seemingly useful algorithm

presented in **Attachment 6** was not employed in most cases. Furthermore, the number of patients subjected to the algorithm is not provided, nor is the use of the algorithm integrated into the sponsor's presentation.

Nevertheless, almost 1800 subjects were studied in the protocol reviewed in preparing this consultation, providing data of sufficient power to permit agreement with the sponsor that raloxifene appears to have a "*benign*" effect on the endometrium at least in terms of "*endometrial thickness*", "*vaginal bleeding*", and "*endometrial biopsy mapping*".

There is a problem, however, related to "*uterine carcinoma*", with at least 2 cases that cannot be clearly attributable to a "*pre-existing abnormality*", and the unexpected finding that there were no cases of cancer seen in subjects on estrogen or HRT.

Recommendations

HFD-510 has asked if the drug has been "**appropriately evaluated with respect to its effect on the endometrium and risk for endometrial cancer**".

1. The response to the first portion of the question is favorable in terms of "*endometrial thickness*", "*vaginal bleeding*", and "*endometrial biopsy mapping*".

2. The findings for the "*estrogen effect grade*" and "*uterine surveillance*", however, are inadequately presented and cannot be evaluated.

3. The response concerning the "**risk for endometrial cancer**" is in doubt and should be subjected to a careful statistical review. (Dr. Bruce Stadel in HFD-580 has indicated that he would be willing to undertake such a review.)

4. Finally, although not addressed in the request for consultation, the sponsor should be asked to provide clearly presented findings concerning clinical evidence of estrogen stimulation, including effects on fibroids and the ovary.

Philip A. Corfman, MD
Medical Reviewer

cc: IND/NDA Arch
HFD-580/Rarick/Jolson/Corfman//wpfiles\20815.nda

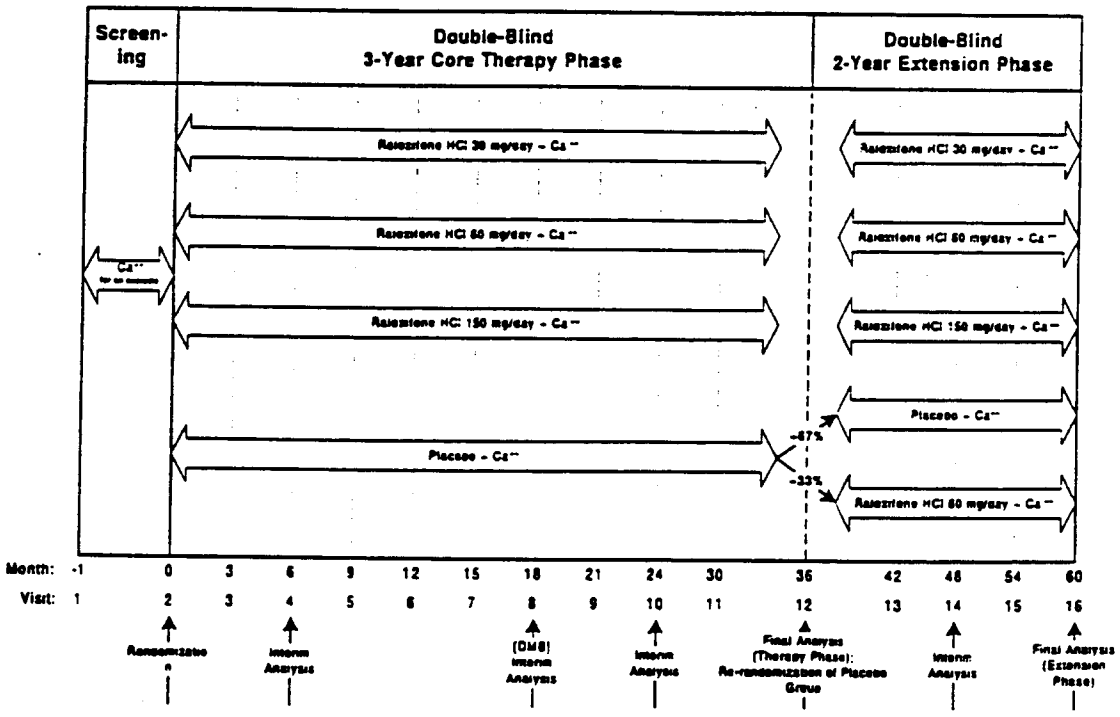
Jolson MD 10/10/97

10/20/97

10-15-97 attached memo from Dr. Stadel

BEST POSSIBLE COPY

This is a Phase 3, multicenter, double-blind, placebo-controlled, randomized study. Approximately 480 subjects will be enrolled and randomly assigned to one of four therapy groups (three doses of raloxifene hydrochloride and placebo) (Figure GGGF.1). All subjects in all groups will be provided daily calcium supplementation throughout the study. Subjects will be treated daily for at least 3 years (36 months) and may elect to continue in a 2-year extension phase. A maximum of 16 visits will be scheduled. Visits will occur at screening, every 3 months for the first 2 years (Months 0 to 24), and every 6 months after the first 2 years (Months 30 to 60) (Attachment GGGF.1).



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This is a Phase 2, single-center, double-blind, randomized, pilot study. The study will consist of five phases: a screening phase, a 24-week double-blind therapy phase, a 6- to 10-week therapy follow-up phase, an optional 18-month open-label extension phase, and a 2-week extension follow-up phase (Figure GGGM.3.1). Up to 48 subjects will be enrolled and randomly assigned to one of two double-blind therapy groups (60-mg dose of raloxifene hydrochloride or 0.625-mg dose Premarin®). Subjects will be treated daily for 24 weeks (6 months) during double-blind therapy. During a 6- to 10-week follow-up phase, subjects with an intact uterus will receive Provera® for 10 to 14 days beginning the day following Visit 7; subjects who have undergone a hysterectomy will not receive any medication. The sponsor may decide to continue the study into an optional 18-month extension phase (see Section 3.10.3). A maximum of 10 visits will be scheduled, not including the optional 18-month extension phase. Visits will occur at screening (Visits 0 and 1) and at Weeks 0, 4, 10, 18, 22, 24, 26, and between Weeks 30 to 34 (Attachment GGGM.1). If a subject continues into the 18-month extension phase, daily open-label treatment with either raloxifene hydrochloride 60 mg, continuous combined HRT (Premarin 0.625 mg and Provera 2.5 mg) or unopposed Premarin® 0.625 mg, depending upon subject decision, will be initiated at Visit 9. In addition, 5 visits will be scheduled to occur after 6, 12, 17, and 18 months of the extension phase with a follow-up visit scheduled for 2 weeks after the 18-month visit.

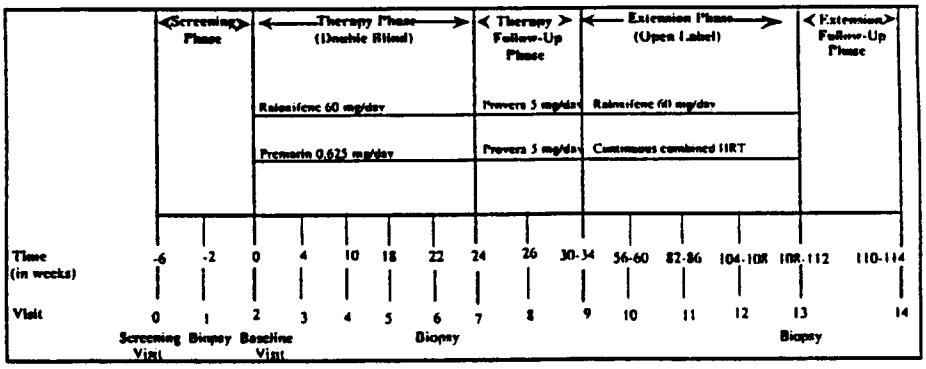

Figure GGGM.3.1. Study design, Protocol H3S-MC-GGGM.
Provera® administration is open-label during the therapy follow-up phase and will be administered for 10 to 14 days starting the day after Visit 7 (therapy follow-up phase). Each subject will choose her therapy group during the extension phase.

This will be a Phase 2, two-site, parallel, placebo-controlled, randomized, double-blind study. This study will consist of four phases (Figure GGGN.1): a screening/washout phase, a double-blind treatment phase, an optional (to the patient) 1-year double-blind extension phase, and an open-label extension phase (not pictured). For the first 2 years, a maximum of 7 visits will be scheduled. Visits will occur at screening, Month 0 (baseline), Months 1, 6, 12, 18, and 24, and once yearly thereafter (Attachment GGGN.1).

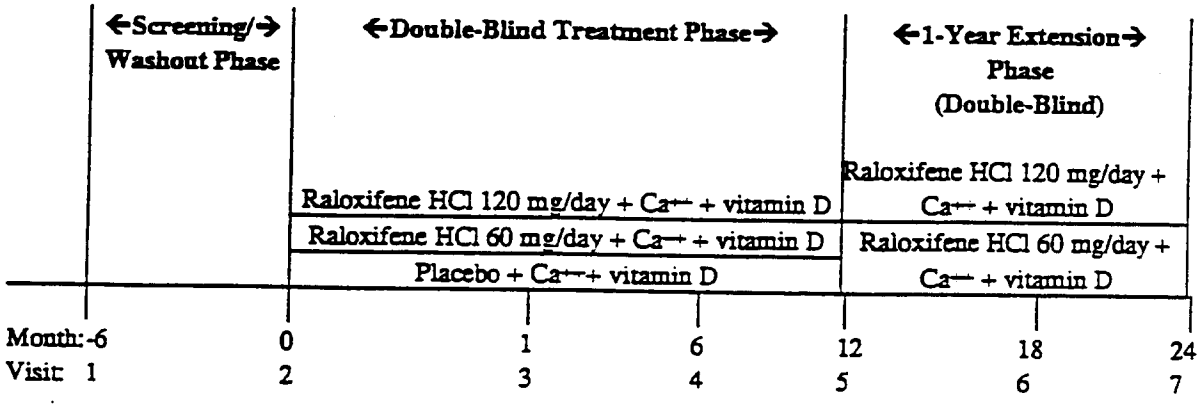

Figure GGGN.1. **Study design, Protocol H3S-MC-GGGN. Ca++ and vitamin D administration are open-label during the entire study, starting at Visit 2. During the 1-year extension, raloxifene hydrochloride administration will be double-blind.**

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ON ORIGINAL

Study H3S-MC-GGGX will be a Phase 3, multicenter, unblinded study. At least 340 subjects will be randomly assigned to treatment with raloxifene hydrochloride or HRT administered in a cyclic fashion.

Therefore, 170 subjects will be assigned to each of the two therapy groups. Subjects in the HRT therapy group will receive one of two cyclic HRT therapies (Section 3.6.1.2). All subjects in all therapy groups will receive calcium supplementation of approximately 400 to 600 mg/day throughout the study from Visits 1 through 7.

This study will consist of two phases: a screening phase and a 2-year therapy phase (Figure GGGX.1). Subjects will be treated daily for 2 years. Visits will occur at screening, baseline (Visit 2) and 3, 6, 12, 18, and 24 months (Visits 3 through 7) of the study (Schedule of Events in Attachment GGGX.1). An interim analysis will be performed at 1 year for the purposes of filing these data in a regulatory submission (see Section 4.5).

Subject preferences (utilities) will be assessed at Visits 2 through 7. Biochemical markers of bone turnover and serum lipids will be assessed at baseline (Visit 2) and Visits 5 and 7. BMD determinations will be assessed twice during the period beginning with Visit 1 and ending with Visit 2; BMD will also be measured at Visits 5 and 7.

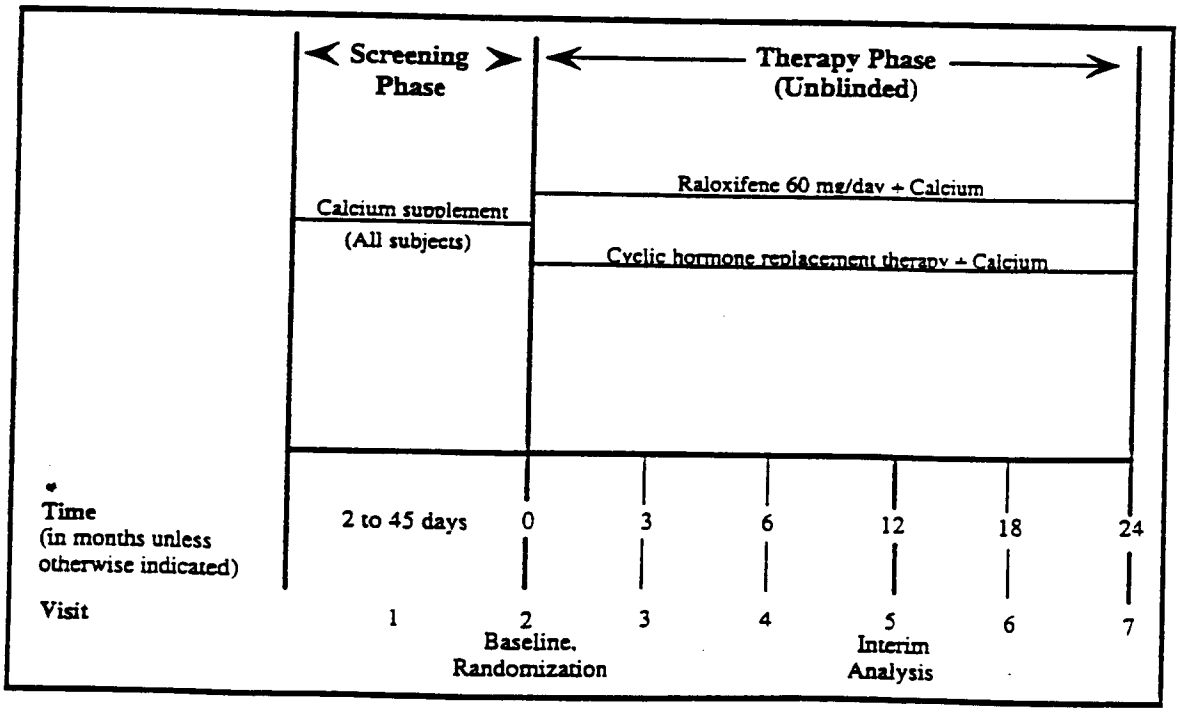

Figure GGGX.1. Illustration of study design, Protocol H3S-MC-GGGX.

Study H3S-MC-GGGX will be a Phase 3, multicenter, unblinded study. At least 340 subjects will be randomly assigned to treatment with raloxifene hydrochloride or HRT administered in a cyclic fashion.

Therefore, 170 subjects will be assigned to each of the two therapy groups. Subjects in the HRT therapy group will receive one of two cyclic HRT therapies (Section 3.6.1.2). All subjects in all therapy groups will receive calcium supplementation of approximately 400 to 600 mg/day throughout the study from Visits 1 through 7.

This study will consist of two phases: a screening phase and a 2-year therapy phase (Figure GGGX.1). Subjects will be treated daily for 2 years. Visits will occur at screening, baseline (Visit 2) and 3, 6, 12, 18, and 24 months (Visits 3 through 7) of the study (Schedule of Events in Attachment GGGX.1). An interim analysis will be performed at 1 year for the purposes of filing these data in a regulatory submission (see Section 4.5).

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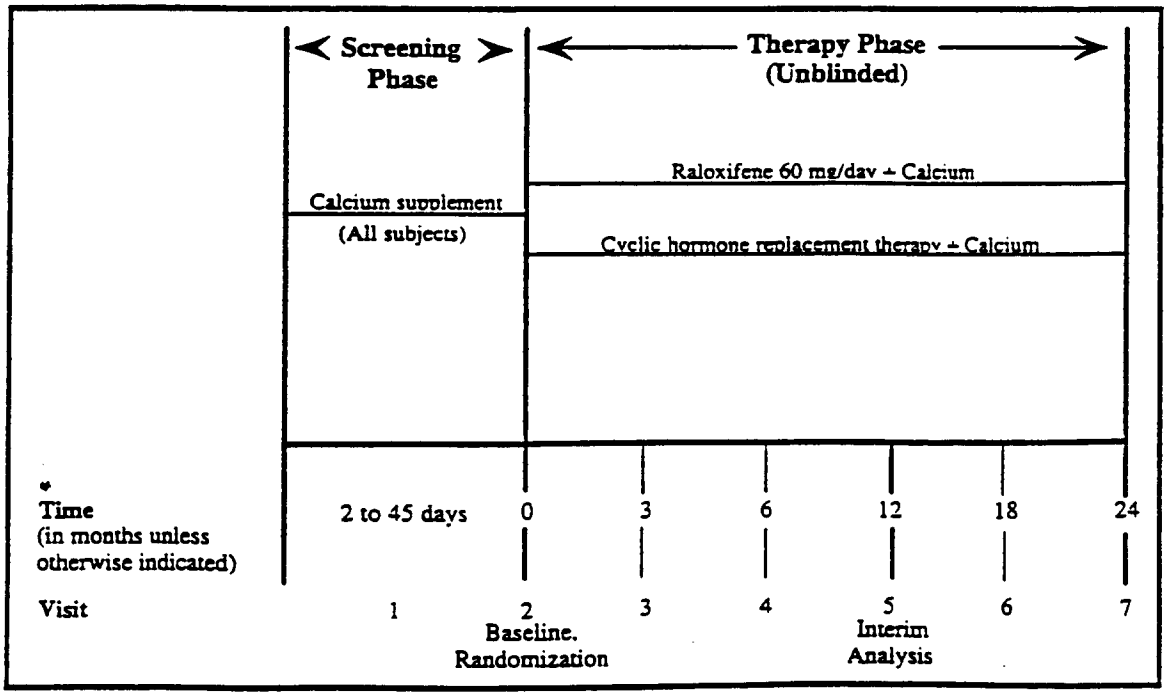


Figure GGGX.1. Illustration of study design, Protocol H3S-MC-GGGX.

This is a Phase 3, multicenter, double-blind, randomized study. Approximately 100 subjects will be enrolled and randomly allocated to one of two therapy groups [raloxifene hydrochloride and continuous HRT (Figure GGGZ.2)]. Subjects will be treated daily for at least 2 years (24 months); the sponsor may decide to offer raloxifene-treated patients raloxifene for up to 2 years after the study has been closed and the results evaluated. All subjects will receive 500 mg oral calcium supplement in addition. A maximum of 6 visits will be scheduled. Visits will occur at screening, baseline (Visit 2), and every 6 months thereafter until end of the study (Attachment GGGZ.1).

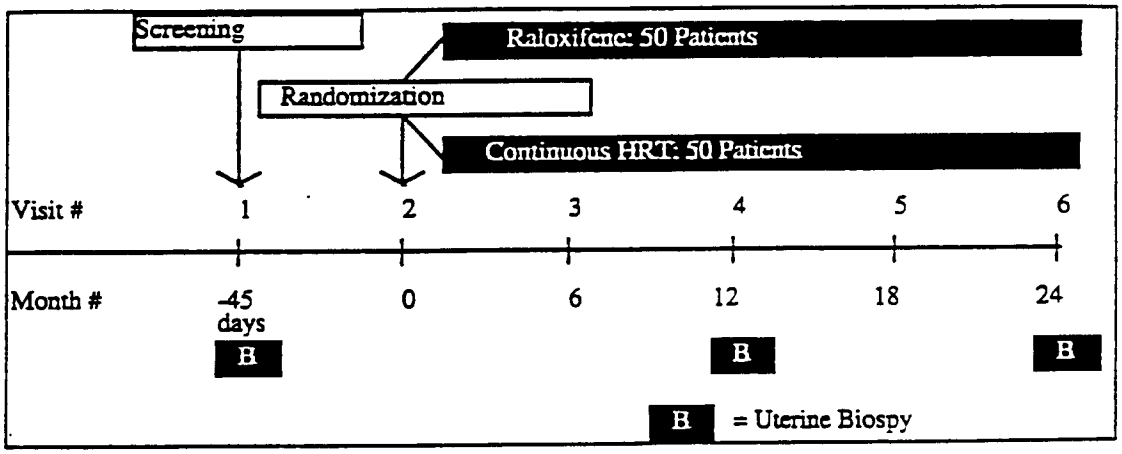


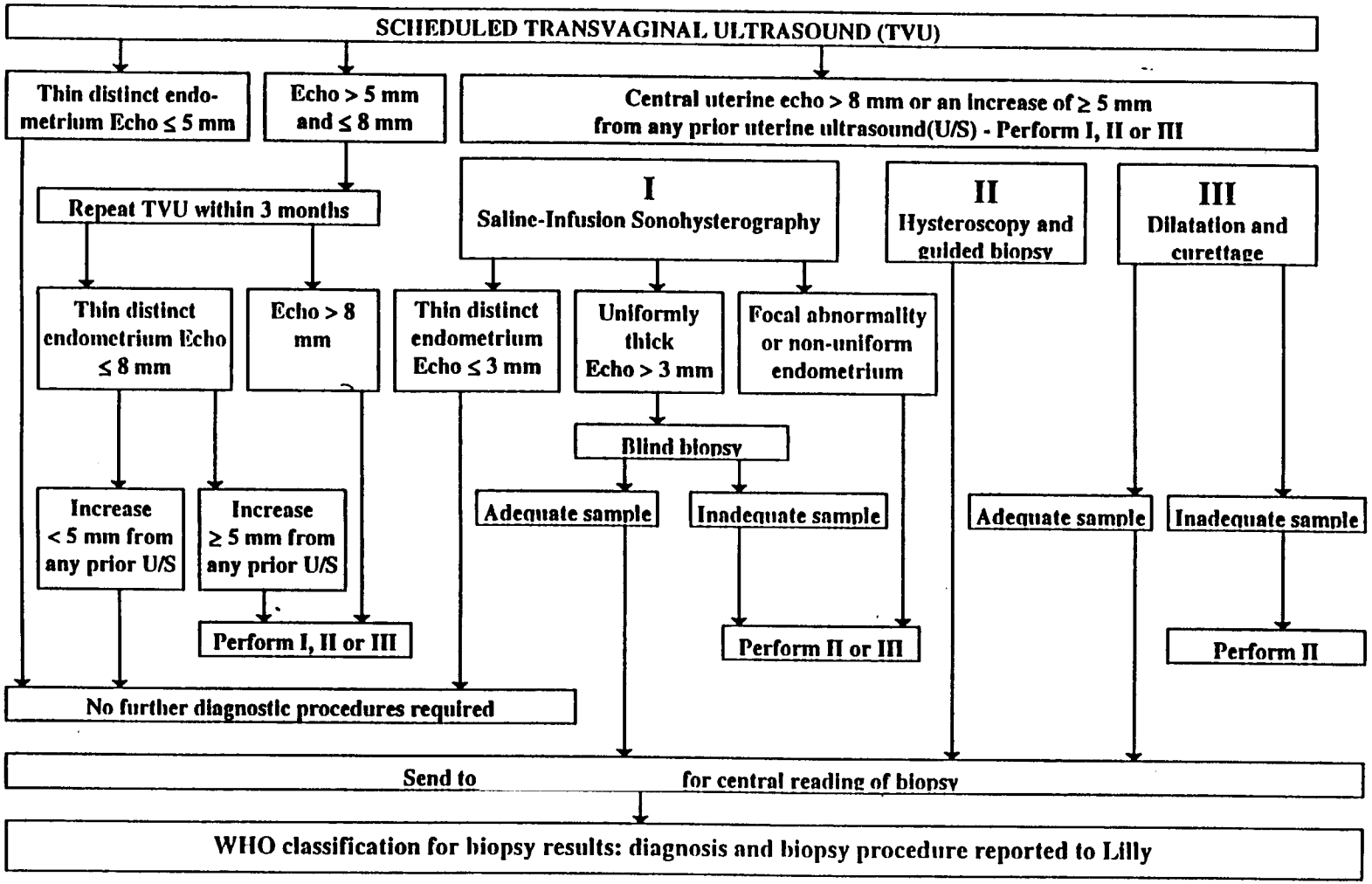
Figure GGGZ.2. Illustration of study design, Protocol H3S-CA-GGGZ.

Interim analyses may be performed when at least 80 subjects have completed Visit 4 (12 months) or had a gynecological assessment done at discontinuation (see Section 4.4). The purpose of the 12 month interim analysis is to assess safety and efficacy. Since the recently completed Phase 2 study (H3S-MC-GGGB) investigated dosing with raloxifene hydrochloride for only 8 weeks, an analysis of the endometrial bioptic material will also be undertaken at 12 months. The purpose of the 1-year analysis will be to evaluate this study for possible regulatory submission by Eli Lilly and Company.

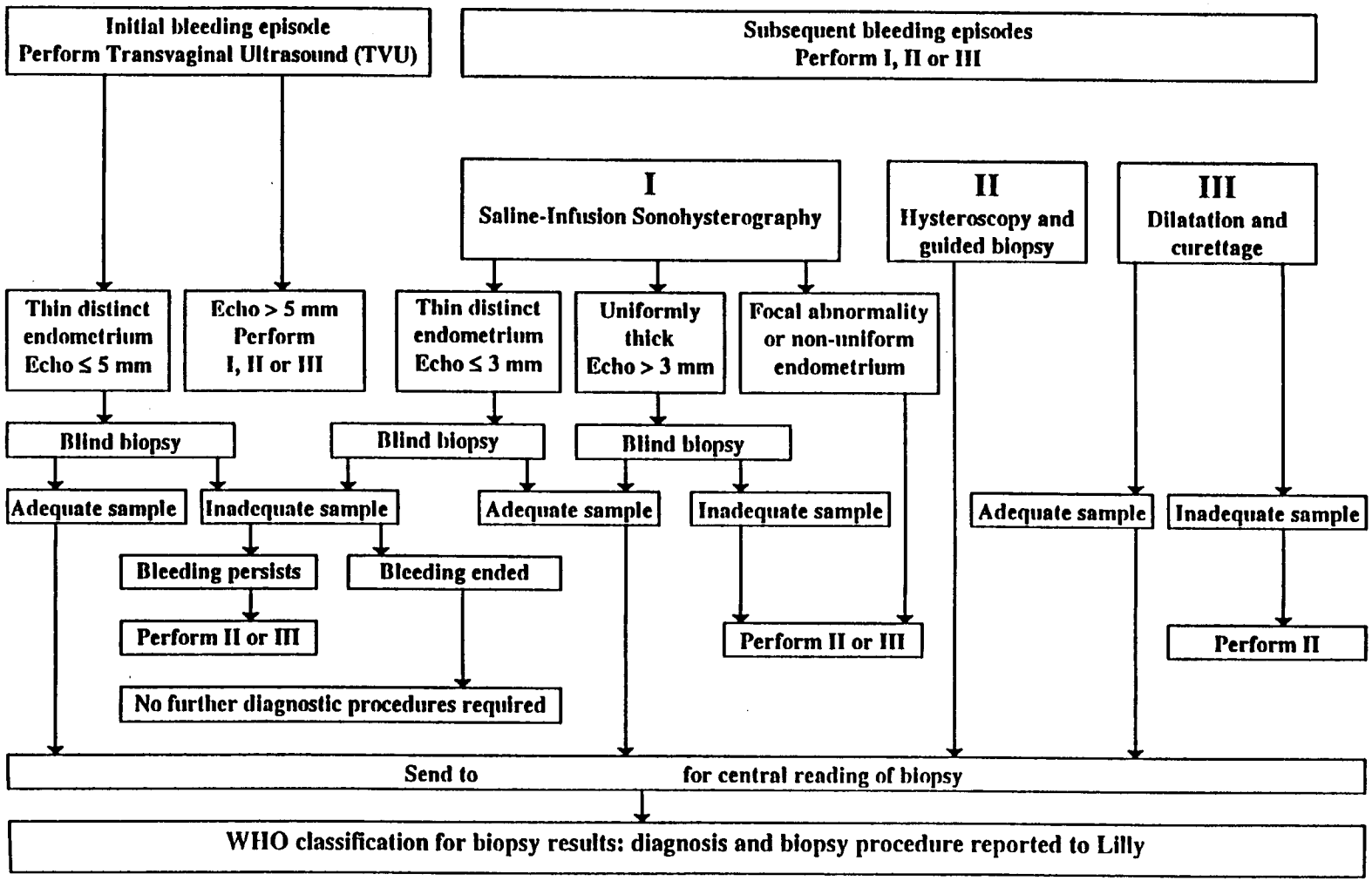
The final analyses will be performed when at least 80 subjects have completed Visit 6 (24 months) or had a gynecological assessment done at discontinuation (see Section 4.4). Data from subjects who complete the protocol after the final analyses will be summarized or analyzed as appropriate. Alternatively, if there are fewer than 40 subjects remaining in each treatment group at study conclusion, the final analysis will be performed when all these subjects have completed the protocol.

A pelvic ultrasound will be done at Visits 1, 4, and 6. The results from sonographic investigation of the uterus will be analyzed and interpreted centrally.
Uterine biopsies will be performed at Visits 1, 4, and 6, *after* the ultrasound is performed. The bioptic material will be analyzed centrally. The pathologist will be kept blinded as to the study drug used (raloxifene hydrochloride or continuous HRT).

ALL SUBJECTS WITH SCHEDULED TRANSVAGINAL ULTRASOUND



ALL SUBJECTS WITH UTERINE BLEEDING



A history and adjudication of each case follows:

Placebo

GGGK-281-0036

Duration of Treatment: 13 months
Presenting Symptom: Abnormality on US detected at baseline, but randomly assigned.
Method of Diagnosis: D&C
Histology: Mucinous carcinoma
Treatment: Hysterectomy and bilateral oophorectomy
Histology: Endometrioid adenocarcinoma - Stage 1BG2
Adjudication: Not adjudicated.

Raloxifene HCl 30 mg

GGGF-300-1574

Duration of Treatment: 5.5 months
Baseline Endometrium Thickness: 2.0 mm
Baseline Biopsy: Not indicated
Presenting Symptom: Bleeding
Six-Month Endometrium Thickness: 12.0 mm
Method of Diagnosis: D&C
Histology: Polymorphous adenocarcinoma.

Treatment: Hysterectomy
Histology: Infiltrating adenocarcinoma with regional lymphadenopathy
Adjudication: Baseline ultrasound was suboptimal and suggests preexisting disease. The treatment effect was impossible to assess.

GGGG-022-4109

Duration of Treatment: 6 months
Baseline Endometrium Thickness: 10.0 mm
Baseline Biopsy: Fragments of stroma and superficial fragmented glands
Presenting Symptom: Nil
Six-Month Endometrium Thickness: 13.0 mm
Method of Diagnosis: Blind biopsy
Histology: Complex hyperplasia with severe atypia
Treatment: Hysterectomy
Histology: Stage 1B, adenocarcinoma
Adjudication: Baseline endometrium was abnormal and the biopsy was inadequate. Impossible to conclude if either hyperplasia or tumor was responsible for the preexisting thick endometrium.

Raloxifene HCl 60 mg

GGGK-742-0487

Duration of Treatment: 7 weeks
Baseline Endometrium Thickness: 14.0 mm
Baseline Biopsy: Hysteroscopy - normal and curettage - insufficient tissue
Presenting Symptom: DVT at 7 weeks. Stopped medication, continued follow-up. Vaginal bleeding at 6 months.
Six-month endometrium thickness: 18.0 mm
Method of Diagnosis: Papanicolaou screening smear
Histology: Endometrial adenocarcinoma
Treatment: Hysterectomy
Histology: Stage 1B, clear cell carcinoma of the endometrium
Adjudication: Baseline endometrium was abnormal and duration of treatment very short, therefore preexisting cancer present at randomization.

Raloxifene HCl 120 mg

GGGK-865-8493

Duration of Treatment: 3 weeks
Baseline Endometrium Thickness: Not indicated
Baseline Biopsy: Not indicated
Presenting Symptom: Initial prerandomization Papanicolaou screening smear reported normal, subsequent evaluation - atypical endometrial glandular cells.
Method of Diagnosis: D&C

Histology: Endometrial adenocarcinoma Grade III
Treatment: Hysterectomy
Histology: Stage 1B, clear cell carcinoma of the endometrium
Adjudication: Preexisting cancer present at randomization.

GGGK-742-3262

Duration of Treatment: 1 day
Baseline Endometrium Thickness: Reported as abnormal of undefined clinical significance.
Baseline Biopsy: Not indicated
Presenting Symptom: Abnormal ultrasound
Method of Diagnosis: D&C
Histology: Endometrial adenocarcinoma
Treatment: Hysterectomy
Histology: Well differentiated adenocarcinoma of the endometrium
Adjudication: Preexisting cancer present at randomization.

Raloxifene HCl 150 mg

GGGG-006-3651

Duration of Treatment: 18 months
Baseline Endometrium Thickness: 1.6 mm
Six-Month Endometrium Thickness: 1.9 mm
12-Month Endometrium Thickness: 0.7 mm
Baseline Biopsy: Not done
Presenting Symptom: Intermittent vaginal spotting commencing at 6 months. Heavy vaginal bleeding at 13 months and continued intermittently to Month 18.
18-Month Endometrium Thickness: Undetermined due to bleeding
Method of Diagnosis: Blind biopsy
Histology: Endometrial adenocarcinoma
Treatment: Hysterectomy
Histology: Stage 1B, Grade 1 adenocarcinoma
Adjudication: In contrast to the original report, the baseline ultrasound was clearly abnormal and the thickness measurement inaccurate. It is impossible to determine if the cancer was preexisting or there was preexisting hyperplasia or other abnormalities to account for the preexisting disease at baseline.

GGHG-160-3312

Duration of Treatment: 5 months
Baseline Endometrium Thickness: 4.0 mm - Submucous myoma, 29x30 mm
Baseline SIS: Normal

Baseline Biopsy: Insufficient tissue for diagnosis
Three-Month Endometrial Thickness: 4.0 mm - Submucous myoma, 30x30 mm
Presenting Symptom: Continuous vaginal bleeding at 6 months
Method of Diagnosis: Chest x-ray prior to hysteroscopy suggests pulmonary metastasis. Hysteroscopy and D&C performed.
Histology: Small clusters of malignant cells of unspecified origin
Treatment: Hysterectomy and bilateral oophorectomy
Histology: Undifferentiated sarcoma of uterus
Adjudication: The patient had vaginal bleeding at enrollment and this was unfortunately overlooked. The baseline ultrasound demonstrated no intraluminal disease. The question of whether the myoma was in fact a sarcoma at enrollment, underwent sarcomatous change, or that a new sarcoma developed during the study cannot be conclusively determined.

Raloxifene HCl 300 mg

JOAA-105-0041

Duration of Treatment: 6 months
Presenting Symptom: Continuous vaginal discharge and bleeding prior to randomization. Metastatic breast cancer patient.
Biopsy: Atypical hyperplasia
Method of Diagnosis: Hysteroscopy and D&C performed.
Histology: Well-differentiated adenocarcinoma
Treatment: Hysterectomy and bilateral oophorectomy
Histology: Grade 1 endometrial adenocarcinoma
Adjudication: In view of history of metastatic disease and uterine bleeding predating randomization, a preexisting condition is the most likely scenario.

Memo to the file

NDA 20-815
11/25/97

This memo is to confirm that a review of the 4-month safety update submitted on October 8, 1997 has been incorporated into my review, which was completed on November 19, 1997.

10/8/97
Eric Colman, M.D.

Gloria Troendle 11-26-97

APPEARS THIS WAY
ON ORIGINAL

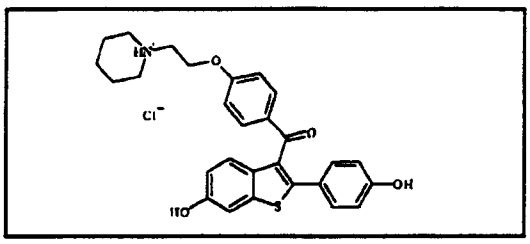
APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020815

CHEMISTRY REVIEW(S)

$C_{28}H_{27}NO_4S.HCl$ Molecular Weight: 510.05
CAS #s 82640-04-8 (hydrochloride salt)
84449-90-1 (free base)



SUPPORTING DOCUMENTS:

RELATED DOCUMENTS: None

CONSULTS: Environmental Assessment (HFD-004)

REMARKS/COMMENTS:
The amendment, dated 7-3-97, provides a revised Environmental Assessment report. The 7-18-97 amendment provides documentation that a product called E-VISTA is no longer marketed and that references to its name will be withdrawn from a number of publications which list this name. The correspondences of 7-10-97 and 8-11-97 and the two correspondences, dated 8-20-97, correct minor errors (mostly typographical) in the original submission. Finally, the 8-27-97 amendment provides for a categorical exclusion from the requirement of an Environmental Assessment.

The applicant referred

CONCLUSIONS & RECOMMENDATIONS:
From a chemistry point of view, this submission is approvable pending satisfactory response to the chemistry deficiencies. The review by the Division of Clinical Pharmacology and Biopharmaceutics, for the proposed dissolution method, and an acceptable CGMP inspection are still pending.

cc:
Orig. NDA 20-815
HFD-510/Division File
HFD-510/Sheldon Markofsky/10-29-97
HFD-510/R. Hedin (CSO)
HFD-510/D-G. Wu (Team Leader)
HFD-580/J. Gibbs

Sheldon Markofsky, Review Chemist 10-29-97

R/D Init by: Team Leader 10/29/97

filename: n20815d.wpd

DIVISION OF Metabolism and Endocrine DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-815 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 10-29-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
NDA (Original)	6-8-97	6-9-97	6-10-97
Amendment	7-3-97	7-7-97	
Amendment	7-18-97	7-19-97	
Correspondence	7-10-97	7-15-97	
Correspondence	8-11-97	8-12-97	
Correspondence	8-20-97	8-22-97	
Correspondence	8-20-97	8-27-97	
Amendment	8-28-97	8-29-97	

NAME & ADDRESS OF APPLICANT:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

APPEARS THIS WAY
ON ORIGINAL

DRUG PRODUCT NAME:
Proprietary: Evista
Nonproprietary: Raloxifene hydrochloride
Code Name/#: LY139481.HCl
Chem. type/Ther. Class: 1 P

PHARMACOL.CATEGORY/INDICATION:
Prevention of postmenopausal osteoporosis

DOSAGE FORM:
Tablets (oral)

STRENGTHS: 60 mg tablets

ROUTE OF ADMINISTRATION: Oral

DISPENSED: ___X___ Rx _____ OTC

CHEMICAL NAMES, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
International Non-proprietary Name (INN): Raloxifene
Non-proprietary Name (USAN): Raloxifene Hydrochloride

Chemical Names (USAN): 1) Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride
2) 6-Hydroxy-2-(*p*-hydroxyphenyl)benzo[*b*]thien-3-yl-p-(2-piperidinoethoxy)phenyl ketone, hydrochloride

DIVISION OF Metabolism and Endocrine DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-815 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 12-5-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	11-13-97	11-14-97	11-18-97
Amendment	11-24-97	11-25-97	11-26-97
Amendment	11-25-97	11-26-97	11-28-97

NAME & ADDRESS OF APPLICANT:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DRUG PRODUCT NAME:
Proprietary: Evista
Nonproprietary: Raloxifene hydrochloride
Code Name/#: LY139481.HCl
Chem. type/Ther. Class: 1 P

PHARMACOL.CATEGORY/INDICATION:
Prevention of postmenopausal osteoporosis

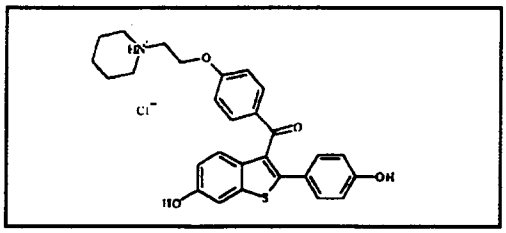
DOSAGE FORM:
Tablets (oral)

STRENGTHS: 60 mg tablets

ROUTE OF ADMINISTRATION: Oral

DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAMES, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
International Non-proprietary Name (INN): Raloxifene
Non-proprietary Name (USAN): Raloxifene Hydrochloride
Chemical Names (USAN): 1) Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride
2) 6-Hydroxy-2-(*p*-hydroxyphenyl)benzo[*b*]thien-3-yl-*p*-(2-piperidinoethoxy)phenyl ketone, hydrochloride
$C_{28}H_{27}NO_4S.HCl$ Molecular Weight: 510.05
CAS #s 82640-04-8 (hydrochloride salt); 84449-90-1 (free base)



SUPPORTING DOCUMENTS:

RELATED DOCUMENTS : None

CONSULTS: none

REMARKS/COMMENTS:

The firm has made the following commitments regarding post-approval stability testing:

CONCLUSIONS & RECOMMENDATIONS:

Satisfactory CMC information has been provided; and the application is approvable, from a Chemistry point of view.

cc:
Orig. NDA 20-815
HFD-510/Division File
HFD-510/Sheldon Markofsky/12-5-97
HFD-510/R. Hedin (CSO)
HFD-510/D-G. Wu (Team Leader)
HFD-580/J. Gibbs

Sheldon Markofsky, Review Chemist

R/D Init by: Team Leader

filename: n20815.2a

12/5/97

Memorandum

Date: November 26, 1997

11/26/97

From: Duu-Gong Wu, Ph.D., Chemistry Team Leader, DNDCII

Subject: Chemistry Review

To: NDA 20-815 [Evista(raloxifene HCl)tablets]

The chemistry review for the subject NDA , including microbiology, trademark review, and establishment evaluation, have been completed and there is no more outstanding chemistry issue. The final chemistry review is currently being revised by the reviewer, Dr. Markofsky. **From chemistry standpoint, this NDA can be approved.**

CC: NDA 20-518
HFD-510 Consult files
HFD-510/S. Markofsky/R. Hedin/DG. Wu

Consult #807 (HFD-510)

EVISTA raloxifene hydrochloride capsules

The following look alike/sound alike conflicts were noted: E-Vista. The Committee felt there was high potential for mix-up with the conflicting names. There were no misleading aspects found in the proposed proprietary name. It is recommended that the sponsor determine if the product E-vista is still marketed and if so, to change there proposed proprietary name accordingly.

The Committee finds the proposed proprietary name unacceptable.

D L Boring 7/16/97, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

TERTIARY CHEMISTRY REVIEW NDA 20-815

REC'D 12/1/97

COMP 12/2/97

APPLICATION STATUS: Recommend Approval

EA: Categorical Exclusion per 21 CFR 25.31(b) as revised in FR notice of 7/29/97 (page 40593).

EER: Acceptable (EES) 11/19/97

NOMENCLATURE: Trade name EVISTA was declared NOT ACCEPTABLE by Labeling & Nomenclature Committee. See Consult # 807 dated 7/16/97 from Labeling & Nomenclature Cmte. However, see also Chemistry Reviews

However, the July 18, 1997 amendment to the NDA contains letters from the former manufacturer of E-VISTA (Eastrace Pharmaceuticals Inc.) to the publishers of American Drug Index, 1996 Edition of the United States Pharmacopeial Convention, Inc., and 1997 Edition of Physicians' GENRX, stating that E-VISTA is no longer manufactured and requesting that this be removed from the respective publications at the next printing.

CHEMISTRY, MANUFACTURING, and CONTROLS:

From the standpoint of chemistry, manufacturing, and controls this application may be approved. See See Chemistry Reviews # 1 and # 2 and Memorandum from Duu-Yong Wu, Ph.D., Chemistry Team Leader, dated November 26, 1997.

Dir. DNDC II (HFD-820)