

The primary efficacy analysis considered the proportion of patients with at least one incident fracture. Additional analyses included new, worsening, and clinical vertebral fractures.

Efficacy Results

Patient Disposition: See flow diagram on page 13.

Overall Population: A statistically significantly greater percentage of placebo patients (25%) discontinued prematurely from the study compared with the Rlx 60 mg (23%) and 120 mg (22%) groups ($p=0.04$ and 0.006 , respectively). However, the percentage of patients who discontinued due to an adverse event was statistically significantly greater in the Rlx 60 mg group (but not the Rlx 120 mg group) compared with the placebo group ($p=0.01$). Lack of therapeutic effect was defined a priori as a loss from baseline of more than 7% of LS BMD or of more than 10% of femoral neck BMD at the 12-month visit; or loss from baseline of more than 11% of LS BMD or of more than 14% of femoral neck BMD at the 24-month visit, or the occurrence of more than two incident vertebral fractures during the study. Four percent of placebo patients and 1.0 % of both raloxifene dose groups met the criteria for lack of therapeutic effect ($p<0.001$).

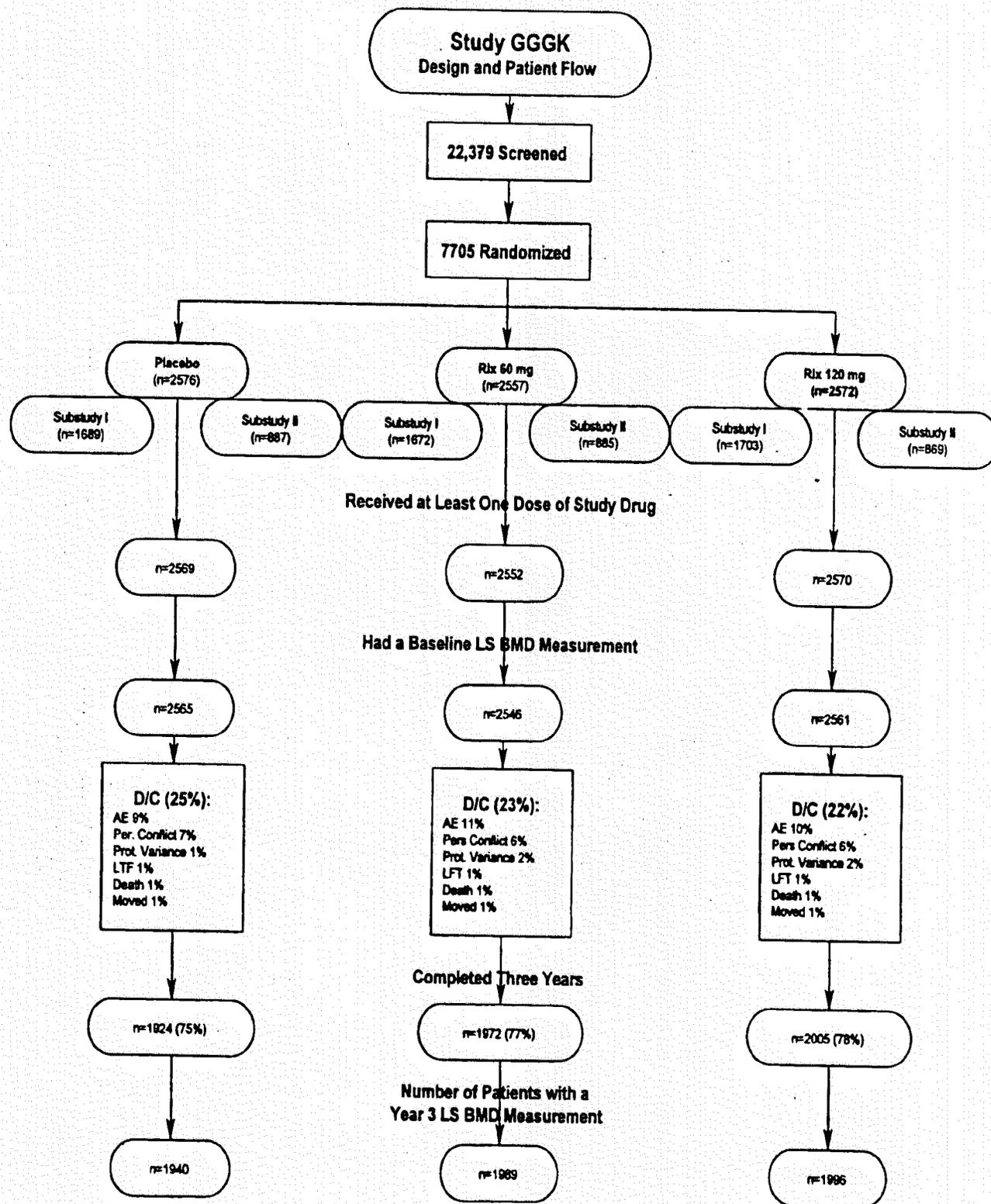
Substudy I: Twenty-two percent of placebo patients, 22% of Rlx 60 mg patients and 21% of Rlx 120 mg patients discontinued early in this substudy. There was a statistically significantly greater percentage of Rlx 60 mg subjects who discontinued because of an adverse event (10.5%) when compared to the rate in the placebo group (8.3%; $p=0.03$). There was no significant difference between the placebo and Rlx 120-mg groups for the percentage of patients discontinuing because of an adverse event. Nearly 3% of the placebo patients and only 0.6% of Rlx 60 mg subjects and 0.5% of Rlx 120 mg subjects met the criteria for lack of therapeutic effect ($p<0.001$).

Substudy II: Thirty-two percent of placebo patients, 25% of Rlx 60 mg patients and 24% of Rlx 120 mg patients discontinued early in this substudy ($p<0.001$ for both doses of Rlx vs. placebo). Although 11.6% of Rlx 60-mg patients discontinued early because of an adverse event compared with 9.8% of placebo patients, the difference was not statistically significant. Lack of therapeutic effect was much more common in the placebo group (5.9%) compared with the Rlx 60 mg group (2.0%; $p<0.001$) and the Rlx 120 mg group (1.8%; $p<0.001$).

Exposure to Study Drug: The mean number of days of exposure to the study drugs were similar for the three groups ~ 932 days.

Baseline Patient Demographics: As shown in the three tables on page 14, the groups were well matched for baseline demographic characteristics. In general, this study consisted of non-smoking Caucasian women ranging in age from 40 to 80 years and normal to slightly heavy body weight.

Of note, in Substudy I, 3% more of the Rlx 60-mg subjects relative to the placebo subjects had had a hysterectomy. While this difference was statistically significant it is unlikely that it would impact on the efficacy findings from the study. As would be predicted, subjects in Substudy II (prevalent fractures) were a bit older than subjects in Substudy II.



Baseline Demographics – Overall Study Population				
Variable	Plc (n=2576)	Rlx 60 mg (n=2557)	Rlx 120 mg (n=2572)	p-value
% Caucasian	96%	96%	95%	0.2
Age (yrs)	66.6	66.5	66.3	0.3
BMI (kg/m ²)	25	25	25	0.9
% Current Smoker	17%	17%	17%	0.9
Years PMP	19	19	19	0.3
% with Hysterectomy	22%	24%	22%	0.2
% with Previous use of HRT	29%	30%	29%	0.6

Baseline Demographics – Substudy I				
Variable	Plc (n=1689)	Rlx 60 mg (n=1672)	Rlx 120 mg (n=1703)	p-value
% Caucasian	96%	96%	95%	0.2
Age (yrs)	65.5	65.4	65.3	0.6
BMI (kg/m ²)	25	25	25	0.9
% Current Smoker	17%	17%	16%	0.7
Years PMP	18	18	17	0.4
% with Hysterectomy	22%	25%	22%	0.04
% with Previous use of HRT	30%	31%	30%	0.5

Baseline Demographics – Substudy II				
Variable	Plc (n=887)	Rlx 60 mg (n=885)	Rlx 120 mg (n=869)	p-value
% Caucasian	95%	96%	96%	0.9
Age (yrs)	68.7	68.5	68.4	0.6
BMI (kg/m ²)	26	26	26	0.7
% Current Smoker	17%	17%	18%	0.6
Years PMP	21	21	21	0.7
% with Hysterectomy	24%	22%	22%	0.5
% with Previous use of HRT	26%	28%	26%	0.9

Study Drug Compliance: Approximately 6.6% of subjects in all three groups were defined as severely noncompliant with study drug (taking less than 70% of study drug during at least two visit intervals). Approximately 97% of subjects in each group reported that they were taking the supplemental calcium and vitamin D as prescribed.

Concomitant Medications: At baseline significantly more Rlx 60 mg subjects (8.7%) compared with placebo subjects (6.5%) were taking hypolipidemic drugs. In addition, more of the Rlx 60 mg subjects vs. placebo patients were taking hypoglycemic agents at baseline: 2.2% vs. 1.2%, respectively. As for new postbaseline medication, significantly more placebo (5.7%) patients began treatment with a hypolipidemic drug compared with the Rlx 60-mg subjects (3.4%). Also, slightly more of the placebo women (1.0%) vs. of the Rlx 60 mg women (0.5%) started therapy with a progestin/androgen during the trial.

Primary Endpoints

Number of Patients with at Least One Incident Vertebral Fracture

The table below provides the data on incident vertebral fractures for the Overall population as well as the Substudy I and II populations.

Summary of Vertebral Fracture Results (LOCF)			
	Plo	Rlx 60 mg	Rlx 120 mg
Overall Population	N*=2292	N=2259	N=2277
Number of Pts with ≥ 1 incident fracture (%)	240 (10.5%)	157 (6.9%)	132 (5.8%)
RR (95% CI) vs. Plo		0.66 (0.55, 0.81) P<0.001	0.55 (0.45, 0.68) P<0.001
Substudy I	N=1522	N=1490	N=1512
Number of Pts with ≥ 1 incident fracture (%)	68 (4.5%)	35 (2.3%)	43 (2.8%)
RR (95% CI) vs. Plo		0.53 (0.35, 0.79) P=0.001	0.62 (0.44, 0.93) P=0.02
Substudy II	N=770	N=769	N=765
Number of Pts with ≥ 1 incident fracture (%)	172 (22.3%)	122 (15.9%)	89 (11.6%)
RR (95% CI) vs. Plo		0.71 (0.58, 0.88) P<0.001	0.52 (0.41, 0.66) P<0.001

*Number of patients with radiographs at baseline and endpoint

These data indicate that treatment with both doses of raloxifene statistically significantly reduce the risk for one or more incident vertebral fractures in women with and without prevalent fractures. The reductions in relative risk for the two active treatment groups compared with placebo treatment (calcium and vitamin D) were impressive, ranging from 29% to 48%.

However, it should be pointed out that, regardless of treatment group, the vast majority of women in Substudy I (low BMD) did not sustain an incident vertebral fracture during the 3-year trial. Here the reductions in absolute risk in the Rlx 60mg and 120 mg groups vs. placebo were quite small: 2.2% and 1.7%, respectively.

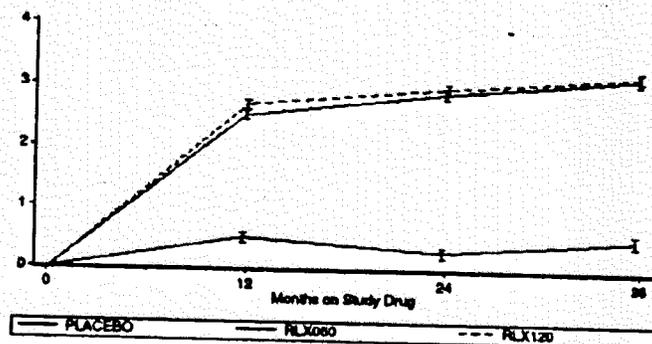
As expected, the women in Substudy II (low BMD and prevalent fracture) sustained greater reductions in absolute risk compared with relative risk reductions for incident vertebral fracture. As with most drugs, patients at highest baseline risk tend to get the most benefit from pharmacological intervention.

Expressed another way, in Substudy I, 45 women required treatment with Rlx 60 mg once daily for 3 years to prevent one patient from having one or more new vertebral fractures. However, only 15 Substudy II women needed to be treated with Rlx 60 mg once daily for 3 years to prevent one patient from having one or more new vertebral fractures.

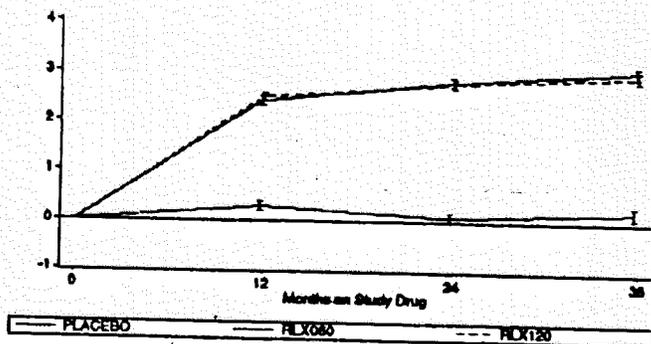
Up to two-thirds of postmenopausal vertebral fractures may be asymptomatic and there significance to the patient is difficult to assess and quantify. It is reasonable, therefore, to examine the effect of raloxifene on clinically apparent fractures, or those documented after patients report symptoms suggestive of an event. In such an analysis of the overall study population, 3.1% of placebo patients compared with 1.8% of Rlx 60-mg patients ($p=0.003$) and 1.5% of Rlx 120-mg patients ($p<0.001$) sustained a new clinically apparent vertebral fracture during the 3-year study. Approximately 77 women would need to be treated with Rlx 60 mg per day for 3 years to prevent one clinically apparent vertebral fracture.

Mean Percentage Change in LS and Femoral Neck BMD (LOCF)

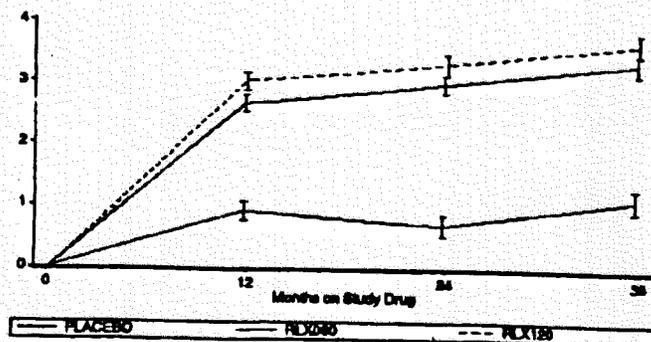
LS BMD for Overall Population: As shown in the figure below, compared to a minor increase from baseline to Month 36 in LS BMD in the placebo group, the two raloxifene groups had a steady increase in LS BMD during the first year of treatment followed by a sharp decrease in the slope of the lines. At Month 36, the difference between the placebo and Rlx 60 mg groups was 2.6% ($p < 0.001$). The two raloxifene doses did not differ significantly.



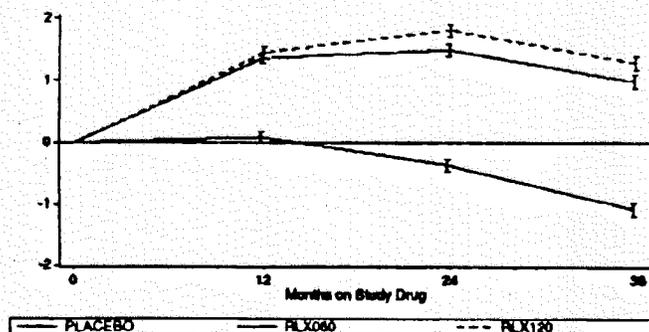
LS BMD for Substudy I: Similar results were obtained for Substudy I patients as for the Overall patient population, as shown in the below figure. At Month 36, the difference between the placebo and Rlx 60 mg groups was 2.9% ($p < 0.001$). The two raloxifene doses did not differ.



LS BMD for Substudy II: As shown in the following figure, the results in the patients with low BMD and prevalent fractures were also similar to the results from the Overall patient population. At the 36 month time point, the difference between the placebo and Rlx 60 mg groups was 2.2% ($p < 0.001$). Although the mean percent increase in LS BMD was slightly greater in the Rlx 120 mg group compared with the Rlx 60 mg group, the difference between the two was not statistically significant.



Femoral Neck BMD for Overall Population: The figure below depicts the mean percent changes in femoral neck BMD in the Overall population. At Month 36, the difference between the placebo and Rlx 60 mg groups was 2.1% ($p<0.001$). At this skeletal site the effect of the Rlx 120 mg dose compared with the Rlx 60 mg dose was statistically significantly greater at $p=0.05$ (placebo-subtracted difference for Rlx 120 mg was 2.4%; $p<0.001$).

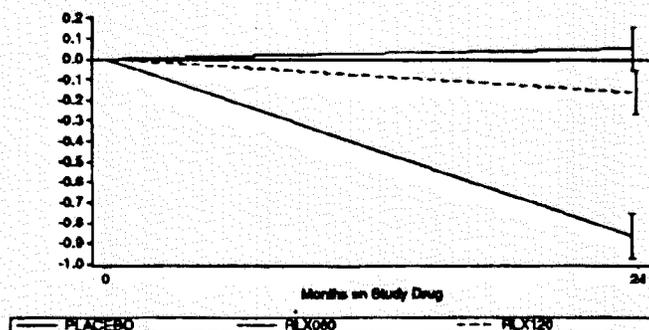


Femoral Neck BMD for Substudy I: The results in this subgroup were similar to those obtained in the Overall population. At Month 36, the difference between the placebo and Rlx 60 mg groups was 2.1% ($p<0.001$). The effect of the Rlx 120 mg dose was significantly greater than the placebo effect (difference of 2.4%; $p<0.001$) and the effect of Rlx 60 mg dose ($p=0.05$).

Femoral Neck BMD for Substudy II: The same pattern of effects were seen in the Substudy II patients as were observed in the Overall population. At Month 36 the placebo-subtracted effect of the Rlx 60 mg dose was 2.0% ($p<0.001$) and 2.3% for the Rlx 120 mg dose ($p<0.001$). In this population the Rlx 120 mg dose was statistically significantly more effective than the Rlx 60 mg dose ($p=0.05$).

Mean Percentage Change in Distal 1/3 Radius BMD

Distal 1/3 Radius BMD for Overall Population (24-month data from a subset of about 730 patients): At this skeletal site, the placebo-treated group had a steady decline in BMD (see figure below). The two raloxifene doses remained fairly stable during the 24-month observation period. The difference between the placebo and Rlx 60 mg groups as Month 24 was 0.9% ($p<0.001$). The two raloxifene doses were not significantly different from one another.

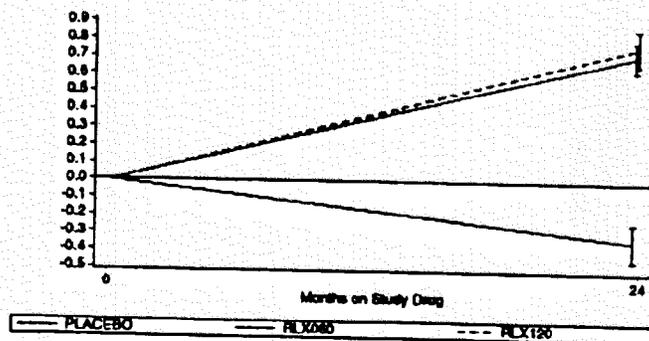


Distal 1/3 Radius BMD for Substudy I: The results in this population of women were similar to that observed in the Overall population. At Month 24, the difference between the placebo and Rlx 60 mg treatments was 0.8% ($p < 0.001$). The difference between placebo and Rlx 120 mg at Month 24 was 0.7% ($p < 0.001$). The two raloxifene doses were not significantly different from one another.

Distal 1/3 Radius BMD for Substudy II: In this population of higher risk women, the difference between placebo and Rlx 60 mg treatments was 1.2% ($p < 0.001$) at Month 24. The difference between the placebo and Rlx 120 mg groups was 0.8% ($p < 0.05$). Again, it is reported that the two raloxifene doses were not significantly different from one another.

Mean Percentage Change in Whole Body BMD

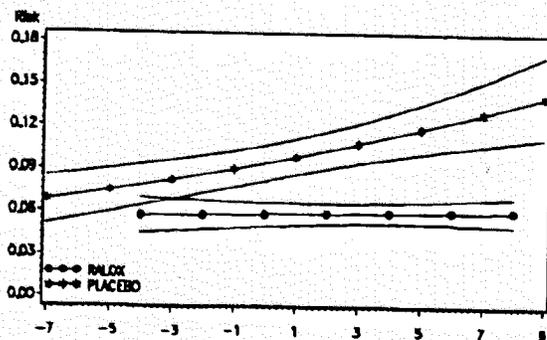
As shown below, for the Overall population analysis, whole body BMD decreased by 0.3% in the placebo group from baseline to Month 24. Whole body BMD increased from baseline to Month 24 in both raloxifene groups such that at Month 24 the differences between placebo and Rlx 60 mg and Rlx 120 mg were both 1.1% ($p < 0.001$). The two raloxifene doses were not significantly different from one another. Similar results were obtained in Substudies I and II.



Correlation Between Change in BMD and Fracture Risk

LS BMD vs. Vertebral Fracture Risk

One would expect an inverse correlation between the change in LS BMD and the risk for vertebral fracture, in both the placebo and raloxifene-treated patients. Unexpectedly however, in the placebo group there was a direct relationship between the change in LS BMD and risk for vertebral fracture. Put simply, as the LS BMD increased in the placebo group the risk for vertebral fracture also increased (see figure below). Equally unexpected, the line depicting the change in LS BMD vs. the change in risk for vertebral fracture in the raloxifene-treated women



was flat. This suggests that the change in LS BMD explains very little of the change in risk for vertebral fracture in this group of drug-treated patients.

The sponsor acknowledged the surprising finding in the placebo group and stated that it "may be related to increasing vertebral fractures or the known confounding effects of posterior element and extra-articular vertebral calcifications on lumbar spine BMD." It is possible that individuals in the placebo group who sustained vertebral fractures had an "artificially" increased LS BMD measurement. It makes less sense to invoke the theory that, over a 3-year period, spinal osteoarthritis led to significant increases in LS BMD.

If in fact the direct relationship between LS BMD and fracture risk in the placebo group is due to vertebral fractures and a resultant artifactual increase in BMD, an analysis of the changes in LS BMD by fracture status after 3 years of treatment might prove supportive. This analysis is shown below.

Number of New and Worsening Vertebral Fractures	N	% Change in LS BMD
0	2166	0.4
1	43	2.3
2	42	3.2
3	17	4.5
>4	10	4.6

The above data do support the idea that the direct relationship between the change in LS BMD and the risk for vertebral fracture is due, in part, to the fractures themselves increasing LS BMD. Further support comes from the fact that femoral neck BMD tended to decrease as the number of lumbar spine vertebral fractures increased.

Secondary Endpoints

Osteoporotic Nonvertebral Fractures

The sponsor defined osteoporotic nonvertebral fractures as fractures of any of the following sites: clavicle, scapula, ribs, sternum, sacrum, coccyx, humerus, forearm, carpus, pelvis, femur, patella, tibia, fibula, ankle, calcaneus, tarsus, and metatarsus. The following types of fractures were excluded from analyses: pathologic fractures, traumatic fractures (ie, result of a motor vehicle accident, result of a beating, or the result of being hit by a moving object), fractures of the skull, face, metacarpals, fingers, and toes. Sites were requested to confirm the fracture either by obtaining a radiologist's written report or by review of the radiograph.

As shown in the table below, there were no statistically significant differences between the placebo and Rlx 60 mg groups in the proportion of patients with at least one incident nonvertebral fracture at any skeletal site.

Incidence of Nonvertebral Fractures			
Fracture Site		Plc	Rlx 60 mg
Any Fx	Number (proportion) with at Least One Incident Fx	240 (9.3%)	225 (8.8%)
	Relative Risk (95% CI) vs. Placebo		0.94 (0.8, 1.1)
Forearm	Number (proportion) with at Least One Incident Fx	86 (3.3%)	74 (2.9%)
	Relative Risk (95% CI) vs. Placebo		0.87 (0.64, 1.2)
Rib/Sternum	Number (proportion) with at Least One Incident Fx	40 (1.6%)	50 (2.0%)

Incidence of Nonvertebral Fractures			
Fracture Site		Plc	Rlx 60 mg
Humerus	Relative Risk (95% CI) vs. Placebo		1.3 (0.83, 1.9)
	Number (proportion) with at Least One Incident Fx	29 (1.1%)	30 (1.2%)
Metatarsus	Relative Risk (95% CI) vs. Placebo		1.4 (0.63, 1.7)
	Number (proportion) with at Least One Incident Fx	24 (0.9%)	19 (0.7%)
Ankle	Relative Risk (95% CI) vs. Placebo		0.80 (0.44, 1.5)
	Number (proportion) with at Least One Incident Fx	28 (1.1%)	19 (0.7%)
Hip	Relative Risk (95% CI) vs. Placebo		0.68 (0.38, 1.2)
	Number (proportion) with at Least One Incident Fx	18 (0.7%)	26 (1.0%)
Lower Leg	Relative Risk (95% CI) vs. Placebo		1.46 (0.80, 2.7)
	Number (proportion) with at Least One Incident Fx	7 (0.3%)	8 (0.3%)
Patella	Relative Risk (95% CI) vs. Placebo		1.15 (0.42, 3.2)
	Number (proportion) with at Least One Incident Fx	9 (0.3%)	6 (0.2%)
Pelvis	Relative Risk (95% CI) vs. Placebo		0.67 (0.24, 1.9)
	Number (proportion) with at Least One Incident Fx	7 (0.3%)	10 (0.4%)
Clavicle	Relative Risk (95% CI) vs. Placebo		1.44 (0.55, 3.8)
	Number (proportion) with at Least One Incident Fx	3 (0.1%)	3 (0.1%)
Scapula	Relative Risk (95% CI) vs. Placebo		1.01 (0.20, 5.0)
	Number (proportion) with at Least One Incident Fx	1 (0.0%)	0 (0.0%)
Sacrum	Relative Risk (95% CI) vs. Placebo		NA
	Number (proportion) with at Least One Incident Fx	2 (0.1%)	2 (0.1%)
	Relative Risk (95% CI) vs. Placebo		1.01 (0.14, 7.2)

Hip fractures result in serious morbidity and increase the risk for mortality in older postmenopausal women. In this study, which was not powered to examine risk for hip fracture, the point estimates for the relative risks for hip fracture in Rlx 60 mg subjects vs. placebo subjects in Substudies I and II were 1.2 and 1.6, respectively. Neither estimate was statistically significant.

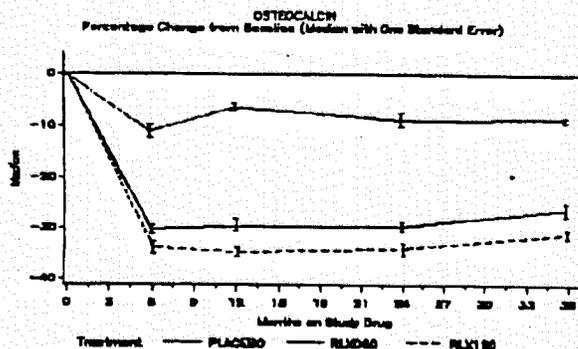
It is worth noting that a lower percentage of subjects treated with Rlx 60 mg (10.5%) compared with placebo (12.0%) reported at least one new clinical (symptomatic) vertebral and any nonvertebral osteoporotic fracture ($p=0.08$) during the 3-year study. This trend was consistent in both of the substudies as well.

Discontinuation Due to Rapid Bone Loss or Multiple Fractures

As defined in the protocol, subjects were discontinued from the study if they met either of the following criteria: lost more than 7% of LS BMD or more than 10% of femoral neck BMD at 12 months and 11% of LS BMD or more than 14% of femoral neck BMD at 24 months, or sustained more than 2 incident fractures. A total of 3.7% of placebo-treated women compared with 1.1% of Rlx 60 mg-treated patients met the early termination criteria. Most of the difference was due to loss of BMD.

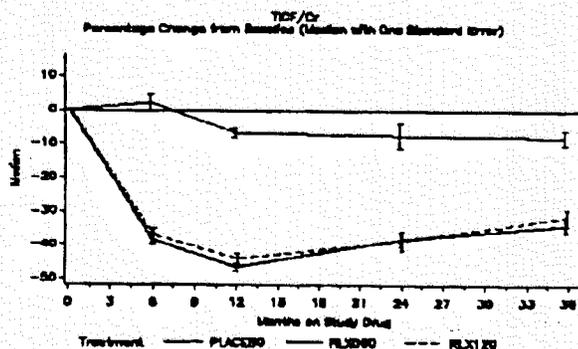
Biochemical Markers of Bone Metabolism

Serum Osteocalcin: The mean baseline values for serum osteocalcin (~ 26 ug/L) were similar for the 3 groups. As shown in the accompanying figure, serum osteocalcin levels were significantly suppressed by 6 months in the 2 raloxifene groups compared with the placebo group. At Month 36/Endpoint, the median percentage decrease from baseline in osteocalcin in the placebo group was -8.6% vs. -26.3% in the Rlx 60 mg group ($p<0.001$) and -31.1% in the Rlx 120 mg group ($p<0.001$).



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Urinary Type I Collagen Fragment to Creatinine Ratio (TICF/Cr): The mean baseline values for TICF/Cr were similar not statistically significantly different among the 3 groups, although the value in the placebo group (275 ug/mmcr) was lower than the value for the Rlx 60 mg group (289 ug/mmcr) ($p=0.07$). As shown below, TICF/Cr values were suppressed at 6 months compared to baseline in the two raloxifene groups, but not in the placebo group. At Month 36/Endpoint, the median percentage reduction from baseline in TICF/Cr in the placebo group was -8.1% compared with -34.0% in the Rlx 60mg group ($p<0.001$) and -31.5% in the Rlx 120 mg group ($p<0.001$).



Serum PTH and 25-Hydroxyvitamin D: At baseline, the median level of iPTH was lower in the Rlx 120-mg group (but not the 60-mg group) vs. the placebo group (3.100 vs. 3.074, $p<0.05$). Not unexpectedly, the median percentage changes from baseline to Endpoint were greater in the two raloxifene groups compared with the placebo group (13.6%, 13.2%, and 3.4% for placebo, Rlx 60 mg and Rlx 120 mg, respectively; $p<0.001$). The greater increases in iPTH seen with raloxifene treatment are most likely directly related to the drug's ability to lower serum calcium levels. This effect has been observed with estrogen and bisphosphonates.

At baseline, the median levels of 25-OH vitamin D were comparable for the three groups (~ 74 nmol/L). At Endpoint, the median levels of vitamin D increased by a lesser amount in the two raloxifene groups (14.8% and 14.3%) compared with the 18.8% increase in the placebo group ($p<0.001$).

Serum Lipids and Biochemical Markers of Cardiovascular Risk

Serum lipids and other biochemical markers of cardiovascular risk, including serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoproteins A1 and B, triglyceride concentration, fibrinogen, and glycosylated hemoglobin (HbA1c), were evaluated to assess the effects of raloxifene on modifiable risk factors for cardiovascular disease. Total cholesterol was measured in all randomly assigned patients at baseline and Months 6, 12, 24 and 36. All other cardiovascular analytes were measured in a subset of approximately 2700 patients at baseline and Months 6, 12, 24, and 36.

Aside from a lower baseline level of triglycerides in the raloxifene vs. the placebo groups, the three groups had similar levels of serum lipids and markers of cardiovascular risk at baseline. At Endpoint there were statistically significant, and perhaps clinically significant, reductions in the levels of total cholesterol, LDL-C, apolipoprotein B, and fibrinogen in the Rx 60 mg group compared with the placebo group (table below). The levels of triglycerides decreased by a statistically significantly greater amount in the placebo group compared with both doses of raloxifene (table below). The difference between the two groups is most likely of little clinical significance, however.

Median Percentage Change from Baseline to Endpoint in Lipids			
Parameter	Plc	Rlx 60 mg	p-value
TC	-1.9%	-7.8%	<0.001
LDL-C	-1.8%	-12.1%	<0.001
HDL-C	4.0%	3.8%	NS
Apo A1	-1.7%	-1.3%	<0.001
Apo B	-3.8%	-11.2%	<0.001
TG	-3.4%	-1.4%	<0.05
Fibrinogen	-2.8%	-12.9%	<0.001
HbA1c	-1.8%	-1.9%	NS

It should be mentioned that in an analysis of only those subjects not taking hypolipidemic medications at baseline or postbaseline, the results for the changes in the lipid parameters were not appreciably different from the results shown in the table above.

Safety Results

Deaths: A total of 23 (0.9%) placebo, 13 (0.5%) Rx 60 mg, and 28 (1.1%) Rx 120 mg subjects are reported to have died during the conduct of this trial. The number of deaths in the higher Rx dose was statistically significantly greater than the number reported in the lower Rx dose ($p < 0.05$), but not compared with the placebo group. Of some interest, the number of deaths attributed to the cardiovascular system was significantly lower in the Rx 60 mg group (0.1%) vs. the placebo group (0.4%) ($p < 0.05$).

Serious Adverse Events: A total of 25% of placebo, 24% of Rx 60 mg, and 24% of Rx 120 mg subjects reported at least one serious adverse event during the trial ($p = 0.3$). Two serious adverse event COSTART terms were reported with greater incidence in patients treated with raloxifene compared with placebo: deep thrombophlebitis and headache.

Deep thrombophlebitis was reported by 5 (0.2%) patients in the placebo group, 17 (0.7%) patients in the Rx 60 mg group, and 19 (0.7%) patients in the Rx 120 mg group ($p < 0.05$ for both

comparisons). This issue is discussed in greater detail in this review under venous thromboembolic events (VTE).

Headache was reported by 3 (0.1%) patients in the placebo group, 11 (0.4%) patients in the Rlx 60-mg group, and 8 (0.3%) patients in the Rlx 120-mg group. A review of the serious adverse event reports for headache revealed a variety of concurrent diagnoses associated with the headache, including hypertension, musculoskeletal neck pain, cerebral hemorrhage, cerebral ischemia, brain neoplasm, and other neurologic disturbances. None of these concurrent diagnoses associated with headache were predominant in the drug vs. placebo-treated groups.

Discontinuations Due to Adverse Events: A significantly greater percentage of patients in the Rlx 60 mg group (10.9%) but not the Rlx 120 mg group (9.6%) discontinued due to an adverse event when compared with the rate in the placebo group (8.8%) ($p < 0.05$; Rlx 60 mg vs. placebo). The majority of the difference between the placebo and Rlx 60 mg group was due to vasodilatation (2 vs. 19) and deep thrombophlebitis (4 vs. 12). Diarrhea and constipation were also reported by a statistically significantly greater number of Rlx 60 mg subjects compared with placebo subjects.

Treatment-Emergent Adverse Events Reported by a Statistically Significantly Higher Percentage of Raloxifene 60 mg Subjects vs. Placebo Subjects: The following COSTART terms were reported by significantly more Rlx 60 mg subjects compared with placebo-treated patients.

Adverse Events Reported by a Significantly Higher Percentage of Rlx 60 mg vs. Placebo-Treated Subjects			
Event	Plc	Rlx 60 mg	p-value
Flu Syndrome	11.4%	13.5%	<0.05
Vasodilatation	6.4%	9.7%	<0.01
Leg Cramps	3.7%	7.0%	<0.05
Diabetes Mellitus	0.5%	1.2%	<0.05
Cervix Neoplasm	0.4%	0.9%	<0.05
Dehydration	0.3%	0.8%	<0.05
Deep Thrombophlebitis	0.2%	0.7%	<0.01

A more detailed account of some of the events reported in the above table is provided below.

Vasodilatation: Vasodilatation is an established adverse event associated with raloxifene. This term most often refers to "hot flushes" and suggests that raloxifene has anti-estrogenic activity in that region of the brain responsible for vasomotor instability.

Leg Cramps: Leg cramps is also an established adverse event associated with the use of raloxifene. The pathogenesis of these "leg cramps" is not known, but does not appear to be related to the thrombogenic potential of the drug.

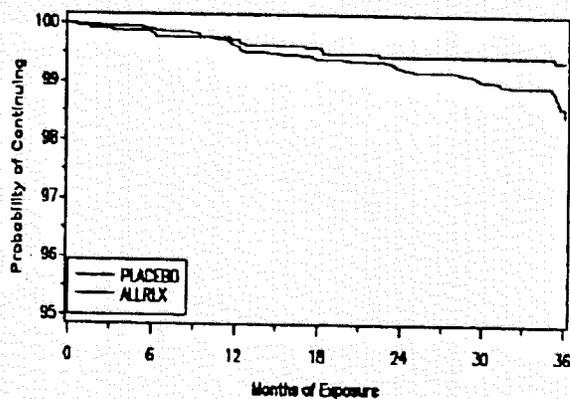
Diabetes: Diabetes mellitus (type 2) was not an exclusion criterion for this study, nor was the use of a hypoglycemic agent. During the conduct of the trial investigators were free to list "diabetes mellitus" as an adverse event. However, investigators were not instructed to record the reason(s) why this adverse event was noted for a particular patient. These factors should be kept in mind when evaluating the following information.

As shown in the following table, diabetes mellitus was reported as a treatment-emergent adverse event by more raloxifene-treated subjects compared with placebo-treated patients.

Summary of Treatment-Emergent Diabetes Mellitus				
Category		Plc	Rlx 60 mg	Rlx 120 mg
Patients without pre-existing evidence of diabetes	Number of patients	2502	2460	2504
	Number (%) with treatment-emergent Diabetes	11 (0.4%)	13 (0.5%)	16 (0.6%)
Patients with pre-existing evidence of diabetes*	Number of patients	74	97	68
	Number (%) with treatment-emergent diabetes	3 (4.1%)	18 (18.6%)	12 (17.6%)
All patients total		14 (0.5%)	31 (1.2%)	28 (1.1%)

* Patients with a preexisting condition of diabetes mellitus or baseline fasting glucose >7.78 mmol/L or baseline use of hypoglycemic agents.

As shown in the figure below, the time-to-event curves indicate that the excess reporting of diabetes as an adverse event occurred during the 3rd year of the trial.



The total population of subjects coded with treatment-emergent diabetes is comprised of two groups: those without evidence of pre-existing diabetes at baseline (no history of diabetes, baseline fasting glucose of < 140 mg/dl or no use of hypoglycemic medication at baseline), and those with some evidence of pre-existing diabetes (history of diabetes, baseline fasting glucose of > 140 mg/dl or use of hypoglycemic medication at baseline).

The disparity in reporting of diabetes as an adverse event comes from those subjects categorized as having evidence of pre-existing diabetes at baseline. There were more subjects in the Rlx 60-mg group (97) and fewer subjects in the Rlx 120-mg group (68) compared with the placebo group (74) classified as having evidence of pre-existing diabetes at baseline. Thus, it cannot be concluded that the increased incidence of reporting of diabetes as an adverse event in the raloxifene-treated vs. placebo-treated patients was due to an imbalance at baseline.

Although there were no significant differences among groups in the median change from baseline to Endpoint for fasting glucose for the entire study population, approximately 4.0% of the Rlx 60 mg subjects vs. 3.0% of placebo subjects ($p < 0.05$) met the criteria for high fasting glucose at

some point in the trial. Further, compared with 0.3% of placebo patients, 0.9% of the Rlx 60 mg and 0.8% of the Rlx 120 mg subjects ($p < 0.05$) met the criteria for extremely high fasting glucose.

Given the limitations of the available data, it is not possible to conclude that treatment with raloxifene increases the risk for diabetes mellitus. The data do, however, raise the possibility that in a select group of "at risk" individuals, raloxifene (directly or indirectly) unfavorably alters glucose metabolism.

Cervix Neoplasm: Cervix neoplasm was reported by 10 (0.4%) of the patients in the placebo group, 23 (0.9%) of the women in the Rlx 60 mg group ($p = 0.02$), and 19 (0.7%) of the patients in the Rlx 120 mg group ($p = ns$). The majority of cervix neoplasm cases were reported with actual terms indicating cervical or endocervical polyp. According to Lilly they do not have access to any pathology reports for these polyps. Consequently, a full assessment of their significance cannot be made.

Dehydration: Dehydration was reported more frequently by the raloxifene-treated women than the placebo-treated patients. Most of the cases were associated with gastrointestinal or infectious processes.

DVT: Deep thrombophlebitis was reported by 5 (0.2%) patients in the placebo group, 17 (0.7%) patients in the Rlx 60-mg group, and 19 (0.7%) patients in the Rlx 120-mg group. Both of the raloxifene groups reported deep thrombophlebitis more frequently compared with placebo ($p = 0.010$ for the Rlx 60-mg group and $p = 0.004$ for the Rlx 120-mg group). Deep vein thrombosis of the leg accounted for 40 of the 41 cases of deep thrombophlebitis, with one reported case of an internal jugular vein thrombosis following central venous catheter placement. Thrombophlebitis is a known risk associated with raloxifene use.

Safety Issues of Particular Interest

Uterus (see consult from HFD-580)

The data collected in this study about the effects of raloxifene on the uterine corpus were gathered according to an observational model. They represent the clinical observations after 36 months of treatment on 5957 patients without a prior hysterectomy at study entry. These patients were followed according to generally accepted clinical management guidelines. In addition, a subset of the patients was monitored by transvaginal ultrasonography (TVU) to assess the impact of raloxifene on endometrial thickness.

At each visit, information on the incidence of vaginal bleeding was collected for all patients. Any patient who reported vaginal bleeding was assessed to determine if the bleeding was of uterine origin and if so, the patient was to undergo a structured evaluation. In addition, endometrial thickness measurements were to be collected annually in a subset of 2155 patients. As a measure of safety, those patients who were found to have endometrial thickness measurements > 5.0 mm were required to have additional evaluation according to a systematic algorithm.

The algorithms used to follow-up on uterine bleeding and increased endometrial thickness are shown below.

