three treatment groups in the proportion of patients who had both a baseline and at least one post baseline endometrial thickness measurement (552 [77.4%] in the placebo group, 542 [74.7%] in the raloxifene 60-mg group, and 550 [76.6%] in the raloxifene 120-mg group) (data on file). There were 144 patients who underwent both a baseline and at least one post baseline endometrial thickness measurement based on the decision of the investigator at sites where longitudinal ultrasonographic assessment was not planned.

- In total, 1,788 randomly assigned patients without a prior hysterectomy had both a baseline and at least one post baseline endometrial thickness measurement and were used in the primary analysis.

Figure GGGK.12.1 graphically depicts the results of the analysis of endometrial thickness.

- There were no statistically significant treatment-group differences in **endometrial thickness** at baseline.
- The number of patients with an **endometrial thickness >5.0 mm** at baseline was similar across all three treatment groups.

- Patients in the **placebo group** showed very small **decreases** in endometrial thickness from baseline at each annual visit (-0.07 mm, -0.22 mm, -0.26 mm, and -0.22 mm change at the 12-month, 24-month, 36-month, and 48-month visits, respectively) (data on file).
  - These *within-group* changes were statistically significant at 24 months (p=0.003), 36 months (p<0.001), and 48 months (p=0.011).
- Patients in the **raloxifene 60-mg group** showed a very small *within-group* **increase** (+0.29 mm) at 12 months, which returned toward baseline thereafter (data on file). At 24 months, the mean increase from baseline was +0.15 mm; at 36 months it was +0.05 mm, and at 48 months it was +0.08 mm.
  - This increase from baseline was statistically significant at 12 months only (p<0.001) and was not statistically significant at 24 months, 36 months, or 48 months.
- Patients in the **raloxifene 120-mg group** showed a small average **increase** (+0.29 mm) from baseline to 12 months, with regression toward baseline (+0.17 mm) at 24 months and at 36 months (+0.02 mm), and increased slightly to +0.11 mm at 48 months (data on file).
  - As with the raloxifene 60-mg group, the only statistically significant difference in endometrial thickness for the raloxifene 120-mg group was observed at the 12-month visit (p<0.001) and the observed differences from baseline at 24, 36, and 48 months were not statistically significant.

In addition, analyses were performed comparing the change in endometrial thickness *among the three treatment groups* (data on file).

- There were statistically significant differences *among the three treatment groups*, and *between the pooled raloxifene group and the placebo group* for change in endometrial thickness at 48 months (p=0.032 and p=0.009, respectively).
- The differences between **the raloxifene 60-mg group and the placebo group** were small, but statistically significant at each annual visit (12 months, 0.36 mm [p=0.001]; 24

months, 0.37 mm [p=0.002]; 36 months, 0.31 mm [p=0.012]; 48 months, 0.3 mm [p=0.028]).

- The difference between **the raloxifene 120-mg group and the placebo group** was statistically significant at the 12-month (0.36 mm difference [p=0.001]), 24-month (0.39 mm difference [p=0.001]), 36-month (0.28 mm difference [p=0.026]), and 48-month visit (0.32 mm difference [p=0.020]).

There were no statistically significant treatment-group differences in the number of patients with an endometrial thickness >5.0 mm at baseline.

- By 48 months, the number of patients who were found to have at least one post baseline endometrial thickness measurement >5.0 mm was 102 (5.1%) for the placebo group, 139 (7.1%) for the raloxifene 60-mg group, and 147 (7.3%) for the raloxifene 120-mg group.
- The difference was statistically significant for the overall analysis and also for the pooled raloxifene group compared with the placebo group (p=0.007 and 0.002, respectively).
- All patients with an endometrial thickness >5.0 mm were to undergo an evaluation following the uterine algorithm for endometrial thickness >5.0 mm; the results are presented in this section.

Endometrial Fluid

While reviewing the data entered for patients on the uterine-related portions of case report forms (CRFs), the sponsor became aware that a number of patients were found to have endometrial fluid on TVU, but this was not reported as a treatment-emergent adverse event. This finding was recorded based on the appearance of a hypo-echogenic region within the endometrial cavity, as seen on TVU. In order to assess the prevalence of endometrial fluid properly and its clinical relevance, sponsor personnel blinded to treatment group reviewed all adverse event terms, regardless of COSTART classification term, and determined those corresponding to fluid in the endometrial cavity.

- The proportion of patients reported as having endometrial-cavity fluid (76 [9.6%] patients in the placebo group, 99 [12.7%] patients in the raloxifene 60-mg group, and 111 [14.0%] patients in the raloxifene 120-mg group) was analyzed using all patients who had any endometrial thickness measurements after baseline as the denominator.
- There were overall statistically significant differences observed in the reporting of endometrial-cavity fluid among the three treatment groups (p=0.023) and also between the pooled raloxifene group and the placebo group (p=0.009) (Table GGGK.12.13).
- No endometrial carcinomas were reported among the cases of endometrial fluid. There were no clinical symptoms related to the presence of endometrial fluid. Specifically, there was no evidence that patients with reported endometrial fluid experienced vaginal discharge or urinary loss any more frequently than the rest of the patient population for each of the three treatment groups.

Table GGGK.12.13. Patients with Treatment-Emergent Fluid in the Endometrial Cavity (Patients with Post baseline Endometrial Thickness Measurements, 48-Month Data)

	Placebo (N=790)	RLX060 (N=782)	RLX120 (N=791)	Total (N=2363)	Overall p-value[a]	Pooled RLX p-value[a]
Fluid in the Endometrial Cavity	76 (9.6%)	99 (12.7%)	111 (14.0%)	286 (12.1%)	0.023	0.009

[a] Chi-square test for total count ≥10.
Abbreviations: RLX = raloxifene; RLX060 = raloxifene 60 mg/day; RLX120 = raloxifene 120 mg/day; N = number of randomly assigned patients with postbaseline endometrial thickness measurements.

In October of 1998 (third year of the study), the GGGK case report forms were updated to include a module to record the amount of endometrial fluid at the maximum point of endometrial thickness. This was done to ensure accurate measurement of endometrial thickness and to enhance the understanding of the relative contribution of endometrial fluid to total endometrial thickness.

- At 48 months, there was no statistically significant difference among the three treatment groups for the mean amount of fluid (2.65 mL in the placebo group, 3.34 mL in the raloxifene 60-mg group, and 3.03 mL in the raloxifene 120-mg group; p=0.212).
    - There was 1 patient in the raloxifene 60-mg group who was ascertained to be an extreme outlier and was removed from the above analysis. (She had no baseline endometrial thickness evaluation and was reported on her first evaluation, beyond 36 months (no specific reason given by the study site for the evaluation), as having an endometrial thickness of 46 mm and endometrial fluid of 44 mL). Her work-up demonstrated endometrial atrophy with no evidence of malignancy. Even with the inclusion of this patient in the analysis, there was no statistically significant difference in the mean amount of fluid between treatment groups (p=0.113) (data on file).

Uterine cavity fluid has become recognized as a common finding among postmenopausal women, reported between 4% and 12% of women studied by TVU (Brooks et al. 1996; Vuento et al. 1996; Gull et al. 1998). A number of factors may contribute to this benign finding, such as age and functional cervical stenosis. The GGGK cohort is in the older age range of populations studied and raloxifene may have anti-estrogenic effects on the cervix. The incidence of endometrial fluid detected in Study GGGK is consistent with the generally reported rates and there is no evidence to support a link between the presence of endometrial fluid and underlying endometrial stimulation or pathology.

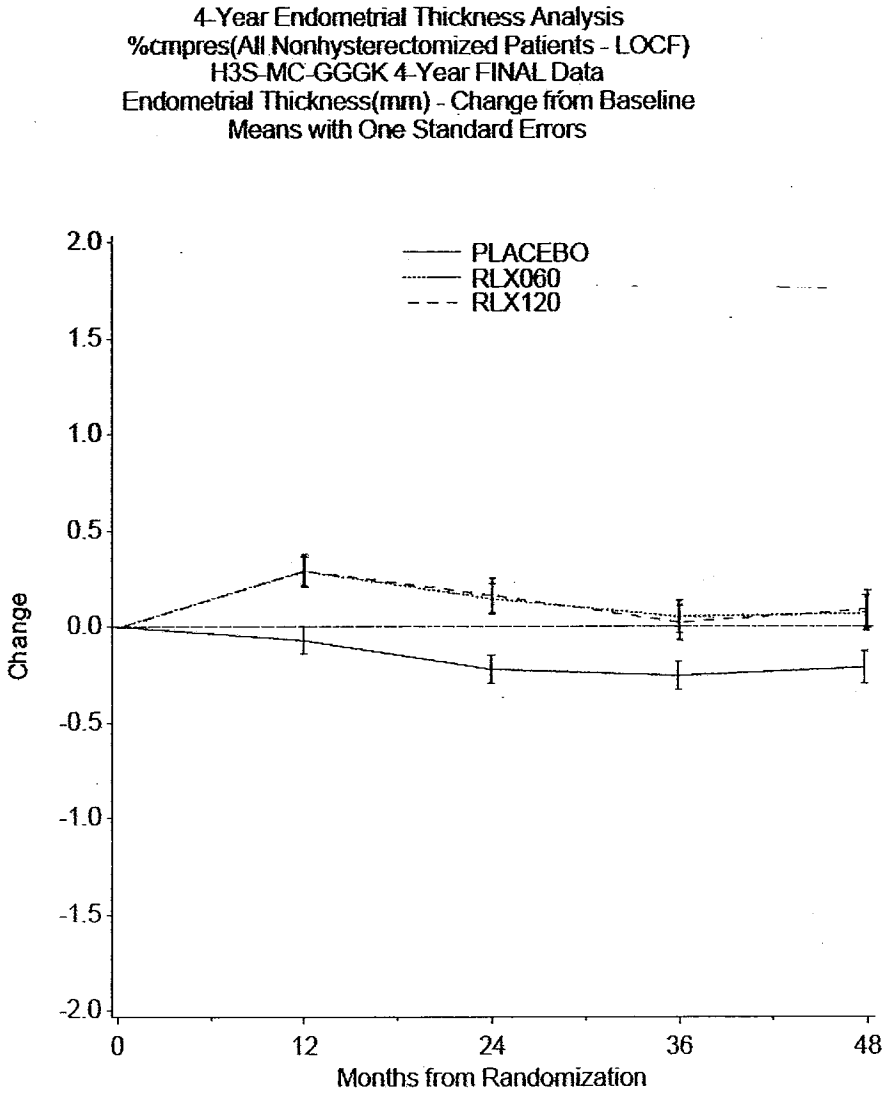


Figure GGGK.12.1. Change in Endometrial Thickness from Baseline (Mean Thickness 2.9 mm) to Endpoint (Patients with Baseline and Post baseline Endometrial Thickness Measurement, 48-Month Data)

Diagnostic Evaluations for Patients with Endometrial Thickness >5.0 mm

All patients with an endometrial thickness >5.0 mm were to undergo an evaluation following the uterine algorithm for endometrial thickness >5.0 mm. Among the 350 patients who had an endometrial thickness >5.0 mm post baseline (and were not evaluated for bleeding) a total of 294 patients were investigated according to the uterine evaluation algorithm (79 patients in the placebo group, 109 patients in the raloxifene 60-mg group, and 106 patients in the raloxifene 120-mg group).

- There was no statistically significant difference in the proportion of patients evaluated for endometrial thickness >5.0 mm post baseline (p=0.182).

The only statistically significant difference among the three treatment groups and between the pooled raloxifene and placebo groups for any clinical diagnoses was atrophy (p=0.001 and p<0.001, respectively), which is the most common finding in postmenopausal women (Table GGGK.12.14).

Table GGGK.12.14. Clinical Diagnoses for Patients with Endometrial Thickness >5.0 mm (International Classification of Diseases, All Randomly Assigned Patients without Prior Hysterectomy, 48-Month Data)

Clinical Diagnosis	Placebo (N=1999)	RLX060 (N=1950)	RLX120 (N=2010)	Total (N=5959)	Overall p-value[a]	Pooled RLX p-value[a]
Myoma	5	7	2	14	0.238	0.863
Polyp	16	26	26	68	0.211	0.078
Atrophy	23	47	56	126	0.001	<0.001
Unspecified Disorder	5	2	6	13	0.389	0.707
Proliferative	3	4	2	9	0.592	1.000
Secretory	0	0	0	0	—	—
Hyperplasia	3	2	0	5	0.255	0.342
Normal	1	0	2	3	—	—
SEETUS	15	17	25	57	0.247	0.245
Adenocarcinoma	2	0	0	2	—	—
Adenofibroma	0	0	0	0	—	—
Hematometra	0	0	0	0	—	—
Mucocele	0	0	1	1	—	—
Endometrial Fluid	5	12	7	24	0.173	0.186
Adenomyosis	1	0	0	1	—	—
Solitary Subendo Cyst	0	0	1	1	—	—
Subendo Cysts	0	1	3	4	—	—
Cystic Focus (Microcysts)	0	0	1	1	—	—
Hetero Echo in Endo	0	0	1	1	—	—
Total Clinical Diagnoses[b]	56	80	83	219	0.039	0.011
Incomplete Data[c]	4	2	2	8	0.678	0.454
Algorithm Complete[d]	27	36	35	98	0.433	0.205
Algorithm Violation[e]	15	23	23	61	0.328	0.136
Lost to Follow-Up[f]	0	2	0	2	—	—

a Chi-square test for total count ≥10; Fisher's Exact test for total count 5 through 9.
b Counts patients with multiple clinical diagnoses only once.
c Insufficient data to establish a clinical diagnosis.
d Patients who completed all mandated steps in the uterine surveillance algorithm, but showed no clinical evidence to pursue further evaluation.
e Algorithm was not followed. No clinical diagnosis made despite the follow-up reported.
f Patient was lost to follow-up.
Abbreviations: N = number of randomly assigned patients without prior hysterectomy; RLX060 = raloxifene 60 mg/day; RLX120 = raloxifene 120 mg/day; SEETUS = spurious evaluation of endometrial thickness of undetermined significance.

Considering the centrally and locally read biopsy results, there was an overall statistically significant difference among the three treatment groups (p=0.047) and between the pooled raloxifene group and the placebo group (p=0.020) for the pathologic diagnosis of polyp (Table GGGK.12.15). There was a statistically significant difference between the pooled raloxifene group and the placebo group for the PEPI diagnosis of "normal postmenopausal endometrium" (p=0.036). There was a statistically significant difference between the pooled raloxifene group and the placebo group for inactive/atrophic endometrium (p=0.048).

Table GGGK.12.15. Combined Centrally and Locally Read Endometrial Biopsy Results (WHO/Blaustein Biopsy Classification) For Patients With Endometrial Thickness >5.0 mm (All Randomly Assigned Patients Without Prior Hysterectomy, 48-Month Data)

Biopsy Result	Placebo (N=1999)	RLX060 (N=1950)	RLX120 (N=2010)	Total (N=5959)	Overall p-value[a]	Pooled RLX p-value[a]
Normal (PEPI Definition)[b]	20	31	36	87	0.096	0.036
Insufficient Tissue	11	14	12	37	0.787	0.622
Surface Endometrium Only	6	8	14	28	0.166	0.173
Inactive/Atrophic Endometrium	3	9	10	22	0.138	0.048
Nonproliferative Tissues	0	0	2	2	—	—
Proliferative	2	5	1	8	0.166	0.726
Polyps	8	21	17	46	0.047	0.020
Hyperplasia	3	2	0	5	0.255	0.342
Benign Neoplasia	2	1	1	4	—	—
Carcinoma	2	0	0	2	—	—
Endometritis	0	0	1	1	—	—

[a] Chi-square test for total count ≥10; Fisher's Exact test for total count 5 through 9.

[b] Normal includes insufficient tissue, surface endometrium, and inactive/atrophic endometrium results (Langer et al. 1997).

Abbreviations: PEPI = Postmenopausal Estrogen/Progestin Interventions Trial; RLX060 = raloxifene 60 mg/day; RLX120 = raloxifene 120 mg/day; N = number of randomly assigned patients without prior hysterectomy; WHO = World Health Organization; RLX = raloxifene.

12.3.3.4.2. Uterine-Related Adverse Events

All adverse event analyses in this section include only those 5,959 women without a prior hysterectomy at study entry. Therefore, the number of adverse events reported in this section may differ from those reported in Section 12.2.2.2, which used all 7,705 randomly assigned patients (including women with a prior hysterectomy at study entry) as the denominator.

12.3.3.4.2.1. Uterine-Related Serious Adverse Events

Among the uterine-related serious adverse events, there were no statistically significant differences among the three treatment groups in the reporting of any of these events except between the pooled raloxifene group and the placebo group in the reporting of the

COSTART term uterine atony (Table GGGK.12.16). Uterine atony was reported as a serious adverse event in 14 (0.7%) patients in the placebo group, 7 (0.4%) patients in the raloxifene 60-mg group, and 5 (0.2%) patients in the raloxifene 120-mg group. The lower incidence in the pooled raloxifene group was statistically significant compared with the placebo group (p=0.028). A summary of the uterine-related serious adverse events is presented in (Table GGGK.12.16).

Table GGGK.12.16. Summary of Uterine-Related Serious Adverse Events (All Randomly Assigned Patients without Prior Hysterectomy, 48-Month Data)

Serious Adverse Event	Placebo (N= 1999)	RLX060 (N= 1950)	RLX120 (N= 2010)	Overall p-Value	Pooled Rlx p-Value
Uterine-Related	29 (1.5%)	22 (1.1%)	23 (1.1%)	.585	.301
UTERINE ATONY	14 (0.7%)	7 (0.4%)	5 (0.2%)a	.078	.028
ENDOMETRIAL CARCINOMA	5 (0.3%)	5 (0.3%)	3 (0.1%)	.718	.707
NEOPLASM	2 (0.1%)	4 (0.2%)	7 (0.3%)	.239	.165
VAGINAL HEMORRHAGE	2 (0.1%)	3 (0.2%)	3 (0.1%)	.913	.726
ENDOMETRIAL DISORDER	1 (0.1%)	2 (0.1%)	2 (0.1%)	.874	.670
UTERINE DISORDER	1 (0.1%)	1 (0.1%)	3 (0.1%)	.630	.670
RUPTURED UTERUS	2 (0.1%)	1 (0.1%)	0 (0.0%)		
UTERINE FIBROIDS ENLARGED	0 (0.0%)	1 (0.1%)	2 (0.1%)		
ENDOMETRIAL HYPERPLASIA	1 (0.1%)	1 (0.1%)	0 (0.0%)		
UTERINE HEMORRHAGE	1 (0.1%)	0 (0.0%)	1 (0.0%)		
UTERINE NEOPLASM	0 (0.0%)	1 (0.1%)	0 (0.0%)		

NOTE: Chi-square tests were used when total count >= 10, else Fisher's exact test was used. Pairwise comparisons were performed when the overall or pooled raloxifene comparison was significant ($p < 0.05$).
a - pairwise comparison statistically significant ($p < 0.05$) different from placebo
b - pairwise comparison statistically significant ($p < 0.01$) different from placebo
c - pairwise comparison statistically significant ($p < 0.001$) different from placebo
d - pairwise comparison of RLX060 statistically significant ($p < 0.05$) different from RLX120

Data: RMP.SAS.HJSH.MCGGGKSC.FINAL
Source: RMP.H3S8K4YR.SASPGM(ARSC01AA) X6221 30NOV00
Output: RMP.H3S0.K4YR(ARSCU1NN)

Endometrial Carcinoma

As of the 48-month visit, 13 cases of endometrial carcinoma in randomly assigned patients had been reported to the sponsor. Endometrial carcinoma was reported by 5 (0.3%) patients in the placebo group, 5 (0.3%) patients in the raloxifene 60-mg group, and 3 (0.1%) patients in the raloxifene 120-mg group. The difference among the three treatment groups was not statistically significant (Table GGGK.12.16).

Table GGGK.12.17 shows the analysis of relative risk of endometrial cancer for patients on raloxifene treatment versus those on placebo. When comparing either raloxifene group to the placebo group, there was no difference in the incidence of endometrial cancer. When comparing the pooled raloxifene group with the placebo group, there was a statistically non significant reduction in the risk of endometrial carcinoma (relative risk = 0.81; 95% confidence interval [0.27, 2.47]).

Table GGGK.12.17. Analysis of Reported Endometrial Carcinoma (All Randomly Assigned Patients without Prior Hysterectomy, 48-Month Data)

Comparison	Placebo Cases (N=1999)	Raloxifene Cases (RLX060: N=1950) (RLX120: N=2010) (Pooled RLX: N=3960)	Relative Risk (95% CI)
Placebo vs RLX060	5 (0.3%)	5 (0.3%)	1.03 (0.30, 3.54)
Placebo vs RLX120	5 (0.3%)	3 (0.1%)	0.60 (0.14, 2.49)
Placebo vs Pooled RLX	5 (0.3%)	8 (0.2%)	0.81 (0.27, 2.47)

Abbreviations: CI = confidence interval; N = number of randomly assigned patients without a prior hysterectomy; RLX060 = raloxifene 60 mg/day; RLX120 = raloxifene 120 mg/day; RLX = raloxifene; vs = versus.

12.3.3.4.2.2. Uterine-Related, Treatment-Emergent, Adverse Events

An adverse event (COSTART term) was defined as treatment-emergent if it began after randomization or was preexisting and worsened in severity after randomization. The only statistically significant, uterine-related, treatment-emergent, adverse event, COSTART term among the three treatment groups and between the pooled raloxifene group and the placebo group was **uterine disorder** ($p=0.002$ and $p<0.001$, respectively) and **endometrial disorder** ($p=0.026$ and $p=0.010$, respectively) (Table GGGK.12.18).

Uterine disorder was the COSTART term used to describe **endometrial fluid** in the majority of cases. Other actual terms referred to adenomyosis, endometrial adhesions, and uterine focal abnormalities. Among all patients without a prior hysterectomy at baseline, uterine disorder was reported by 79 (4.0%) patients in the placebo group, 108 (5.5%) patients in the raloxifene 60-mg group, and 130 (6.5%) patients in the raloxifene 120-mg group.

Endometrial disorder was the COSTART term most frequently used to describe thickened endometrium. Endometrial disorder was reported by 26 (1.3%) patients in the placebo group, 48 (2.5%) patients in the raloxifene 60-mg group, and 42 (2.1%) patients in the raloxifene 120-mg group.

There was a statistically significant difference between the pooled raloxifene group and the placebo group for the adverse event COSTART term of **neoplasm**, which was used to describe the actual term of endometrial or uterine polyp ($p=0.021$). Neoplasm was reported by 29 (1.5%) patients in the placebo group, 46 (2.4%) patients in the raloxifene 60-mg group, and 47 (2.3%) in the raloxifene 120-mg group.

The purpose for monitoring endometrial-related events in Study GGGK was to evaluate the appearance of serious gynecological pathology, specifically endometrial hyperplasia or carcinoma. Results of uterine surveillance suggest no increase in the risk of either endometrial hyperplasia or carcinoma with up to 48 months of raloxifene administration.

A summary of all uterine-related, treatment-emergent, adverse events is presented in (Table GGGK.12.18).

Table GGGK.12.18. Summary of Uterine-Related Treatment-Emergent, Adverse Events (All Randomly Assigned Patients without Prior Hysterectomy, 48-Month Data)

Treatment-Emergent Adverse Event	Placebo (N= 1999)	RLX060 (N= 1950)	RLX120 (N= 2010)	Overall p-Value	Pooled RLX p-Value
Any Uterine-Related Treatment-Emergent Adverse Event	246 (12.3%)	282 (14.5%)a	284 (14.1%)	.103	.035
UTERINE DISORDER	79 (4.0%)	108 (5.5%)a	120 (6.5%)c	.002	<.001
VAGINAL HEMORRHAGE	63 (3.2%)	67 (3.4%)	54 (2.7%)	.387	.840
UTERINE FIBROIDS ENLARGED	54 (2.7%)	48 (2.5%)	55 (2.7%)	.842	.819
NEOPLASM	29 (1.5%)	46 (2.4%)a	47 (2.3%)a	.069	.021
ENDOMETRIAL DISORDER	26 (1.3%)	48 (2.5%)b	42 (2.1%)	.026	.010
UTERINE ATONY	33 (1.7%)	40 (2.1%)	40 (2.0%)	.408	.324
UTERINE HEMORRHAGE	5 (0.3%)	11 (0.6%)	10 (0.5%)	.286	.121
ENDOMETRIAL HYPERPLASIA	5 (0.3%)	8 (0.4%)	3 (0.1%)	.279	.846
UTERINE NEOPLASM	4 (0.2%)	8 (0.4%)	4 (0.2%)	.337	.468
ENDOMETRIAL CARCINOMA	5 (0.3%)	5 (0.3%)	3 (0.1%)	.718	.707
RUPTURED UTERUS	3 (0.2%)	2 (0.1%)	1 (0.0%)	.625	.410
WITHDRAWAL BLEEDING	2 (0.1%)	0 (0.0%)	1 (0.0%)		

NOTE: Chi-square tests were used when total count >= 10, else Fisher's exact test was used. Pairwise comparisons were performed when the overall or pooled raloxifene comparison was significant ($p < 0.05$).
a - pairwise comparison statistically significant ($p < 0.05$) different from placebo
b - pairwise comparison statistically significant ($p < 0.01$) different from placebo
c - pairwise comparison statistically significant ($p < 0.001$) different from placebo
d - pairwise comparison of RLX060 statistically significant ($p < 0.05$) different from RLX120

Data: RMP.SAS.H3SM.MCGGKESC.FINAL
Source: RMP.H3SSE4YR.SASPGM(ARTC81AA) X6221 30NOV00
Output: RMP.H3SO.K4YR(ARTCU1NN)

12.3.3.4.3. Cervix-Related Adverse Events

All 7,705 randomly assigned patients, regardless of hysterectomy status at baseline, were included in the analysis of cervix-related adverse events, since it was unknown whether patients who had a prior hysterectomy also had a trachelectomy (removal of the cervix).

12.3.3.4.3.1. Cervix-Related Serious Adverse Events

No statistically significant differences were observed among the three treatment groups for any cervix-related, serious adverse events (Table GGGK.12.19).

Table GGGK.12.19. Cervix-Related Serious Adverse Events (All Randomly Assigned Patients, 48-Month Data)

Serious Adverse Event	Placebo (N= 2576)	Rlx060 (N= 2557)	Rlx120 (N= 2572)	Overall p-Value	Pooled Rlx p-Value
Cervix-Related	4 (0.2%)	2 (0.1%)	7 (0.3%)	.234	.039
CERVIX CARCINOMA IN SITU	2 (0.1%)	1 (0.0%)	4 (0.2%)	.471	1.000
CERVIX NEOPLASM	2 (0.1%)	0 (0.0%)	1 (0.0%)		
PAPANICOLAOU SMEAR SUSPICIOUS	1 (0.0%)	1 (0.0%)	1 (0.0%)		
CERVICITIS	1 (0.0%)	0 (0.0%)	1 (0.0%)		
CERVIX DISORDER	0 (0.0%)	0 (0.0%)	2 (0.1%)		

NOTE: Chi-square tests were used when total count >= 10, else Fisher's exact test was used. Pairwise comparisons were performed when the overall or pooled raloxifene comparison was significant (p < 0.05).
a - pairwise comparison statistically significant (p < 0.05) different from placebo
b - pairwise comparison statistically significant (p < 0.01) different from placebo
c - pairwise comparison statistically significant (p < 0.001) different from placebo
d - pairwise comparison of RLX060 statistically significant (p < 0.05) different from RLX120

Data: RMP.SAS.H3SM.MCGGGKSC.FINAL
Source: RMP.H3SSK4YR.SASPGM(AESC01AA) X6221 30NOV00
Output: RMP.H3SO.K4YR(AESCU2NN)

12.3.3.4.3.2. Cervix-Related, Treatment-Emergent, Adverse Events

All cervix neoplasm cases were reported with actual terms indicating cervical/cervical uterine polyp.

- Cervix neoplasm was reported as a treatment-emergent adverse event by 17 (0.7%) patients in the placebo group, 30 (1.2%) patients in the raloxifene 60-mg group, and 28 (1.1%) patients in the raloxifene 120-mg group.
- A statistically significant difference was observed between the pooled raloxifene group and the placebo group for cervix neoplasm (p=0.047) (Table GGGK.12.20).

In contrast to the endometrial polyps, which were diagnosed primarily by evaluations mandated in the uterine surveillance algorithm, cervical polyps were reported only as a spontaneous adverse event and diagnosed by the study sites. There was no systematic monitoring of the uterine cervix mandated from the onset of the protocol, and most of the cervical polyps were reported with no histopathologic confirmation and no further information provided to the applicant. Thus, the increased frequency of the Coding
Symbol and Thesaurus for Adverse Reaction Terminology (COSTART) term cervix neoplasm, representing primarily cervical polyps, was noted only as a spontaneously reported adverse event. Overall, benign cervical polyps were a rare adverse event, reported in <1% of patients in any treatment group. Because the medical literature generally does not attach clinical significance to the finding of cervical polyps (Kurman 1994), and because no action was

mandated by the protocol for cervical polyps, no conclusions are possible regarding the presence of cervical polyps.

Table GGGK.12.20. Cervix-Related Treatment-Emergent Adverse Events (All Randomly Assigned Patients, 48-Month Data)

Treatment-Emergent Adverse Event	Placebo (N= 2576)	Rlx060 (N= 2557)	Rlx120 (N= 2572)	Overall p-Value	Pooled Rlx p-Value
Any Cervix-Related Treatment-Emergent Adverse Event	92 (3.6%)	98 (3.8%)	97 (3.8%)	.875	.614
PAPANICOLAOU SMEAR SUSPICIOUS	31 (1.2%)	31 (1.2%)	34 (1.3%)	.913	.811
CERVIX DISORDER	32 (1.2%)	26 (1.0%)	29 (1.1%)	.747	.505
CERVIX NEOPLASM	17 (0.7%)	30 (1.2%)	20 (1.1%)	.133	.047
CERVICITIS	25 (1.0%)	21 (0.8%)	18 (0.7%)	.563	.328
CERVIX CARCINOMA IN SITU	1 (0.0%)	2 (0.1%)	4 (0.2%)	.375	.426

NOTE: Chi-square tests were used when total count >= 10, else Fisher's exact test was used. -Pairwise comparisons- were performed when the overall or pooled raloxifene comparison was significant (p < 0.05).
a - pairwise comparison statistically significant (p < 0.05) different from placebo
b - pairwise comparison statistically significant (p < 0.01) different from placebo
c - pairwise comparison statistically significant (p < 0.001) different from placebo
d - pairwise comparison of RLX060 statistically significant (p < 0.05) different from RLX120

Data: RMP.SAS.H3SM.MCGGGK5C.FINAL
Source: RMP.H3SSK4YR.SASPGM(ARTC81AA) X6221 30NOV00
Output: RMP.H3SO.K4YR(ARTCU2HN)

12.3.3.5. Other Reproductive Tissues

All 7,705 randomly assigned patients, regardless of hysterectomy status at baseline, were included in the analysis of other reproductive tissues.

- Overall, treatment with raloxifene showed no difference compared with placebo for its effects on reproductive tissues other than the uterus, including the vulva, vagina, and the ovaries.

12.3.3.5.1. Vagina/Vulva-Related Adverse Events

The COSTART terms uterine hemorrhage and vaginal hemorrhage are included in both the uterine-related and vaginal-related sections of this study report because the origin of the bleeding (eg, vagina or uterus) may be indistinguishable. Reports of uterine- or vaginal-related bleeding differ between the two sections of the study report due to inclusion of all randomly assigned patients in this section.

- No statistically significant differences were observed among the three treatment groups for any **serious adverse events related to the vagina or vulva** (Table GGGK.12.21). The patient reported to have vulvar carcinoma in the raloxifene 60-mg group was also reported to have a serious adverse event of vaginitis describing vulvar pruritus.
- No statistically significant differences were observed among the three treatment groups for **any vagina/vulva-related, treatment-emergent, adverse events** (Table GGGK.12.22).

Table GGGK.12.21. Vagina/Vulva-Related Serious Adverse Events (All Randomly Assigned Patients, 48-Month Data)

Serious Adverse Event	Placebo (N= 2576)	Rlx060 (N= 2557)	Rlx120 (N= 2572)	Overall p-Value	Pooled Rlx p-Value
Vagina_Vulva-Related	5 (0.2%)	6 (0.2%)	5 (0.2%)	.935	.853
VAGINAL HEMORRHAGE	2 (0.1%)	3 (0.1%)	3 (0.1%)	.829	.726
CARCINOMA	1 (0.0%)	2 (0.1%)	0 (0.0%)		
VAGINITIS	0 (0.0%)	2 (0.1%)	1 (0.0%)		
UTERINE HEMORRHAGE	1 (0.0%)	0 (0.0%)	1 (0.0%)		
LEUKORRHEA	0 (0.0%)	0 (0.0%)	1 (0.0%)		
VULVOVAGINAL DISORDER	1 (0.0%)	0 (0.0%)	0 (0.0%)		

NOTE: Chi-square tests were used when total count >= 10, else Fisher's exact test was used. Pairwise comparisons were performed when the overall or pooled raloxifene comparison was significant ($p < 0.05$).
a - pairwise comparison statistically significant ($p < 0.05$) different from placebo
b - pairwise comparison statistically significant ($p < 0.01$) different from placebo
c - pairwise comparison statistically significant ($p < 0.001$) different from placebo
d - pairwise comparison of RLX060 statistically significant ($p < 0.05$) different from RLX120

Data: RMP.SAS.H3SM.MCGGGKSC.FINAL
Source: RMP.H3SSK4YR.SASPGM(AESC@1AA) X6221 30NOV00
Output: RMP.H3SO.K4YR(AESCU3NN)

Table GGGK.12.22. Vagina/Vulva-Related Treatment-Emergent Adverse Events (All Randomly Assigned Patients, 48-Month Data)

Treatment-Emergent Adverse Event	Placebo (N= 2576)	Rlx060 (N= 2557)	Rlx120 (N= 2572)	Overall p-Value	Pooled Rlx p-Value
Any Vagina_Vulva-Related Treatment-Emergent Adverse Event	325 (12.6%)	309 (12.1%)	293 (11.4%)	.400	.243
VAGINITIS	216 (8.4%)	196 (7.7%)	203 (7.9%)	.623	.355
VAGINAL HEMORRHAGE	69 (2.7%)	73 (2.9%)	60 (1.3%)	.492	.825
LEUKORRHEA	40 (1.6%)	30 (1.2%)	29 (1.1%)	.331	.139
VULVOVAGINAL DISORDER	21 (0.8%)	16 (0.6%)	11 (0.4%)	.210	.129
VAGINAL MONILIASIS	10 (0.4%)	19 (0.7%)	15 (0.6%)	.240	.131
UTERINE HEMORRHAGE	5 (0.2%)	11 (0.4%)	10 (0.4%)	.297	.124
GENITAL LEUKOPLAKIA	0 (0.0%)	3 (0.1%)	2 (0.1%)	.176	.176
CARCINOMA	1 (0.0%)	2 (0.1%)	0 (0.0%)		

NOTE: Chi-square tests were used when total count >= 10, else Fisher's exact test was used. Pairwise comparisons were performed when the overall or pooled raloxifene comparison was significant ($p < 0.05$).
a - pairwise comparison statistically significant ($p < 0.05$) different from placebo
b - pairwise comparison statistically significant ($p < 0.01$) different from placebo
c - pairwise comparison statistically significant ($p < 0.001$) different from placebo
d - pairwise comparison of RLX060 statistically significant ($p < 0.05$) different from RLX120

Data: RMP.SAS.H3SM.MCGGGKSC.FINAL
Source: RMP.H3SSK4YR.SASPGM(ARTC@1AA) X6221 30NOV00
Output: RMP.H3SO.K4YR(ARTCU3NN)

12.3.3.5.2. Ovarian-Related Adverse Events

- No statistically significant differences were observed among the three treatment groups for any **ovarian-related serious adverse events** (Table GGGK.12.23).
- No statistically significant differences were observed among the three treatment groups for any **ovarian-related, treatment-emergent, adverse events** (Table GGGK.12.24).

Table GGGK.12.23. Ovarian-Related Serious Adverse Events (All Randomly Assigned Patients, 48-Month Data)

Serious Adverse Event	Placebo (N= 2576)	Rlx060 (N= 2557)	Rlx120 (N= 2572)	Overall p-Value	Pooled Rlx p-Value
Ovarian-Related	13 (0.5%)	12 (0.5%)	10 (0.4%)	.818	.641
OVARIAN DISORDER	8 (0.3%)	10 (0.4%)	7 (0.3%)	.747	.879
CARCINOMA	6 (0.2%)	3 (0.1%)	3 (0.1%)	.477	.223

NOTE: Chi-square tests were used when total count >= 10, else Fisher's exact test was used. Pairwise comparisons were performed when the overall or pooled raloxifene comparison was significant (p < 0.05).
a - pairwise comparison statistically significant (p < 0.05) different from placebo
b - pairwise comparison statistically significant (p < 0.01) different from placebo
c - pairwise comparison statistically significant (p < 0.001) different from placebo
d - pairwise comparison of RLX060 statistically significant (p < 0.05) different from RLX120

Data: RMP.SAS.H3SM.MOGGGKSC.FINAL
Source: RMP.H3SSK4YR.SASPGM(ARSC@1AA) X6221 30NOV00
Output: RMP.H3SO.K4YR(ARSCU4MN)

Table GGGK.12.24. Ovarian-Related Treatment-Emergent Adverse Events (All Randomly Assigned Patients, 48-Month Data)

Treatment-Emergent Adverse Event	Placebo (N= 2576)	Rlx060 (N= 2557)	Rlx120 (N= 2572)	Overall p-Value	Pooled Rlx p-Value
Any Ovarian-Related Treatment-Emergent Adverse Event	47 (1.8%)	47 (1.8%)	43 (1.7%)	.882	.827
OVARIAN DISORDER	41 (1.6%)	42 (1.6%)	40 (1.6%)	.969	.991
CARCINOMA	6 (0.2%)	3 (0.1%)	3 (0.1%)	.477	.223
SALPINGITIS	2 (0.1%)	4 (0.2%)	0 (0.0%)	.094	1.000

NOTE: Chi-square tests were used when total count >= 10, else Fisher's exact test was used. Pairwise comparisons were performed when the overall or pooled raloxifene comparison was significant (p < 0.05).
a - pairwise comparison statistically significant (p < 0.05) different from placebo
b - pairwise comparison statistically significant (p < 0.01) different from placebo
c - pairwise comparison statistically significant (p < 0.001) different from placebo
d - pairwise comparison of RLX060 statistically significant (p < 0.05) different from RLX120

Data: RMP.SAS.H3SM.MOGGGKSC.FINAL
Source: RMP.H3SSK4YR.SASPGM(ARTC@1AA) X6221 30NOV00
Output: RMP.H3SO.K4YR(ARTCU4MN)

12.3.3.6. Cardiovascular System

12.3.3.6.1. Venous Thromboembolism

This section summarizes venous thromboembolism events (VTE) as reported to the sponsor through 1 November 1999, based on data in the 48-month clinical trial reporting database for Study GGGK, supplemented by the Lilly safety database. For the analyses presented in this section, VTE was defined as follows:

- Any acute venous thrombosis involving a deep peripheral vein (commonly known as deep vein thrombosis [DVT]), or
- Acute pulmonary embolism (PE), or
- Other acute serious vein thromboses, including mesenteric, intracerebral and retinal vein thrombosis (RVT)

The analyses exclude arterial thromboses, such as those causing stroke, myocardial infarction, and peripheral arterial occlusion. Superficial vein thrombophlebitis will not be specifically discussed in this section. All reported cases of DVT, PE, and other serious vein thromboses were included in the primary analyses without regard to likelihood of diagnostic accuracy, presence of known risk factors preceding event (ie, spontaneous versus provoked), or likelihood of causal relationship to study drug.

Venous thromboembolic events were grouped into three overlapping categories: 1) all VTEs; 2) all VTEs except RVT; and 3) all PE. Events for the two raloxifene doses were examined separately and pooled. The relative risk (with 95% CI) for each VTE category is presented in the table below.

- The estimates of relative risks for the pooled raloxifene group compared with the placebo group varied between 1.89 and 3.48; the risks for Categories 1 and 2 were significantly greater than 1.0.
- There were no statistically significant differences among the three treatment groups in Category 3; however, the magnitudes of relative risks were similar to Categories 1 and 2, which had higher incidence rates.
- There were no significant differences between the two raloxifene treatment groups in any category, and the magnitude of the relative risk for each raloxifene group was similar in each category.
- There is no evidence to suggest an increased risk of RVT during raloxifene treatment at this time (relative risk = 0.50, 95% CI [0.15, 1.69]).

Table GGGK.12.25. Analysis of All Venous Thromboembolism Events Reported Through 1 November 1999 (All Randomly Assigned Patients)

Category	Number/Rate/Relative Risk	Placebo (N=2576) 8352 Pt-Yrs	RLX060 (N=2557) 8429 Pt-Yrs	RLX120 (N=2572) 8530 Pt-Yrs	Pooled RLX (N=5129) 16,959 Pt-Yrs
Category 1: All VTEs (DVT/PE/RVT)	Number of cases Rate per 1000 patient-years Relative risk versus placebo (95% CI)	17 2.04	30 3.56 1.78 (0.99, 3.19)	34 3.56 2.00 (1.14, 3.53)	64 3.77 1.89 (1.12, 3.19)
Category 2: All VTEs Excluding RVT (DVT/PE)	Number of cases Rate per 1000 patient-years Relative risk versus placebo (95% CI)	12 1.44	28 3.32 2.35 (1.22, 4.52)	31 3.63 2.59 (1.37, 4.90)	59 3.48 2.47 (1.36, 4.49)
Category 3: ALL PEs (With or Without DVT)	Number of cases Rate per 1000 patient-years Relative risk versus placebo (95% CI)	4 0.48	11 1.31 2.77 (0.93, 8.28)	11 1.29 2.75 (0.92, 8.24)	22 1.30 2.76 (1.00, 7.65)

Abbreviations: DVT = deep vein thrombosis; N = number of randomly assigned patients; PE = pulmonary embolism; pt-yrs = patient-years; RVT = retinal vein thrombosis; VTE = venous thromboembolism; RLX = raloxifene; RLX060 = raloxifene 60 mg/day; RLX120 = raloxifene 120 mg/day; CI = confidence interval.

Table GGGK.12.26 and Table GGGK.12.27 present the time course of reported VTE in Categories 1 and 2, respectively. These analyses indicate:

- A period of significantly increased risk for VTE among raloxifene-treated patients in the first 4 months of treatment.
  - The absolute magnitude of risk (ie, event incidence rate) for the pooled raloxifene group was highest in the first 4 months for both Category 1 (7.98 events per 1000 patient-years) and Category 2 (7.33 events per 1000 patient-years).
- No statistically significant differences between the pooled raloxifene group and the placebo group in the 4- to 12-month, 12- to 24-month, 24- to 36-month, and the >36-month time periods.
  - The absolute magnitude of risk for the pooled raloxifene group decreased over time with rates for the entire period of observation of 3.77 events per 1000 patient-years for all VTE and 3.48 events per 1000 patient-years after excluding RVT.
- After 3 years, the VTE risk has returned to placebo levels (especially for the 60-mg dose).

Figure GGGK.12.2 presents the Kaplan-Meier analyses of time-to-event analysis for VTEs in Category 1.

Table GGGK.12.26. Time Course of All Venous Thromboembolism Events Reported Through 1 November 1999 (All Randomly Assigned Patients)

Time Interval	Number/Rate/Relative Risk	Placebo (N=2576)	RLX060 (N=2557)	RLX120 (N=2572)	Pooled RLX (N=5129)
All Cases	Number of cases	17	30	34	64
	Rate per 1000 patient-years	2.04	3.56	3.99	3.77
	Relative risk versus placebo		1.78	2.00	1.89
	(95% CI)		(0.99, 3.19)	(1.14, 3.53)	(1.12, 3.19)
0-4 Months	Number of cases	1	5	8	13
	Rate per 1000 patient-years	1.22	6.15	9.80	7.98
	Relative risk versus placebo		5.04	8.01	6.53
	(95% CI)		(0.73, 34.67)	(1.40, 45.87)	(1.12, 38.03)
4-12 Months	Number of patients at risk	2432	2401	2406	4807
	Number of cases	2	8	5	13
	Rate per 1000 patient-years	1.27	5.16	3.21	4.18
	Relative risk versus placebo		4.05	2.53	3.29
	(95% CI)		(0.97, 16.91)	(0.52, 12.29)	(0.81, 13.37)
12-24 Months	Number of patients at risk	2300	2257	2274	4531
	Number of cases	2	7	5	12
	Rate per 1,000 patient-years	0.92	3.24	2.29	2.76
	Relative risk versus placebo		3.57	2.53	3.05
	(95% CI)		(0.82, 15.50)	(0.52, 12.29)	(0.74, 12.61)
24-36 Months	Number of patients at risk	2047	2071	2101	4172
	Number of cases	7	7	10	17
	Rate per 1000 patient-years	3.57	3.49	4.91	4.20
	Relative risk versus placebo		0.99	1.39	1.19
	(95% CI)		(0.35, 2.81)	(0.53, 3.63)	(0.50, 2.87)
>36 Months	Number of patients at risk	1854	1908	1931	3839
	Number of cases	5	3	6	9
	Rate per 1000 patient-years	2.75	1.58	3.11	2.35
	Relative risk versus placebo		0.58	1.15	0.87
	(95% CI)		(0.14, 2.39)	(0.35, 3.77)	(0.29, 2.59)

Abbreviations: N = number of randomly assigned patients; RLX = raloxifene; RLX060 = raloxifene 60 mg/day; RLX120 = raloxifene 120 mg/day; CI = confidence interval.

Table GGGK.12.27. Time Course of Venous Thromboembolism Events Excluding RVT (DVT/PE Only) Reported Through 1 November 1999 (All Randomly Assigned Patients)

Time Interval	Number/Rate/Relative Risk	Placebo (N=2576)	RLX060 (N=2557)	RLX120 (N=2572)	Pooled RLX (N=5129)
All Cases	Number of cases	12	28	31	59
	Rate per 1000 patient-years	1.44	3.32	3.63	3.48
	Relative risk versus placebo		2.35	2.59	2.47
	(95% CI)		(1.22, 4.52)	(1.37, 4.90)	(1.36, 4.49)
0-4 Months	Number of cases	1	4	8	12
	Rate per 1000 patient-years	1.22	4.92	9.80	7.36
	Relative risk versus placebo		4.03	8.01	6.03
	(95% CI)		(0.53, 30.46)	(1.40, 45.87)	(1.01, 36.03)
4-12 Months	Number of patients at risk	2432	2401	2406	4807
	Number of cases	2	8	5	13
	Rate per 1000 patient-years	1.27	5.16	3.21	4.18
	Relative risk versus placebo		4.05	2.53	3.29
	(95% CI)		(0.97, 16.91)	(0.52, 12.29)	(0.81, 13.37)
12-24 Months	Number of patients at risk	2300	2257	2274	4531
	Number of cases	1	6	5	11
	Rate per 1000 patient-years	0.46	2.77	2.29	2.53
	Relative risk versus placebo		6.11	5.06	5.58
	(95% CI)		(0.96, 38.97)	(0.74, 34.77)	(0.91, 34.24)
24-36 Months	Number of patients at risk	2047	2071	2101	4172
	Number of cases	4	7	7	14
	Rate per 1000 patient years	2.04	3.49	3.43	3.46
	Relative risk versus placebo		1.73	1.71	1.72
	(95% CI)		(0.51, 5.81)	(0.51, 5.73)	(0.57, 5.14)
>36 Months	Number of patients at risk	1854	1908	1931	3839
	Number of cases	4	3	6	9
	Rate per 1000 patient years	2.20	1.58	3.11	2.35
	Relative risk versus placebo		0.73	1.44	1.09
	(95% CI)		(0.16, 3.23)	(0.41, 5.06)	(0.34, 3.52)

Abbreviations: DVT = deep vein thrombosis; PE = pulmonary embolism; RVT = retinal vein thrombosis; N = number of randomly assigned patients; RLX = raloxifene; RLX060 = raloxifene 60 mg/day; RLX120 = raloxifene 120 mg/day; CI = confidence interval.

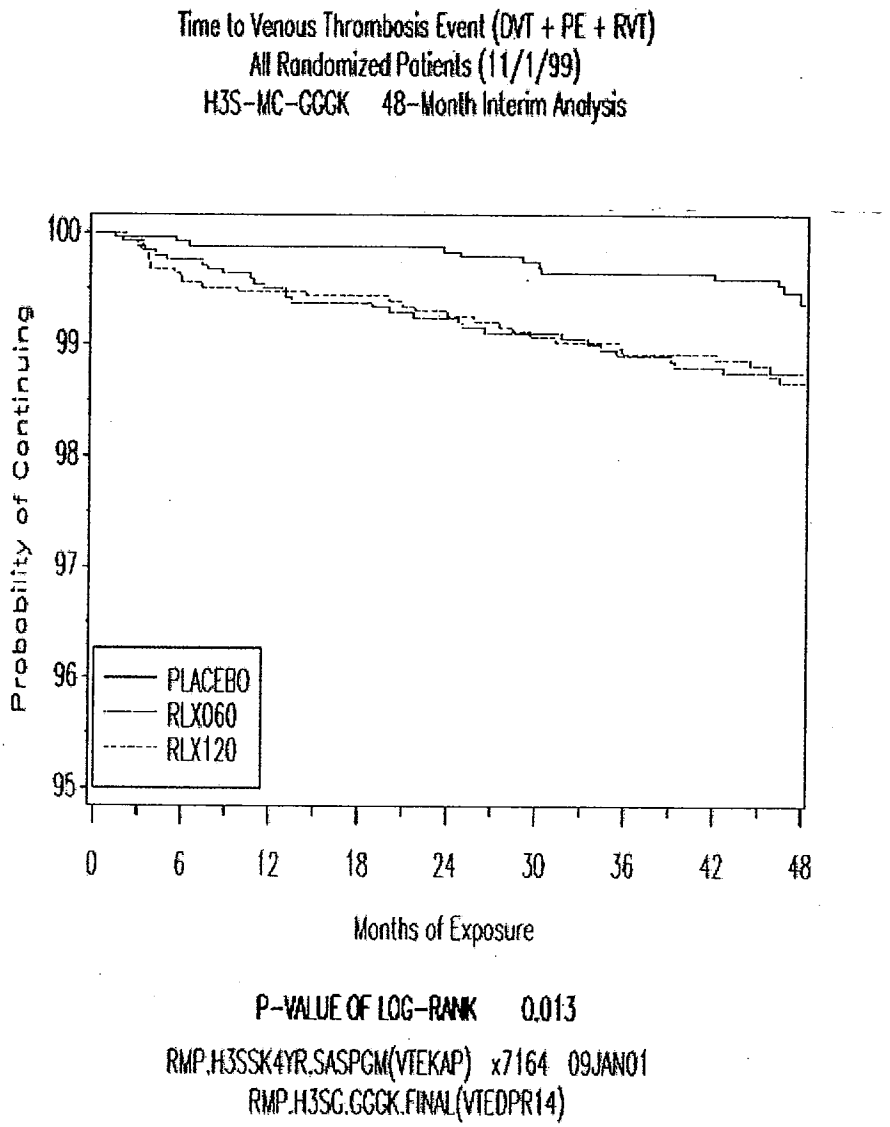


Figure GGGK.12.2. Kaplan-Meier Time-to-Event Analysis (All Venous Thromboembolism Events Reported Through 1 November 1999, All Randomly Assigned Patients, 48-Month Data)

12.3.3.6.2. Electrocardiograms

In order to assess for incident myocardial infarctions (MI) in the study population, a standard 12-lead electrocardiogram (ECG) was performed at baseline and at the ECG endpoint (48 months or at the patient's early discontinuation). The ECGs were then analyzed Relative risks of having developed ECG abnormalities consistent with MI for each of the raloxifene groups and for the pooled raloxifene group compared with the placebo group along with the 95% confidence intervals are presented in (Table GGGK.12.28).

- Although there was a trend towards a reduction in the number of patients with ECG-diagnosed MI among the raloxifene-treated patients compared with the placebo-treated patients, no statistical differences between the different treatment groups was seen. When the raloxifene data was pooled, there was a near statistically significant reduction in the proportion of patients with new ECG-diagnosed MI, with the magnitude of the reduction approximately 20%.

Table GGGK.12.28. Summary of Endpoint Results (All Randomly Assigned Patients, 48-Month Data)

NOVACODE	Placebo (N=2286)	RLX060 (N=2276)	RLX120 (N=2277)	Pooled RLX (N=4553)	Overall p-value[a]	Placebo Versus RLX060 p-value[a]	Placebo Versus RLX120 p-value[a]	Pooled RLX p-value[a]
Number (proportion) of patients with new MI or acute ST-T changes	110 (4.8%)	89 (3.9%)	89 (3.9%)	178 (3.9%)	0.215	0.136	0.135	0.080
RR (95% CI) compared with placebo		0.813 (0.618, 1.068)	0.812 (0.618, 1.068)	0.812 (0.644, 1.025)				
Number (proportion) of patients with new MI	9 (0.4%)	8 (0.4%)	5 (0.2%)	13 (0.3%)	0.556	0.815	0.288	0.456
RR (95% CI) compared with placebo		0.893 (0.345, 2.310)	0.558 (0.187, 1.662)	0.725 (0.310, 1.694)				

[a] Chi-square test for total count ≥10; Fisher's Exact test for total count 5 through 9.
Abbreviations: RLX060 = raloxifene 60 mg/day; RLX120 = raloxifene 120 mg/day; RLX = raloxifene; CI = confidence interval; RR = relative risk; MI = myocardial infarction, N = number of randomly assigned patients with an endpoint NOVACODE evaluation.

12.3.3.7. Adverse Events Leading to Discontinuation

Table GGGK.12.29 summarizes discontinuations due to adverse events coded by COSTART term for those event terms that led to a total of five or more discontinuations in the first 48 months of the study.

- A total of 910 (11.8%) of the 7,705 randomly assigned patients discontinued the study early because of an adverse event (285 [11.1%] patients in the placebo group, 327 [12.8%] patients in the raloxifene 60-mg group, and 298 [11.6%] patients in the raloxifene 120-mg group).
- There was no overall statistically significant difference among the three treatment groups and between the pooled raloxifene group and the placebo group in the proportion of discontinuations due to adverse events.

Table GGGK.14.16 in Section 14.3.5 provides a summary of statistically significant discontinuations due to adverse events by 6-month visit intervals.

A supplemental analysis was performed excluding the most frequent reasons for discontinuation for which there was a statistically significant difference between the pooled raloxifene group and the placebo group.

- When vasodilatation, deep thrombophlebitis, and breast carcinoma were excluded, there was no overall statistically significant difference in the remaining discontinuations due to an adverse event.

Table GGGK.12.29. Discontinuations Due to an Adverse Event (Events Reported By At Least 5 Patients, All Randomly Assigned Patients, 48-Month Data)

Event Classification	Placebo (N= 2576)	Rlx060 (N= 2557)	Rlx120 (N= 2572)	Overall p-Value	Pooled Rlx p-Value
BREAST CARCINOMA	33 (1.3%)	12 (0.5%)b	9 (0.3%)c	<.001	<.001
VASODILATATION	2 (0.1%)	22 (0.9%)c	14 (0.5%)b	<.001	<.001
DEEP THROMBOPHLEBITIS	5 (0.2%)	13 (0.5%)	15 (0.6%)a	.076	.026
DIARRHEA	0 (0.0%)	6 (0.2%)a	6 (0.2%)a	.049	.014
CONSTIPATION	1 (0.0%)	7 (0.3%)a	1 (0.0%) d	.017	.288
BREAST PAIN	2 (0.1%)	6 (0.2%)	0 (0.0%) d	.016	.726
VAGINITIS	0 (0.0%)	1 (0.0%)	6 (0.2%)a	.011	.104

NOTE: Chi-square tests were used when total count >= 10, else Fisher's exact test was used.
a - pairwise comparison statistically significant (p < 0.05) different from placebo
b - pairwise comparison statistically significant (p < 0.01) different from placebo
c - pairwise comparison statistically significant (p < 0.001) different from placebo
d - pairwise comparison of RLX060 statistically significant (p < 0.05) different from RLX120

Source: RMP.H3SSE4YR.SASPGM(DCADV@21) @@167 04JAN01
Data: RMP.SAS.H3SM.NCGGGKSC.FINAL
Output: RMP.H3SO.GGGK.FINAL(DCADV3YN)

12.3.3.7.1. Greater Incidence in Raloxifene Patients and Potentially Clinically Relevant

- There was an increased incidence of **discontinuation due to deep thrombophlebitis** in the pooled raloxifene group compared with the placebo group, as previously reported in the 36-month clinical study report.

- The highest incidence of discontinuations occurred in the raloxifene 120-mg group (15 patients, 0.6%). The raloxifene 60-mg group had 13 discontinuations (0.5%) and the placebo group had five (0.2%).

- There was an increased incidence of **discontinuation due to vasodilatation** overall and in the pooled raloxifene group compared with the placebo group.
  - A significantly higher incidence in discontinuations was reported by both the raloxifene 60-mg group (22 patients, 0.9%) and the raloxifene 120-mg group (14 patients, 0.5%) compared with the placebo group (2 patients, 0.1%).
- Reflecting the incidence of treatment-emergent adverse events, the rates of discontinuation were statistically significantly different among the three treatment groups only during the first 6 months of the study.

12.3.3.7.2. Lower Incidence in Raloxifene Patients and Potentially Clinically Relevant

- There was a lower incidence of **discontinuation due to breast carcinoma** overall and in the pooled raloxifene group compared with the placebo group, with similarly low incidence in the raloxifene 60-mg group and the raloxifene 120-mg group compared with the placebo group.
  - A significantly lower incidence in discontinuations was reported by both the raloxifene 60-mg group (12 patients, 0.5%) and the raloxifene 120-mg group (9 patients, 0.3%) compared with the placebo group (33 patients, 1.3%).

12.4. Clinical Laboratory Evaluation

12.4.1. Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

Appendix 16.2.8 contains a listing of all laboratory measurements by patient. Section 14.3.4 contains a listing of all patients who had an abnormal laboratory value during the study.

12.4.2. Brief Summary of Methods for Laboratory Measurements

12.4.2.1. Central Tendency (Change from Baseline to Endpoint)

As a measure of central tendency, the median percentage change from baseline and the overall statistical significance from analysis of variance (ANOVA) with ranked data are presented in Table GGGK.14.20 (Serum Chemistry), Table GGGK.14.21 (Serum Liver-Related Chemistry), Table GGGK.14.22 (Hematology [RBC and Related]), and Table GGGK.14.23 (Hematology [WBC and Related]) (Section 14.3.5).

A summary of the results from the categorical analyses (normal/abnormal) of urinalysis chemistry and urinalysis microscopic are included in Table GGGK.14.24 and Table GGGK.14.25, respectively, in (Section 14.3.5).

12.4.2.2. Distribution of Extreme Values at Endpoint

A large clinical trial such as Study GGGK provides high statistical power to detect very small and probably clinically insignificant differences in baseline to endpoint changes among the three treatment groups. *Therefore **categorical analyses** comparing the proportion of patients with extreme laboratory values were performed.*

Because this is such a large cohort, it was possible to create *internal population-based* reference ranges for laboratory parameters (shown in Table GGGK.14.26 in Section 14.3.5).

- Using the distribution of the observed baseline laboratory data for the GGGK cohort as the reference, outliers and extreme outliers at endpoint were defined as follows:

Outliers:

Low outliers: below the 2.5 percentile of the baseline distribution
High outliers: above the 97.5 percentile of the baseline distribution
Extreme Outliers:
Low-extreme outliers: below the 0.5 percentile of the baseline distribution
High-extreme outliers: above the 99.5 percentile of the baseline distribution

Figure GGGK.12.3 through Figure GGGK.12.11 summarize the laboratory analytes for which the overall chi-square test indicated a statistically significant difference among the three treatment groups in the proportion of patients with below-reference or above reference laboratory values at endpoint for outliers. A summary of the outlier and extreme outlier categorical analyses for statistically significant laboratory analytes is located in Table GGGK.14.27 and Table GGGK.14.28, respectively, in (Section 14.3.5).

12.4.2.3. Distribution of Extreme Changes from Baseline to Endpoint (Delta Outliers and Delta-Extreme Outliers)

The proportion of patients among the three treatment groups with large changes (delta outliers) and with extreme changes (delta-extreme outliers) was analyzed. If the baseline value lies just below the upper limit of the reference range, a small change could make the endpoint value an outlier. Delta reference ranges (defined by the distribution of differences between baseline and endpoint for the placebo group) can be used to consider the magnitude of change, whereas the ordinary reference ranges can be considered as the threshold.

Because this is such a large cohort, it was possible to create internal, population-based, delta reference ranges. Table GGGK.14.29 in Section 14.3.5 shows the newly defined delta reference ranges based on the GGGK placebo cohort. The "delta outliers" and "delta-extreme outliers" were defined as follows:

Delta Outliers:

Low-delta outliers: below the 2.5 percentile of the baseline to endpoint change distribution for the placebo group
High-delta outliers: above the 97.5 percentile of the baseline to endpoint change distribution for the placebo group

Delta-Extreme Outliers:

Low-delta-extreme outliers: below the 0.5 percentile of the baseline to endpoint change distribution for the placebo group
High-delta-extreme outliers: above the 99.5 percentile of the baseline to endpoint change distribution for the placebo group.

The analyses of extreme outliers, delta outliers, and delta-extreme outliers will not be discussed unless the results of these analyses differ from the low- and high-outlier results or provide additional relevance to the observations. A summary of the delta outlier and delta-extreme outlier categorical analyses for statistically significant laboratory analytes is located in Table GGGK.14.30 and Table GGGK.14.31, respectively (Section 14.3.5).

12.4.3. Evaluation of Each Laboratory Parameter

In the following analyses of safety laboratory tests, the various analytes have been assigned to laboratory groups.

Analytes collected as numeric data:

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

Analytes reported as categorical (abnormal/normal) data:

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

12.4.3.1. Potentially Clinically Significant Laboratories

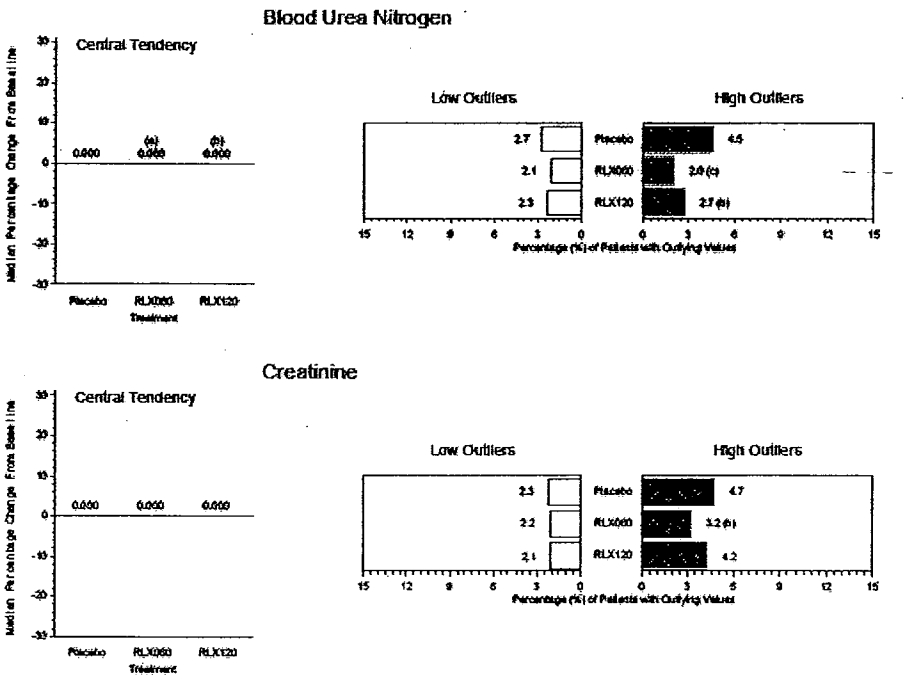
The following analytes will be discussed because they showed either a statistically significant change from baseline to endpoint or significant outlier changes.

12.4.3.2. Renal-Related Analytes (Blood Urea Nitrogen and Creatinine)

Figure GGGK.12.3 summarizes the median percentage change from baseline to endpoint and the percentage of patients with low- and high-outlying values for the serum chemistry analytes, BUN, and creatinine.

No clinically relevant changes were observed for the renal analytes in raloxifene-treated patients compared with the placebo group. Since raloxifene is primarily metabolized in the liver and undergoes very little renal excretion (<6%), it is unlikely that raloxifene treatment would affect these analytes.

Renal Analytes



☒ Indicates overall statistical significance

☐ Indicates no overall statistical significance

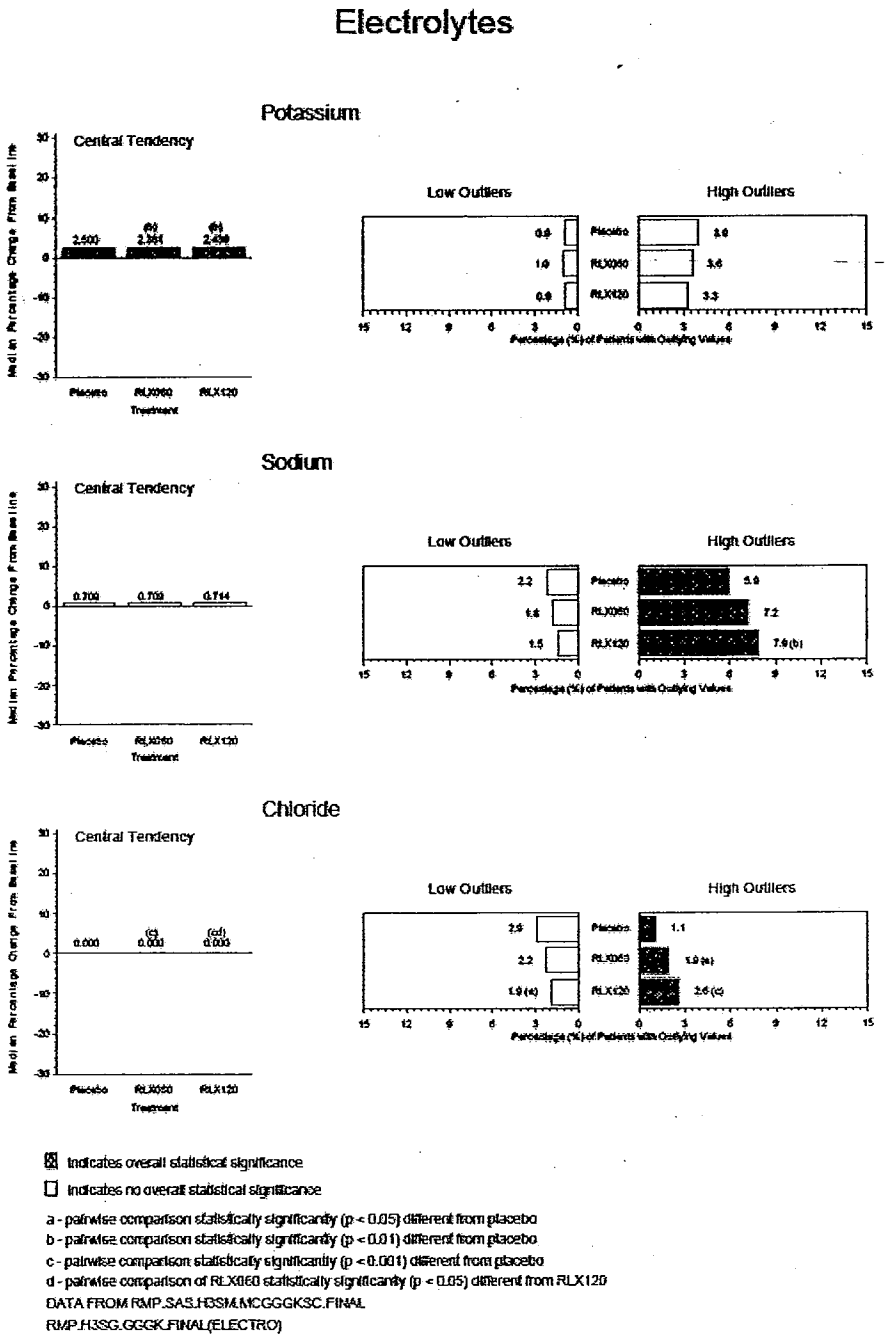
a - pairwise comparison statistically significantly ($p < 0.05$) different from placebo
b - pairwise comparison statistically significantly ($p < 0.01$) different from placebo
c - pairwise comparison statistically significantly ($p < 0.001$) different from placebo
d - pairwise comparison of RLX060 statistically significantly ($p < 0.05$) different from RLX120
DATA FROM RMP.BAS.H38M.MCGGGK8C.FINAL
RMP.H38G.GGGK.FINAL(RENAL)

Figure GGGK.12.3. Renal Analytes (All Randomly Assigned Patients, 48-Month Data)

12.4.3.3. Electrolytes (Potassium, Sodium, and Chloride)

Figure GGGK.12.4 summarizes the median percentage change from baseline to endpoint and the percentage of patients with low- and high-outlying values for the serum chemistry analytes potassium, sodium, and chloride.

- No clinically significant changes in potassium were observed in patients treated with raloxifene compared with patients receiving placebo. There were small, central tendency increases for potassium in each treatment group, but these increases were greater in the placebo group.
- While no statistically significant increases from baseline to endpoint for serum sodium were observed in the raloxifene groups compared with the placebo group, a statistically significantly greater proportion of patients in the raloxifene 120-mg group compared with the placebo group were in the high-outlier ($p=0.008$), but not the extreme high-outlier, high delta-outlier, nor extreme high-delta outlier categories at endpoint.
- The median percentage changes from baseline to endpoint for chloride in each treatment group was 0.00; however, there was a statistically significant mean percentage increase from baseline to endpoint for chloride in both raloxifene groups compared with the placebo group (-0.02% in the placebo group, +0.3% in the raloxifene 60-mg group, and +0.5% in the raloxifene 120-mg group; $p<0.001$) (Table GGGK.14.20).
    - Additionally, a statistically significantly greater proportion of patients in both raloxifene groups were in the high-outlier category at endpoint for serum chloride ($p<0.001$), but not the extreme high-outlier, the high delta or the extreme high delta-outlier categories.
        - *Estrogen repletion in postmenopausal women has been associated with significant increases in serum chloride levels and decreases in serum bicarbonate levels (Adami et al. 1992).*
- There were very few patients and no statistically significant differences among the three treatment groups in the proportion of patients in the high-outlier category for chloride that also had high outlying values for blood urea nitrogen, creatinine, or potassium.
- Bicarbonate testing was not performed by the central laboratory and, therefore, it is not known whether any of the patients with an elevated chloride also experienced hyperchloremic metabolic acidosis. Regardless, the increase in chloride is not likely to be clinically significant since no concurrent increases in urea nitrogen, creatinine, and potassium were observed overall in raloxifene-treated patients or in hyperchloremic patients.



☒ Indicates overall statistical significance
☐ Indicates no overall statistical significance

a - pairwise comparison statistically significantly ($p < 0.05$) different from placebo
b - pairwise comparison statistically significantly ($p < 0.01$) different from placebo
c - pairwise comparison statistically significantly ($p < 0.001$) different from placebo
d - pairwise comparison of RLX060 statistically significantly ($p < 0.05$) different from RLX120
DATA FROM RMP.SAS.H3SM.MCGGGKSC.FINAL
RMP.H3SG.GGGK.FINAL(ELECTRO)

Figure GGGK.12.4. Electrolytes (All Randomly Assigned Patients, 48-Month Data)

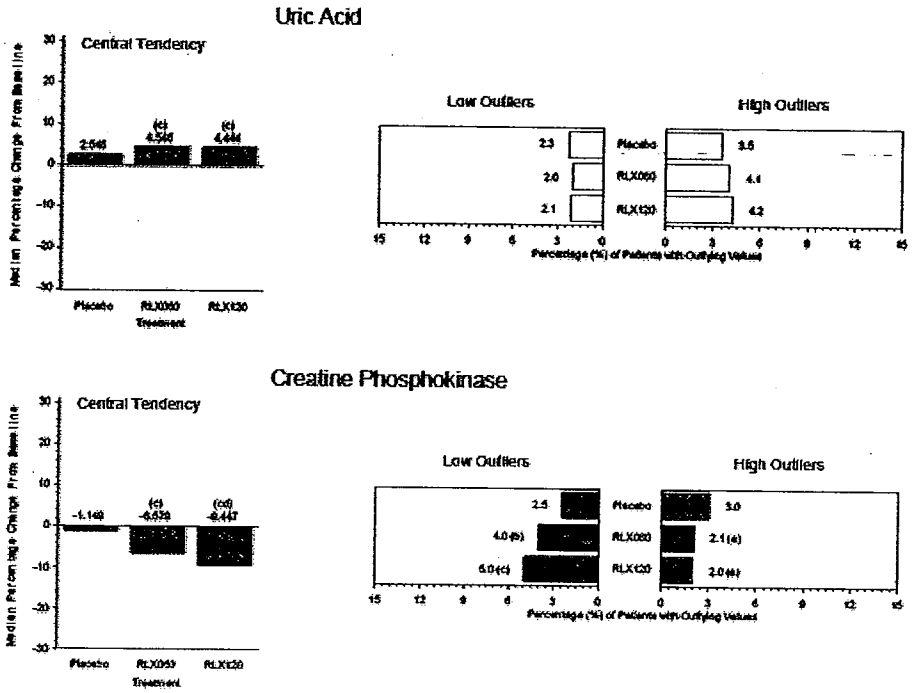
12.4.3.4. Miscellaneous Serum Chemistry (Uric Acid and Creatine Phosphokinase)

Figure GGGK.12.5 summarizes the median percentage change from baseline to endpoint and the percentage of patients with low- and high-outlying values for the serum chemistry analytes, uric acid, and creatine phosphokinase (CPK).

- A statistically significant **increase in uric acid** from baseline to endpoint was observed for both raloxifene groups compared with the placebo group (overall $p<0.001$). The increase in uric acid was deemed clinically benign for several reasons:
  - No statistically significant difference in the proportion of high outliers or high-delta outliers among the three treatment groups
  - Change in uric acid was not correlated with changes in urea nitrogen
  - Overall increases were small (12 μ mol/L or 0.2 mg/dL)
  - No differences in the reporting of gout (12 patients in the placebo group, 10 patients in the raloxifene 60-mg group, and 7 patients in the raloxifene 120-mg group) or hyperuricemia (7 patients in the placebo group, 6 patients in the raloxifene 60-mg group, and 4 patients in the raloxifene 120-mg group) as treatment-emergent adverse events.
- Increases in uric acid have been observed in other clinical raloxifene studies, although these elevations were not statistically significant (initial regulatory submission of raloxifene for the indication of prevention of osteoporosis in postmenopausal women).

- A statistically significant **decrease in CPK** from baseline to endpoint was observed for both raloxifene groups compared with the placebo group (overall $p<0.001$). A statistically significantly greater proportion of patients in the raloxifene groups were in the low-outlier category at endpoint ($p<0.001$), and conversely, a greater proportion of patients in the placebo group were in the high-outlier category at endpoint (overall $p<0.001$). Statistically significantly more raloxifene 120-mg patients were low-delta outliers for CPK at endpoint compared with the placebo group ($p=0.024$). The reduction in CPK with raloxifene treatment is of unknown clinical significance, but diseases of clinical significance cause increases in CPK, not decreases. Thus, the reductions in CPK are not likely to be clinically important.

Miscellaneous Serum Chemistry



☒ Indicates overall statistical significance
☐ Indicates no overall statistical significance

a - pairwise comparison statistically significantly ($p < 0.05$) different from placebo
b - pairwise comparison statistically significantly ($p < 0.01$) different from placebo
c - pairwise comparison statistically significantly ($p < 0.001$) different from placebo
d - pairwise comparison of RLX060 statistically significantly ($p < 0.05$) different from RLX120
DATA FROM RMP.SAS.H3SM.MCGGGKSC.FINAL
RMP.H3SG.GGGK.FINAL(SERUM)

Figure GGGK.12.5. Miscellaneous Serum Chemistry (All Randomly Assigned Patients, 48-Month Data)

12.4.3.5. Skeletal Homeostasis (Calcium, Inorganic Phosphorus, Alkaline Phosphatase, Albumin, and Total Protein)

Figure GGGK.12.6 summarizes the *median percentage change* from baseline to endpoint and the *percentage of patients* with low- and high-outlying values for the analytes associated with skeletal homeostasis, calcium, phosphorus, and alkaline phosphatase.
Because changes in calcium are related to changes in serum proteins, albumin and total protein are included here.

- A statistically significant increase in **calcium** from baseline to endpoint was observed for placebo-treated patients compared with decreases observed in both raloxifene groups (overall $p<0.001$). Additionally, significantly more patients in the placebo group were in the high-outlier, high-delta outlier, and extreme-high delta outlier categories at endpoint. Conversely, a greater proportion of patients in the raloxifene groups was in the low-outlier ($p<0.001$), extreme-low outlier ($p=0.046$), low–delta ($p<0.001$) and extreme low-delta outlier ($p=0.018$) categories for calcium at endpoint. Of note, parathyroid hormone (PTH) levels were assessed only at baseline, randomization, and at the 6-month visit.
    - *These findings are consistent with skeletal anti-resorptive effects and have been observed with other anti-resorptive agents and estrogens (Selby et al. 1985).*
- A statistically significant decrease in **phosphorus** from baseline to endpoint was observed for both raloxifene groups compared with the placebo group ($p<0.001$). Similarly, there was a statistically significantly greater proportion of patients in the low-outlier ($p<0.001$), extreme-low outlier ($p<0.001$), low–delta ($p<0.001$), and extreme-low delta ($p<0.001$) outlier categories in both raloxifene groups compared with the placebo group.
    - *The reduction is consistent with a skeletal anti-resorptive effect of raloxifene. Postmenopausal women treated with ethynyl estradiol had significant reductions in serum phosphorus that the authors attributed to the inhibitory effect of estradiol on bone resorption (Selby et al. 1985).*
- A statistically and clinically significant decrease from baseline to endpoint was observed for **alkaline phosphatase** in both raloxifene groups compared with the placebo group ($p<0.001$). Additionally, a statistically significantly greater proportion of patients in both raloxifene groups was in the low-outlier ($p<0.001$), extreme-low outlier ($p<0.001$), and low-delta outlier ($p<0.001$) categories for alkaline phosphatase at endpoint.
    - *This clinically significant reduction is likely related to a skeletal anti-resorptive effect similar to that observed with estrogen (Voetberg et al. 1994) and other skeletal anti-resorptive agents (Lufkin et al. 1998).*
- The treatment differences observed with **albumin** paralleled those observed with calcium with an overall statistically significant baseline-to-endpoint decrease noted with both raloxifene groups ($p<0.001$). Similarly, a greater proportion of patients in the raloxifene groups were in the low-outlier ($p<0.001$) and low-delta outlier ($p<0.001$) categories for albumin at endpoint.
    - *The reduction in albumin is similar to that observed with estrogen (Honger and Rossing 1969).*
- A small, statistically significant decrease from baseline to endpoint was observed for **total protein** in both raloxifene groups compared with the placebo group ($p<0.001$).

Additionally, a statistically significantly greater proportion of patients in the raloxifene groups was in the low-outlier ($p<0.001$), extreme-low outlier ($p=0.002$), and low-δ outlier ($p<0.001$) categories for total protein at endpoint.

- *The reduction in total protein is similar to that observed with estrogen and has been observed in other raloxifene clinical studies. The effects on total protein appear to be similar in magnitude to the effects on albumin and may be related to an increase in plasma volume.*

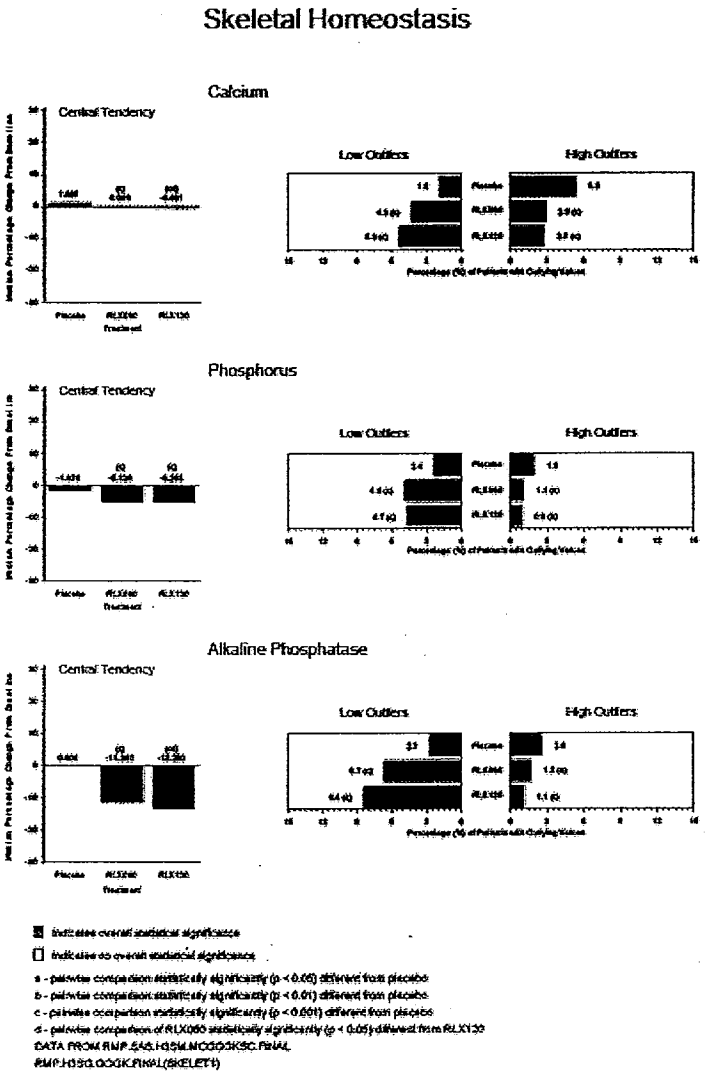


Figure GGGK.12.6. Skeletal Homeostasis (All Randomly Assigned Patients, 48-Month Data)

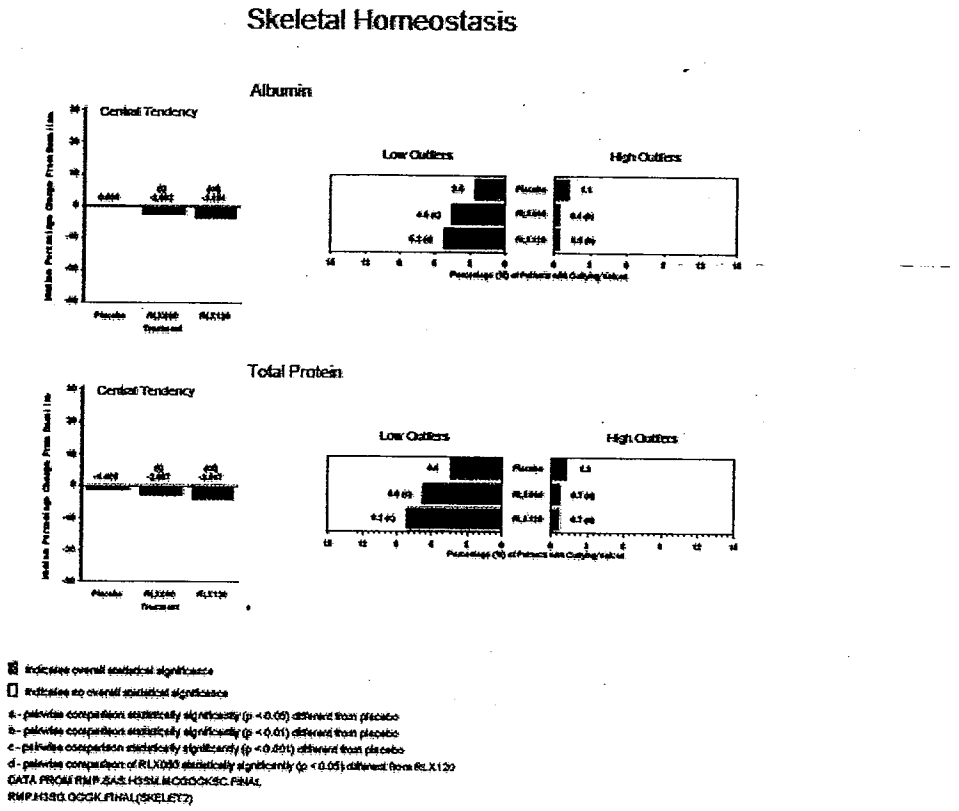


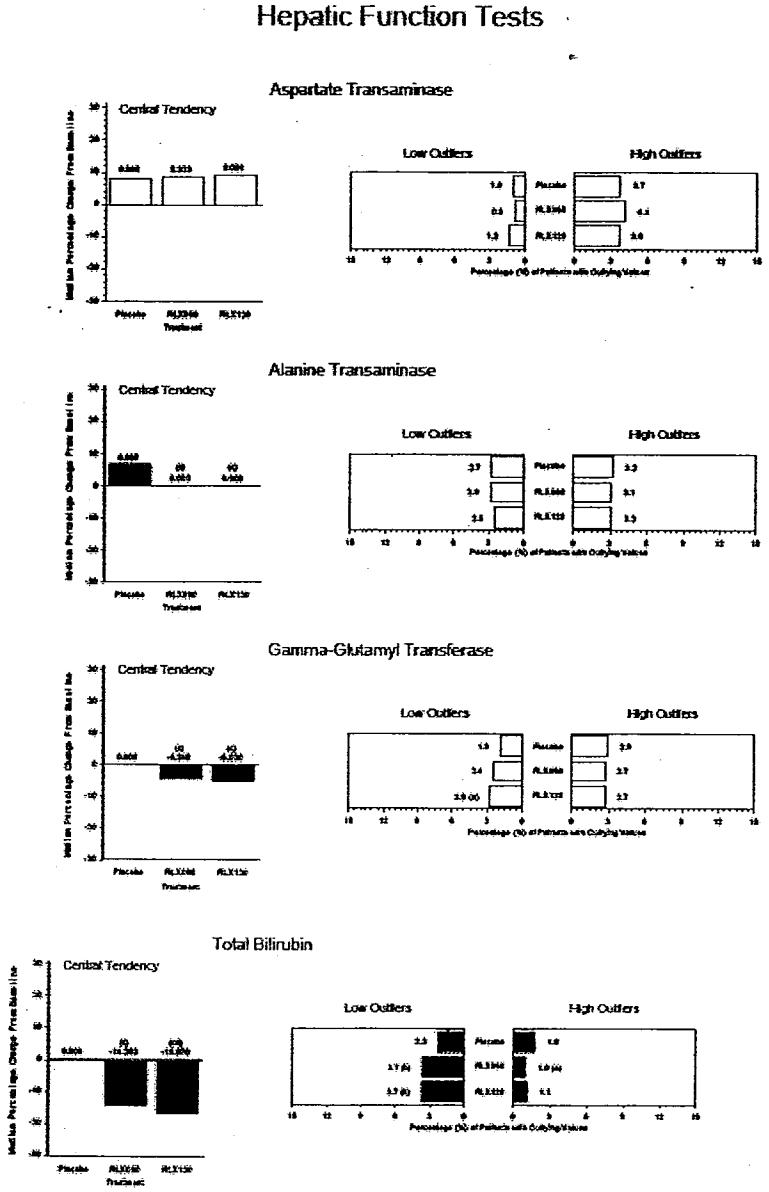
Figure GGGK.12.6. Skeletal Homeostasis (All Randomly Assigned Patients, 48-Month Data)

12.4.3.6. Hepatic Function Tests (Aspartate Transaminase [AST], Alanine Transaminase [ALT, Gamma-Glutamyl Transferase [GGT], Total Bilirubin)

Figure GGGK.12.7 summarizes the median percentage change from baseline to endpoint and the percentage of patients with low- and high-outlying values for the serum liver-related chemistry analytes AST, ALT, GGT, and total bilirubin.

- No statistically significant *baseline-to-endpoint differences* were observed for **AST** among the three treatment groups. Statistically significantly more *patients* in both raloxifene groups were in the extreme-high outlier *category* at endpoint compared with the placebo group (p=0.024). Statistically significantly more patients in the raloxifene 120-mg group had extremely high changes in AST at endpoint compared with the placebo group (p=0.022).
- For the liver-related analytes, **ALT** and **total bilirubin**, there were statistically significant median percentage decreases from baseline to endpoint in each raloxifene group compared with the placebo group (both p<0.001). However, a statistically significantly higher proportion of raloxifene 120-mg patients were in the extreme-high outlier category for ALT at endpoint compared with the placebo group (p=0.027). A statistically significantly greater proportion of raloxifene-treated patients were in the low-outlier (p=0.006) and low-delta outlier (p=0.001) categories for bilirubin at endpoint and statistically significantly more raloxifene 120-mg patients were in the extreme-low change category for bilirubin at endpoint compared with the placebo group (p=0.033).
- A statistically significant median percentage decrease from baseline to endpoint was observed for **GGT** for both raloxifene groups compared with the placebo group (p<0.001). Statistically significantly more raloxifene 120 mg-treated patients had low outlier (=0.037), extreme-low outlier (p=0.037), and low-delta outlier (p=0.008) values for GGT at endpoint compared with the placebo group.

Despite its extensive hepatic metabolism, as demonstrated in previous raloxifene clinical studies, raloxifene does not appear to be associated with liver-related abnormalities.
These therapeutic treatment effects were supported by no findings of statistically significant, liver-related, treatment-emergent, adverse events among the three treatment groups. The liver-related, treatment-emergent, adverse events reviewed were cholelithiasis, cholecystitis, liver function tests abnormal, liver fatty deposit, biliary pain, hepatic neoplasia, hepatitis, hepatomegaly, jaundice, gamma-glutamyl transpeptidase increased, cholangitis, cholestatic jaundice, hepatoma, biliary atresia, and liver necrosis.



Indicates overall statistical significance

Indicates no overall statistical significance

a - pairwise comparison statistically significantly ($p < 0.05$) different from placebo
b - pairwise comparison statistically significantly ($p < 0.01$) different from placebo
c - pairwise comparison statistically significantly ($p < 0.001$) different from placebo
d - pairwise comparison of RLX060 statistically significantly ($p < 0.05$) different from RLX120

DATA FROM RMP.SAS.HSSM.MOGGGKSC.FINAL
RMP.H15G.GGGK.FINAL(HEPATIC2)

Figure GGGK.12.7. Hepatic Function Tests (All Randomly Assigned Patients, 48-Month Data)

12.4.3.7. Hematology (Red Blood Cell-Related Parameters)

Figure GGGK.12.8 summarizes the *median percentage change* from baseline to endpoint and the *percentage of patients* with low- and high-outlying values for the red blood cell-related hematology indices: **hemoglobin, hematocrit, and erythrocyte count**.
Statistically significant decreases from baseline to endpoint were observed for **hemoglobin** in both raloxifene groups compared with the placebo group ($p<0.001$).
There were no statistically significant low or extreme-low outliers for hemoglobin at endpoint compared with the placebo group. However, a significantly greater proportion of patients in the raloxifene 120-mg group compared with the placebo group were in the low-delta–outlier ($p=0.007$), but not extreme-low delta outlier, category for hemoglobin at endpoint. Conversely, at endpoint a statistically significantly larger proportion of placebo-treated patients were in the high-outlier ($p=0.033$), high–delta ($p=0.002$), and extreme-high delta ($p=0.020$) outlier categories for hemoglobin compared with raloxifene-treated patients.
Statistically significant decreases from baseline to endpoint were observed for **hematocrit** in both raloxifene groups compared with the placebo group ($p<0.001$). There were no statistically significant low or extreme low outliers for hematocrit at endpoint for either raloxifene group compared with the placebo group. However, a statistically significantly greater proportion of patients in the raloxifene 120-mg group compared with the placebo group were in the low delta ($p=0.041$), but not extreme low-delta outlier, category for hematocrit at endpoint. Conversely, at endpoint a statistically significantly larger proportion of placebo-treated patients were in the high–outlier ($p=0.050$), high-delta ($p=0.008$), and extreme-high delta categories ($p=0.041$ compared with raloxifene 60 mg, not significant for raloxifene 120 mg) for hematocrit compared with raloxifene-treated patients.
Statistically significant decreases from baseline to endpoint were observed for **erythrocyte count** in both raloxifene groups compared with the placebo group ($p<0.001$).
A statistically significantly higher proportion of raloxifene 120 mg-treated patients were low outliers ($p=0.047$), but not extreme low outliers, compared with the placebo group.
A statistically significantly higher proportion of patients in both raloxifene groups were low-delta outliers ($p=0.001$), but not extreme-low delta outliers, compared with the placebo group.

The absolute values of the decreases in these analytes were small.
A review of the GGGK clinical trial database was conducted to look for treatment differences in adverse events or discontinuations because of adverse events that were potentially related to low RBC indices. The events reviewed included anemia, melena, rectal hemorrhage, gastrointestinal hemorrhage, hemorrhage, and hematemesis. *Compared with the placebo group, no statistically significant treatment differences were observed for anemia, melena, rectal hemorrhage, gastrointestinal hemorrhages, or hemorrhage.* A statistically greater proportion of patients in the raloxifene 120-mg group reported hematemesis compared with the placebo group ($p<0.01$).
Oral contraceptives have been shown to significantly decrease both hematocrit and hemoglobin (Tollan 1992), presumably due to an increase in plasma volume causing a dilutional effect on the measurement of these analytes. Similarly, tamoxifen has been shown to cause a significant decline in hemoglobin and albumin due to a proposed hemo-dilutional effect (Grey et al. 1997). The changes in hematocrit and hemoglobin for patients treated with raloxifene are similar in

magnitude to the changes observed in women on oral contraceptives and tamoxifen and may be due to an estrogen-like component of the selective estrogen receptor modulator (SERM) profile.

Figure GGGK.12.8 summarizes the median percentage change from baseline to endpoint and the percentage of patients with low- and high-outlying values for the RBC-related, hematology indices **mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).**

A statistically significant increase from baseline to endpoint was observed for **MCV** in both raloxifene groups compared with the placebo group. However, there were no statistically significant treatment group differences in high outliers, extreme-high outliers, high delta outliers, or extreme-high delta outliers for raloxifene compared with the placebo group. A statistically significantly higher proportion of placebo-treated patients were low outliers for MCV compared with both doses of raloxifene ($p=0.007$). There were no median percentage changes from baseline to endpoint for **MCH** in any treatment group; however, there was a statistically significant mean percentage increase from baseline to endpoint for MCH in both raloxifene groups compared with the placebo group (-0.3% for the placebo group, 0.2% for the raloxifene 60-mg group, and 0.2% for the raloxifene 120-mg group; [$p<0.001$]). A statistically significantly higher proportion of patients in the raloxifene 60-mg group had high changes ($p=0.002$), but not extreme-high changes, in MCH compared with the placebo group. A statistically significant decrease from baseline to endpoint was observed for **MCHC** in the raloxifene 120-mg group compared with the placebo group ($p<0.05$). These changes were small and did not result in statistically significant outliers for the raloxifene groups.

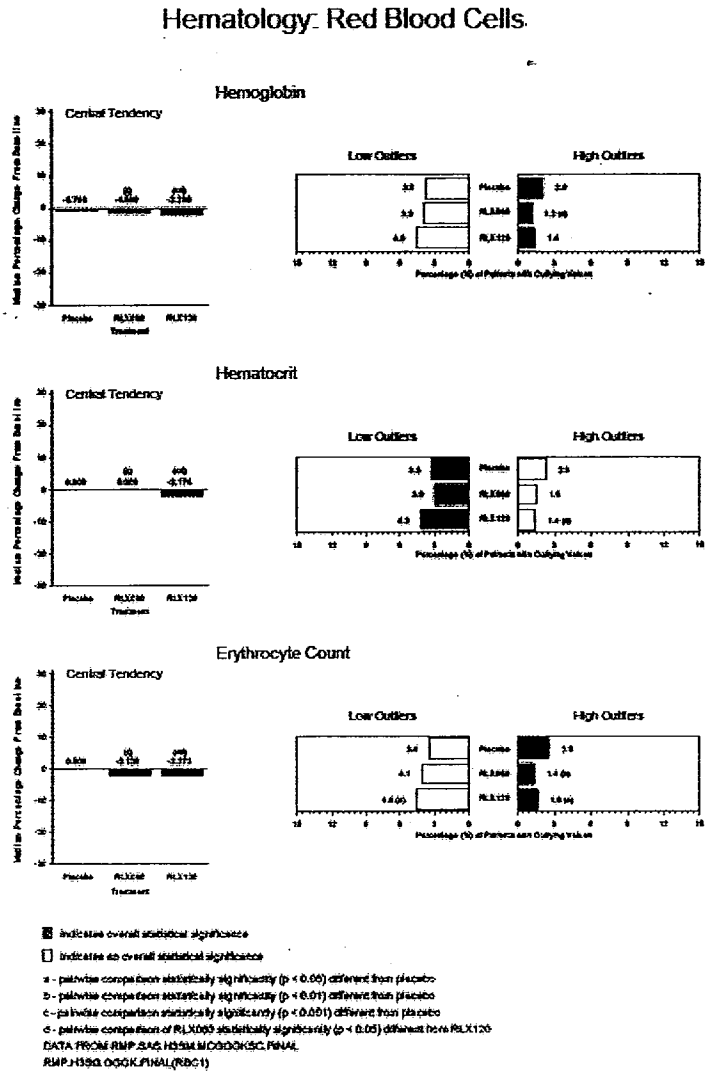


Figure GGGK.12.8. Hematology (Red Blood Cell-Related Parameters, All Randomly Assigned Patients, 48-Month Data)

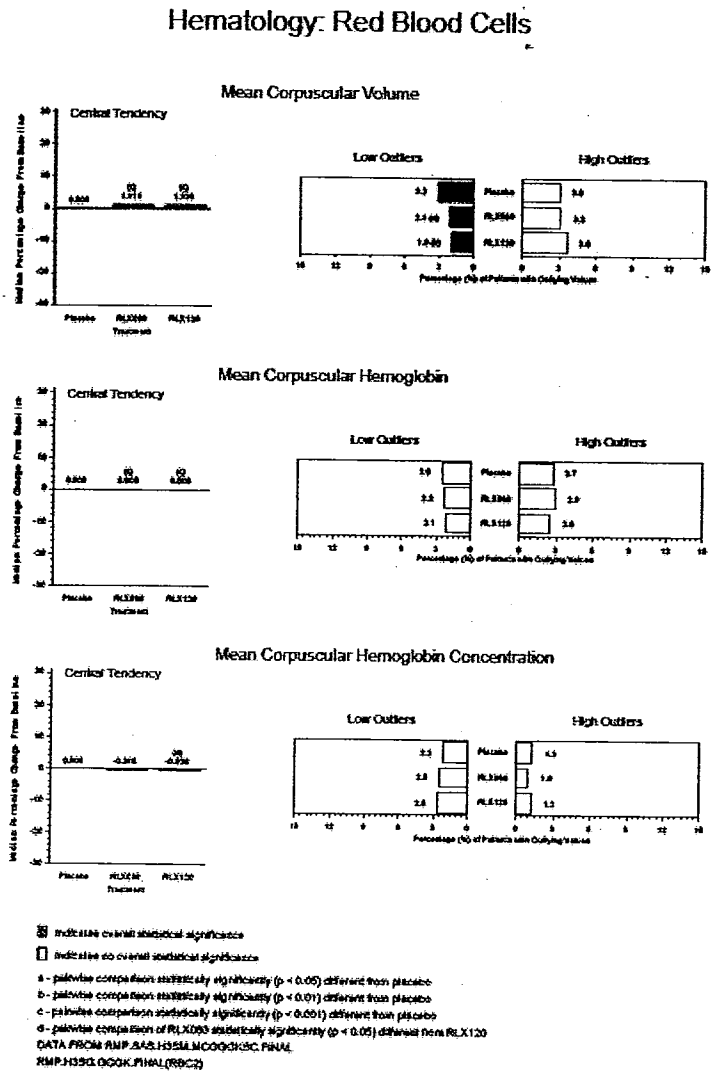


Figure GGGK.12.8. Hematology (Red Blood Cell-Related Parameters, All Randomly Assigned Patients, 48-Month Data)

12.4.3.8. Hematology (White Blood Cell-Related Parameters)

Figure GGGK.12.9 summarizes the median percentage changes from baseline to endpoint and the percentage of patients with low- and high-outlying values for the white blood cell-related hematology indices leukocyte count, neutrophils, lymphocytes, and monocytes.

A statistically significant increase from baseline to endpoint was observed for **leukocyte count** ($p<0.001$), **segmented neutrophils** ($p<0.001$), **lymphocytes** ($p<0.001$), and **monocytes** ($p=0.002$) in both raloxifene groups compared with the placebo group. The changes in these analytes were small and did not result in significantly more high outliers in raloxifene-treated patients compared with placebo patients, except for leukocyte count where significantly more raloxifene 60-mg patients had high changes compared with placebo patients ($p=0.030$).

A review of the GGGK clinical trial database was conducted to look for treatment differences in adverse events or discontinuations because of adverse events that were potentially related to elevated white blood cell indices. The events reviewed included urinary tract infection, pneumonia, bronchitis, sinusitis, and infection. No statistically significant treatment differences were observed for these events among the three treatment groups.

There were no statistically significant treatment-group differences in central tendency or in the proportion of patients with high or low outliers for basophils or eosinophils.

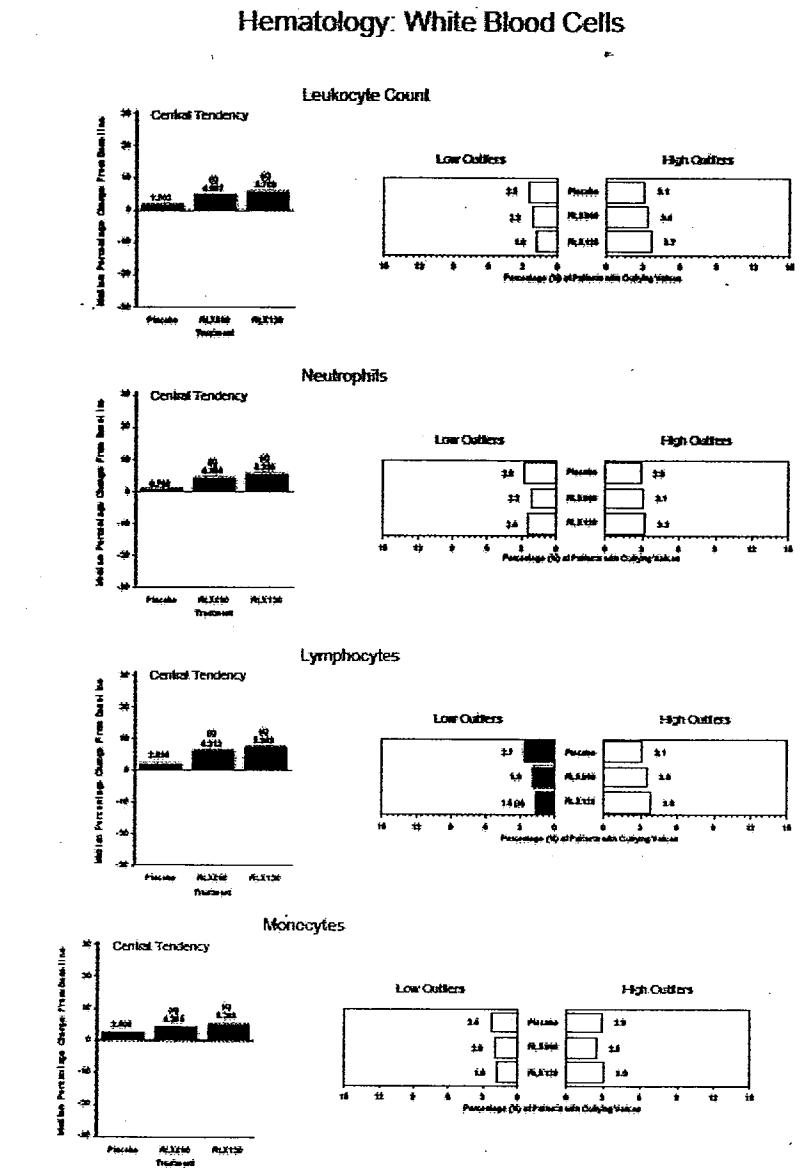


Figure GGGK.12.9. Hematology (White Blood Cell-Related Parameters, All Randomly Assigned Patients, 48-Month Data)

12.4.3.9. Platelets

Figure GGGK.12.10 summarizes the median percentage change from baseline to endpoint and the percentage of patients with low- and high-outlying values for platelets.

A statistically significant decrease from baseline to endpoint was observed for platelets in both raloxifene groups compared with the placebo group ($p<0.001$). There were no treatment-group differences in the proportion of patients with low outliers for platelets, however, statistically significantly more patients in the raloxifene 60-mg group were low-delta outliers at endpoint for platelets compared with the placebo group ($p=0.007$).
Conversely, statistically significantly more placebo-treated patients were high outliers for platelet count compared with the raloxifene 120-mg patients ($p=0.027$).

A review of the GGGK clinical trial reporting database was conducted to look for treatment differences in *adverse events or discontinuations because of adverse events potentially related to low platelet count*. The events reviewed included purpura, vaginal hemorrhage, hemorrhage, hematuria, and melena. *No statistically significant treatment differences were observed for these events.* Incidentally, hematuria was reported as a treatment-emergent adverse event less frequently by the raloxifene 120-mg group (43, 1.7%) compared with the placebo group (70, 2.7%) with $p<0.05$ and purpura was reported as a treatment-emergent adverse event less frequently by the raloxifene 60-mg group (208, 8.1%) compared with the placebo group (257, 10.0%) with $p<0.05$. A reduction in platelet count has been observed in previous raloxifene clinical trials. Both the raloxifene 60-mg group and the raloxifene 120-mg group decreased platelets in a magnitude similar to tamoxifen. A review of available literature revealed that tamoxifen decreased platelets by 7% to 9% in a 2-year study (Love et al. 1992).

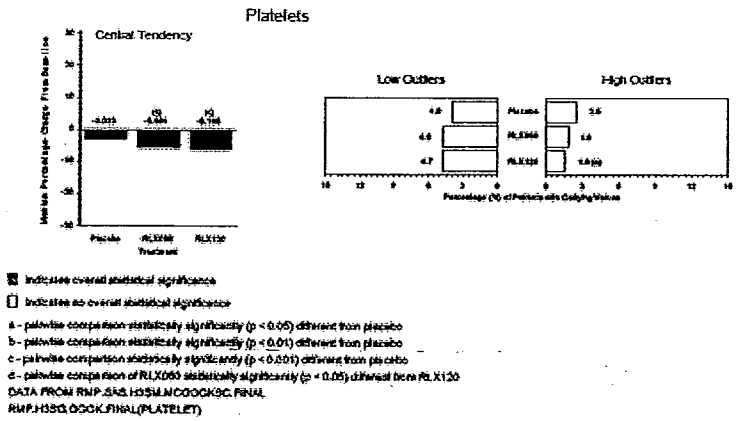


Figure GGGK.12.10. Platelets (All Randomly Assigned Patients, 48-Month Data)

12.4.3.10. Fasting Glucose

Figure GGGK.12.11 summarizes the median percentage change from baseline to endpoint and the percentage of patients with low- and high-outlying values for fasting glucose.

There was no statistically significant difference among the three treatment groups in the median percentage increase from baseline to endpoint for fasting glucose. However, statistically significantly more raloxifene 60-mg patients were high outliers for fasting glucose compared with placebo patients (4.1% and 2.9%, respectively, p=0.036).
Additionally, at endpoint, statistically significantly more raloxifene 120-mg patients were high delta (p=0.015), but not extreme-high delta outliers for fasting glucose compared with the placebo group (3.4% for raloxifene 120 mg, 2.3% for placebo). Statistically significantly more placebo-treated patients were in the extreme-low delta category at endpoint compared with the raloxifene 120-mg group (p=0.029).

To more fully characterize these changes in fasting glucose, additional analyses were performed to evaluate differences among the three treatment groups at baseline, at endpoint, and in change and percentage change in fasting glucose from baseline to endpoint. These analyses are presented in Table GGGK.12.30. Imbalances in baseline fasting glucose were found among the three treatment groups, with a statistically significantly higher percentage of patients in the raloxifene 60-mg group (2.3%) having a baseline fasting glucose level above 140 mg/dL compared with the placebo group (1.4%) (p=0.012). After adjusting for this baseline imbalance in fasting glucose (>140 mg/dL), there were no statistically significant differences in endpoint fasting glucose for the high outlier and high-extreme outlier, cutoffs between either dose of raloxifene and placebo.

After controlling for the baseline imbalance in fasting glucose, there remained a statistically significant difference in the percentage of high-delta outliers between the raloxifene 120-mg group and the placebo group (raloxifene 120-mg 3.2%, placebo 2.1%, p=0.024). However, there was no difference between the raloxifene 60-mg group and the placebo group in high-delta outliers and no difference between dose and placebo in high-extreme delta outliers. A subsequent analysis looked at the percentage of patients whose fasting glucose increased by >20%, >40%, and >60% from baseline to endpoint.
Compared with the placebo group, there were no statistically significant differences between either raloxifene group for the patients with >20% or >60% increases in fasting glucose. However, there remained a statistically significant difference in the >40% increase in the raloxifene 120-mg group compared with the placebo group (p=0.022).

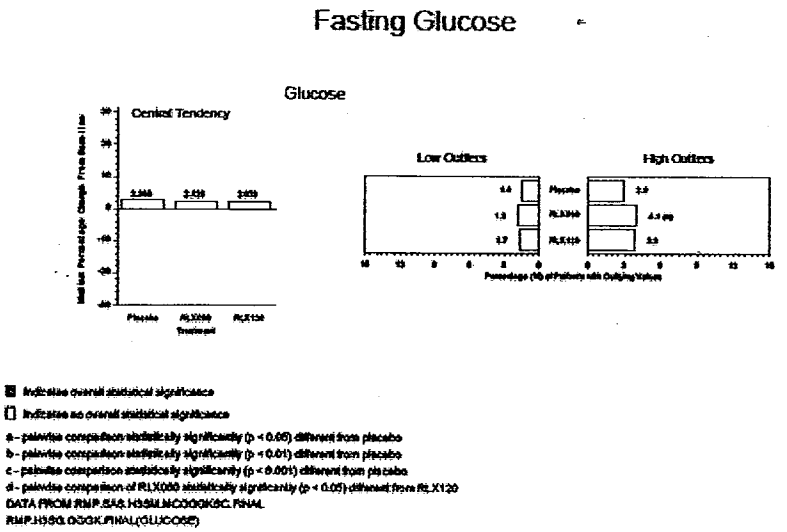


Figure GGGK.12.11. Fasting Glucose (All Randomly Assigned Patients, 48-Month Data)

Table GGGK.12.30. Summary of Further Fasting Glucose Analyses (All Randomly Assigned Patients, 48-Month Data)

		Placebo (N=2576)	RLX060 (N=2557)	RLX120 (N=2572)	Pooled RLX (N=5129)	Overall p-value	Pooled p-value
Baseline Fasting Glucose >140 mg/dL (7.78 mmol/L)	**Number (%) of patients**	**36 (1.4%)**	**60 (2.3%)**	**46 (1.8%)**	**106 (2.1%)**	**0.040**	**0.039**
Outliers[c]	**Number (%) of high outliers (>7.27 mmol/L)**	**72 (2.8%)**	**98 (3.8%)**	**94 (3.7%)**	**192 (3.7%)**	**0.398**	**0.223**
	Number (%) of high extreme outliers (>11.5 mmol/L)	**10 (0.4%)**	**15 (0.6%)**	**17 (0.7%)**	**32 (0.6%)**	**0.487**	**0.595**
Patients With Baseline Fasting Glucose >7.78 mmol/L	Number of patients	N=36	N=60	N=46			
	Number (%) of high outliers (>7.27 mmol/L)	25 (69.4%)	48 (80.0%)	38 (82.6%)			
	Number (%) of high extreme outliers (>11.5 mmol/L)	4 (11.1%)	15 (25.0%)	14 (30.4%)			
Patients With Baseline Fasting Glucose ≤7.78 mmol/L	Number of patients	N=2540	N=2497	N=2526			
	Number (%) of high outliers (>7.27 mmol/L)	47 (1.9%)	50 (2.0%)	56 (2.2%)			
	Number (%) of high extreme outliers (>11.5 mmol/L)	6 (0.2%)	0 (0.0%)	3 (0.1%)			
Delta Outliers[c]	**Number (%) of high delta outliers (>1.5 mmol/L)**	55 (2.1%)	65 (2.5%)	83 (3.2%)a	148 (2.9%)	0.051	0.116
	Number (%) of high extreme delta outliers (>3.6mmol/L)	12 (0.5%)	15 (0.6%)	14 (0.5%)	29 (0.6%)	0.985	0.897
Patients With Baseline Fasting Glucose >7.78 mmol/L	Number of patients	N=36	N=60	N=46	N=106		
	Number (%) of high delta outliers (>1.5 mmol/L)	7 (19.4%)	16 (26.7%)	14 (30.4%)	30 (28.3%)		
	Number (%) of high extreme delta outliers (>3.6 mmol/L)	3 (8.3%)	10 (16.7%)	4 (8.7%)	14 (13.2%)		
Patients With Baseline Fasting Glucose ≤7.78 mmol/L	Number of patients	N=2540	N=2497	N=2526	N=5023		
	Number (%) of high outliers (>1.5 mmol/L)	48 (1.9%)	49 (2.0%)	69 (2.7%)	118 (2.3%)		
	Number (%) of high extreme outliers (>3.6 mmol/L)	9 (0.4%)	5 (0.2%)	10 (0.4%)	15 (0.3%)		
Percentage Change[c]	**Number (%) with >20% increase**	182 (7.1%)	155 (6.1%)	196 (7.6%)b	351 (6.8%)	0.058	0.590
	Number (%) with >40% increase	27 (1.0%)	35 (1.4%)	47 (1.8%)a	82 (1.6%)	0.066	0.083
	Number (%) with >60% increase	13 (0.5%)	14 (0.5%)	15 (0.6%)	29 (0.6%)	0.935	0.925
Patients With Baseline Fasting Glucose >7.78 mmol/L	Number of patients	N=36	N=60	N=46	N=106		
	Number (%) with >20% increase	6 (16.7%)	15 (25.0%)	11 (23.9%)	26 (24.5%)		
	Number (%) with >40% increase	2 (5.6%)	9 (15.0%)	4 (8.7%)	13 (12.3%)		
	Number (%) with >60% increase	2 (5.6%)	6 (10.0%)	2 (4.3%)	8 (7.5%)		
Patients With Baseline Fasting Glucose ≤7.78 mmol/L	Number of patients	N=2540	N=2497	N=2526	N=5023		
	Number (%) with >20% increase	176(6.9%)	140(5.6%)	185(7.3%)	325(6.5%)		
	Number (%) with >40% increase	25(1.0%)	26(1.0%)	43(1.7%)	69(1.4%)		
	Number (%) with >60% increase	11(0.4%)	8(0.3%)	13(0.5%)	21(0.4%)		

[a] Significantly different ($p<0.05$) from placebo.
[b] Significantly different ($p<0.05$) from RLX060.
[c] Analyses are based on Cochran-Mantel-Haenszel statistics stratified by baseline fasting glucose (>7.78 mmol/L).
Abbreviations: RLX = raloxifene; RLX060 = raloxifene 60 mg/day; RLX120 = raloxifene 120 mg/day; N = number of randomly assigned patients.

12.4.3.11. Urinalysis

12.4.3.11.1. Urinalysis Microscopic

With GGGK Protocol Amendment (c), approved 11 January 1996, urinalysis with microscopic exam was required at the12-month, 24-month, 36-month, and 48-month visit. Thus, not all patients had a baseline urinalysis with microscopic examination. At endpoint, treatment-related differences were observed for urinary RBCs, yeast, and bacteria.

- The increase in **urinary RBCs** was statistically significantly greater in the placebo group compared with both raloxifene groups ($p<0.001$) (Table GGGK.14.25).
    - In the GGGK clinical trial database, statistically significantly fewer raloxifene-treated patients compared with placebo-treated patients reported **hematuria** (70 [2.7%] patients in the placebo group, 50 [2.0%] patients in the raloxifene 60-mg group and 43 [1.7%] patients in the raloxifene 120-mg group; $p=0.026$) (Table GGGK.14.2).
- Conversely, the increase in **yeast** was statistically significantly greater in the raloxifene groups compared with the placebo group ($p<0.001$). The increase in bacteria was statistically significantly greater in the raloxifene 60-mg group compared with both the placebo group and the raloxifene 120-mg group ($p=0.002$, $p=0.034$, respectively).
    - In the GGGK clinical trial database, there were no statistically significant differences in the reporting of urinary tract infections among the three treatment groups (267 [10.4%] patients in the placebo group, 264 [10.3%] patients in the raloxifene 60-mg group, and 245 [9.5%] patients in the raloxifene 120-mg group). No other statistically significant treatment-related differences were observed for any other microscopic urinalysis (Table GGGK.14.25 in Section 14.3.5).

12.4.3.11.2. Urinalysis Chemistry

Some patients in the placebo, the raloxifene 60-mg, and the raloxifene 120-mg groups had proteinuria (12.7%, 10.8%, and 11.6%, respectively) and/or occult blood (25.0%, 21.4%, and 21.5%, respectively).

- The increase in **proteinuria** was significantly greater in the placebo group compared with the raloxifene 60-mg group ($p=0.036$) (Table GGGK.14.24 in Section 14.3.5).
- The increase in **occult blood** was significantly greater in the placebo group compared with both raloxifene groups ($p=0.003$). No significant treatment-related differences in any of the other urine chemistry analytes were found.

12.4.12. Individual Clinically Significant Abnormalities

In general, there were few large outliers or excursions from baseline to 12-month, 24-month, 36-month, and 48-month endpoints for any of the safety laboratory tests.
Clinically significant laboratory abnormalities that resulted in a serious adverse event are discussed in the following section. These patients were identified from the scatter-plot diagrams of baseline versus endpoint for each clinical laboratory analyte based upon the reference ranges

from the GGGK cohort (Table GGGK.14.26) located in Figure GGGK.14.1 in (Section 14.3.5). Section 14.3.4 also provides a by-patient listing of all abnormal laboratory values.

12.4.12.1. Serum Chemistry

Patient 064-4899 (raloxifene 120 mg) experienced a 2.2-fold increase from baseline to 16.8 mmol/L in **blood urea nitrogen** at the 24-month visit. Her **serum creatinine** at that visit was elevated at 150 µ mol/L, consistent with baseline. The patient had started treatment with furosemide 1-month prior for shortness of breath. She had also been hospitalized twice in the previous 3 months for angina followed by granulomatous interstitial pneumonitis. Blood sampling at the 36-month visit and the 48-month visit indicated an approximate return to baseline in blood urea nitrogen. *A relationship with raloxifene can be reasonably excluded in this case.*

Patient 742-3408 (placebo) experienced increases in **GGT** (246 U/L), **blood urea nitrogen** (14.9 mmol/L), and **serum creatinine** (132 µmol/L) at the 12-month visit. The patient was diagnosed with **nephritis** and began treatment with prednisolone at that time.
Notably, at the patient's baseline visit, an elevated GGT, hypoalbuminemia, and hematuria were present. Blood sampling at the 24-month, 36-month, and 48-month visits continued to indicate laboratory elevations in GGT (254 U/L, 265 U/L, and 292 U/L, respectively), blood urea nitrogen (21.8 mmol/L, 13.7 mmol/L, and 12.2 mmol/L, respectively), and serum creatinine (154 µ mol/L, 130 µ mol/L, 118 µ mol/L, respectively).

Patient 966-1970 (raloxifene 60 mg) experienced a 2.7-fold increase from baseline in **blood urea nitrogen** to 17.3 mmol/L at the 24-month visit. **Serum creatinine** concentration remained normal. The patient reported tiredness, nausea, headache, and two syncopal episodes approximately 2 weeks prior to the blood sampling. No additional testing or follow-up of the increased analyte was performed. At the 36-month visit and the 48-month visit, the blood urea nitrogen concentration was within normal limits. *A relationship with raloxifene can be reasonably excluded in this case.*

Patient 603-6512 (raloxifene 120 mg) experienced a 2.4-fold increase from baseline in **blood urea nitrogen** to 12.8 mmol/L and a 2.3-fold increase from baseline in **creatinine** to 244 µmol/L at the 36-month visit. *Four months prior to this visit, adverse events of poor peripheral perfusion and abnormal renal function were reported.* The patient experienced a 5.2–fold increase from baseline in blood urea nitrogen to 27.8 mmol/L and a 3.6–fold increase from baseline in creatinine to 375 µmol/L at the 42-month visit. The patient discontinued from the study at this visit due to microscopic polyangeitis with secondary acute renal failure. *A relationship with raloxifene can be reasonably excluded in this case.*

Patient 069-7285 (raloxifene 120 mg) experienced a 1.5-fold increase from baseline in **creatinine** to 265 µmol/L at the 30-month visit. No follow-up laboratory results were reported. The patient reported *baseline renal insufficiency* as evidenced by a baseline creatinine of 177 µ mol/L. The patient had a history of *diabetes and hypertension* and experienced *unstable angina*

during the course of the study. The patient discontinued from the study at the 30-month visit due to chest pain and her multiple medical problems.
A relationship with raloxifene can be reasonably excluded in this case.

Patient 084-5907 (raloxifene 60 mg) experienced a 2.5-fold increase from baseline in **fasting glucose** to 19.6 mmol/L at the 24-month visit. A repeat blood sampling drawn 1 week later again indicated an elevated glucose at 14.9 mmol/L. The patient's **baseline glucose** was slightly elevated, but she indicated she was not fasting at the time of the blood sample. At the 24-month visit, the patient indicated she had been drinking alcohol in the afternoon due to boredom. **Centripetal obesity** (body mass index [BMI] = 27.4 kg/m2) was noted at baseline. One month following the 24-month visit, a diagnosis of **type II diabetes mellitus** was made and glipizide therapy was initiated. A normal glucose was reported at the 36-month and 48-month visit. Although the patient had a baseline glucose elevation and associated risk factors for hyperglycemia, *a causal relationship with raloxifene cannot be excluded.*

Patient 244-2036 (raloxifene 60 mg) experienced a 2.1-fold increase from baseline in **fasting glucose** to 18.5 mmol/L at her early discontinuation visit on 19 August 1996,
1 year into the study. The patient had discontinued study drug on 13 September 1995 after experiencing a myocardial infarction. She discontinued from the study due to immobilization caused by her cardiac problems. The patient's baseline fasting glucose was moderately elevated at 9.0 mmol/L. Taking into consideration the patient's baseline glucose elevation and her discontinuation of study drug 11 months prior to the 2.1-fold increase, *a relationship with raloxifene can be reasonably excluded in this case.*

Patient 291-5358 (placebo) experienced a 2.9-fold increase from baseline in **fasting glucose** to 20.2 mmol/L at the 24-month visit. The patient was hospitalized in [redacted] due to polyuria and thirst and was diagnosed with **diabetes mellitus**. The patient discontinued early from the study due to refusal to undergo certain study procedures. b(6)

Patient 607-6709 (raloxifene 120 mg) experienced an approximate 6-fold increase from baseline in **fasting glucose** to 26.2 mmol/L at the 12-month visit. The patient has a known **history of diabetes mellitus** since 1967 requiring treatment with insulin. Blood sampling at the 24-, 36-, and 48-month visits indicated fasting glusoses of 12.8 mmol/L, 6.8 mmol/L, and 9.6 mmol/L, respectively. Despite the patient's preexisting diabetes mellitus, *a causal relationship with raloxifene and worsening of the patient's glycemic control cannot be excluded.*

Patient 993-6384 (placebo) experienced a 2.2-fold increase from baseline in **fasting glucose** to 17.2 mmol/L at the 12-month visit. Repeat blood sampling obtained 2 weeks later again revealed an elevated glucose (19.7 mmol/L). The patient was diagnosed with diabetes mellitus and started therapy with glipizide and metformin. Blood glucose results at the 24-, 36-, and 48-month visits revealed improved glycemic control.

Patient 744-4720 (raloxifene 120 mg) experienced a 3.0-fold increase from baseline in **fasting glucose** to 26.8 mmol/L at the 36-month visit. The patient has a history of **diabetes mellitus** since 1994 and has required treatment with insulin since that time. One month following the 36-

month visit, the patient was diagnosed with a pituitary adenoma resulting in Cushing's syndrome. The patient discontinued from the study approximately 3 months following the 36-month visit. At the early discontinuation procedures, the fasting glucose was only slightly elevated at 7.6 mmol/L. Although the patient had baseline diabetes mellitus and a pituitary adenoma causing possible glucose intolerance, *a causal relationship with raloxifene cannot be excluded.*

Patient 056-1977 (raloxifene 120 mg) experienced an increased baseline **CPK** value of 4930 U/L. The creatine kinase myocardial band (CK-MB) relative index at that time was <0.1 ngL/UmL. Repeat blood sampling drawn 6 days later indicated normal CPK results. The patient was subsequently randomly assigned to study drug, but discontinued after 14 doses due to development of **a total body rash**.

12.4.12.2. Serum Liver-Related Chemistry

Patient 058-5435 (raloxifene 120) experienced increases from baseline in the liver related analytes **AST** (25-fold to 503 U/L), **ALT** (59.8-fold to 777 U/L), **alkaline phosphatase** (3.5-fold to 263 U/L), **GGT** (47.3-fold to 710 U/L), and **total bilirubin** (3.8-fold to 27 µmol/L) at the 48-month visit. Liver function tests were repeated by the patient's primary medical doctor 2 days following the 48-month visit and were reported to be lower; however, no laboratory values were provided. An abdominal ultrasound was performed and confirmed cholelithiasis. The patient was scheduled for a cholecystectomy. *A relationship with raloxifene cannot be reasonably excluded in this case.*

Patient 282-640 (raloxifene 60 mg) experienced increases from baseline in **AST** (30-fold to 600 U/L) and **ALT** (35.2-fold to 1,058 U/L) at the 48-month visit. The patient complained of epigastric pain and has been referred to a gastroenterologist for evaluation.
In the absence of an etiology, a relationship cannot be excluded in this case.

Patient 071-0349 (raloxifene 120 mg) experienced an elevated **GGT** at the baseline visit (112.0 U/L and 695.0 U/L), at the 3-month visit (554 U/L and 411.0 U/L), at the 6-month visit (152 U/L and 172 U/L), at the 12-month visit (858.0 U/L and 270 U/L), and at the 24-month visit (98.0 U/L). The GGT was within normal range at the 36-month visit (66.0 U/L); however, it was again elevated at the 48-month visit (173 U/L).
Approximately 9 months after commencement of study drug, the patient was diagnosed with cholelithiasis and biliary duct stricture and underwent a cholecystectomy with biliary duct stent placement. Notably, the patient had a history of cholelithiasis in 1961.
A relationship with raloxifene can be reasonably excluded in this case.

Patient 291-5380 (placebo) experienced a 6.1-fold increase from baseline in **GGT** to 906 U/L at the 36-month visit. Baseline elevations in AST, ALT, and GGT were observed with subsequent increases in these analytes noted at each annual visit. A liver ultrasound performed following the 12-month visit demonstrated a fatty liver. The patient reported drinking less than three alcoholic beverages per week. Review of the patient's medication list did not note any possible offending agents to account for the liver function test increases. No follow-up laboratory results have been

reported. The patient discontinued from the study following the 36-month visit due to the liver function test abnormalities.

Patient 405-8093 (placebo) experienced a 20.6-fold increase from baseline in **GGT** to 370 U/L and a 4.6-fold increase in ALT to 179 U/L at the 12-month visit. The patient was diagnosed with cholelithiasis with choledocholithiasis requiring cholecystectomy. At the 12-month visit, 2 months following the cholecystectomy, the patient's liver function tests were elevated. Four months later, the patient was diagnosed with pancreatitis and underwent bougienage of the common bile duct due to stricture. Subsequent blood sampling obtained at 6-month intervals revealed normal liver-related analytes.

Patient 803-6227 (raloxifene 60 mg) experienced a 48-fold increase from baseline in **GGT** to 2455 U/L at the 24-month visit. Elevations in **AST** (150 U/L), **ALT** (244 U/L), and **alkaline phosphatase** (598 U/L) were also noted. Repeat blood sampling obtained 2 days later indicated GGT 2297 U/L, AST 103 U/L, ALT 213 U/L, and alkaline phosphatase 586 U/L. Study drug was discontinued at that time. An ultrasound showed a gallstone obstructing the common bile duct. The patient was hospitalized for endoscopic retrograde cholangiopancreatography and required eventual lithotripsy.
Laboratory examination 6 months later at the 30-month visit revealed normalization of all liver-related analytes. Study drug was restarted at that time. Liver-related analytes remained normal at the 36- and 48-month visit. *A relationship with raloxifene and the cholelithiasis cannot be reasonably excluded in this case.*

Patient 058-5451 (raloxifene 60 mg) experienced a 3.6-fold increase from baseline in **alkaline phosphatase** to 344 U/L and a 2.7-fold increase in **GGT** to 302 U/L at the 24-month visit. An abdominal ultrasound revealed cholelithiasis and multiple solid lesions within the liver suspicious for metastatic neoplasia. Colon carcinoma with liver metastases was diagnosed by biopsy. The patient died on [redacted] *A relationship with raloxifene can be reasonably excluded in this case.* b(6)

Patient 243-0086 (raloxifene 120 mg) experienced a 4.2-fold increase from baseline in **alkaline phosphatase** to 342 U/L and a 7.3-fold increase in **GGT** to 312 U/L at the 12-month visit. Epigastric echography revealed a solitary liver lesion. Liver biopsy showed chronic hepatitis and primary liver cell carcinoma. The patient died on [redacted] *A relationship with raloxifene can be reasonably excluded in this case.* b(6)

Patient 604-7269 (raloxifene 60 mg) experienced increases in **total bilirubin** at baseline (43 μ mol/L) and at each subsequent annual visit (51 μ mol/L, 32 μ mol/L, 34 μ mol/L, and 40 μ mol/L, respectively). Other liver-related analytes were normal or only mildly elevated with the exception of the 48-month visit **AST** of 84.0 U/L, a 1.4-fold increase from baseline. The patient reported hepatitis since 1982 and has received treatment with spironolactone since 1992. Approximately 3 years after commencement of study drug, an abdominal ultrasound revealed a small liver nodule as well as cholelithiasis. A needle biopsy of the liver was performed with results compatible with, but not conclusive for, carcinoma of the liver. *A relationship with raloxifene can be reasonably excluded in this case.*

Patient 806-7404 (raloxifene 120 mg) experienced a decrease in **albumin** from 42 g/L at baseline to 26 g/L at the 12-month visit. The patient was diagnosed with a pulmonary aspergillosis infection approximately 4 months after commencement of study drug. A weight loss of 6 kg was also noted. The study site felt that the laboratory abnormalities were secondary to the patient's severe infection. The patient discontinued early from the study due to the *Aspergillus* infection. *A causal relationship with raloxifene can be reasonably excluded in this case.*

12.4.12.3. Hematology (RBC and Related)

Patient 085-6241 (placebo) experienced decreases in **hemoglobin** from 137 g/L at baseline to 75 g/L and **hematocrit** from 0.38 at baseline to 0.27 at the 36-month visit.
Follow-up by the patient's primary physician revealed an antral mass and a diagnosis of moderately differentiated invasive gastric adenocarcinoma was confirmed. One month after the 36-month visit, the patient underwent surgical resection followed by radiation therapy and chemotherapy. Blood sample at the 48-month visit revealed hemoglobin of 106 g/L and hematocrit of 0.32.

Patient 055-0715 (raloxifene 120 mg) experienced a 1.36-fold increase from baseline in **erythrocytes** to 8.2 TI/L at the 48-month visit. Erythrocyte counts were also elevated at the baseline visit (6.0 TI/L), at the 12-month visit (6.70 TI/L), and at the 24-month visit (6.30 TI/L). Five months after commencement of study drug, the patient experienced syncope, atrial fibrillation, and hypotension thought by the cardiologist to be secondary to exhaustion and dehydration. In addition, 1 year following the commencement of study drug, the patient was diagnosed with polycythemia vera.

Patient 071-0163 (placebo) experienced a decrease from baseline in **hematocrit** to 0.26 at the 24-month visit. A decrease to 0.33 was also noted at the 12-month visit. Follow-up of the anemia by the patient's personal physician demonstrated adenocarcinoma of the ascending colon. Chemotherapy was initiated the following month. No follow-up laboratory results have been reported. The patient discontinued from the study at the 36-month visit due to her husband's poor health and lack of transportation.

Patient 804-7565 (raloxifene 120 mg) experienced a decrease in **hematocrit** from 0.36 at baseline to 0.26 and a decrease in hemoglobin from 119 g/L to 81 g/L 3 months after commencement of study drug. Erythrocyte count and MCHC were also decreased, although an increase in MCV was observed. No additional laboratory testing or follow-up is available. The patient discontinued from the study at that time due to hot flushes. The patient had a history of peptic ulcer disease since 1980 and was receiving treatment with nizatidine. In the absence of a clear etiology, a causal relationship with raloxifene cannot be excluded in this case.

Patient 964-1588 (placebo) experienced a decrease in **hematocrit** from 0.36 at baseline to 0.163 at the 12-month visit. Hemoglobin and RBC and WBC counts were also low. The patient had required a blood transfusion the previous month. Bone marrow biopsy indicated a

myelodysplastic syndrome. The patient discontinued from the study due to the long-term necessary blood transfusions for this disorder.

12.4.12.4. Hematology (WBC and Related)

Patient 243-0151 (raloxifene 60 mg) experienced a 1.4-fold increase from baseline to 12.7 GI/L in **white blood cells** at the 12-month visit. Notably, at the baseline visit, an elevated lymphocyte count was present (5.6 GI/L). Progressive elevations in white blood cells and lymphocytes were noted at each subsequent visit. Blood sampling at the 36-month visit indicated the highest laboratory values at 16.2 GI/L and 10.81 GI/L, respectively. The patient discontinued from the study at the 48-month visit due to **chronic lymphocytic leukemia**. *A relationship to study medication can be reasonably excluded.*

Patient 753-0247 (placebo) experienced a 14.3-fold increase from baseline to 67.2 GI/L in **white blood cells** and a 19.5-fold increase from baseline to 49.0 GI/L in segmented neutrophils at the 48-month visit. The patient was subsequently referred to a specialist and underwent additional testing. A diagnosis of **chronic myelocytic leukemia** was confirmed by bone marrow biopsy. Treatment with allopurinol and hydroxycarbamide was initiated and the patient's blood counts improved with therapy.

Patient 743-4512 (raloxifene 120 mg) experienced an elevated **platelet count** (671 GI/L) and white **blood cell count** (13.1 GI/L) at the baseline visit and the patient was referred to a hematologist. A diagnosis of **chronic myelogenic leukemia** was confirmed by bone marrow biopsy and the patient discontinued from the study approximately 5 months after commencement of study drug. *A relationship with raloxifene can be reasonably excluded in this case.*

Patient 851-9234 (raloxifene 120 mg) experienced a 2.3-fold increase from baseline to 13.68 GI/L in segmented neutrophils, and a 1.8-fold increase to 16.0 GI/L in **white blood cells** at the 3-month visit. At baseline, the patient presented with normocytic normochromic anemia, and a hematology consultation was obtained. A diagnosis of non-secreting **multiple myeloma** was confirmed by bone marrow aspiration and the patient discontinued from the study approximately 43 days after commencement of study drug therapy. *A relationship with raloxifene can be reasonably excluded in this case.*

Patient 993-6392 (raloxifene 60 mg) experienced increases in white blood cells to 14.6 GI/L and neutrophils to 10.4 GI/L at the 12-month visit. Approximately 4 months prior, the patient had been diagnosed with polymyalgia rheumatica and temporal arteritis.
High-dose prednisone was started at that time. The patient discontinued study drug 2 months after the initiation of high-dose steroids and discontinued from the study 3 months later due to the investigator's concerns about diagnoses and steroid treatments.
At early discontinuation visit procedures, elevations in white blood cells to 17.2 GI/L and neutrophils to 16.0 GI/L were noted. *A relationship with raloxifene can be reasonably excluded in this case.*

Patient 742-4134 (placebo) experienced elevated platelet counts at baseline (919 GI/L), at the 3-month visit (880 GI/L), at the 12-month visit (1067 GI/L), and at her 18-month early discontinuation visit (1023 GI/L). The thrombocytosis was present since 1977. Since a myeloproliferative disorder could not be ruled out, the investigator recommended the patient's discontinuation from the study.

12.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1. Vital Signs

No statistically significant differences were observed among the three treatment groups for **systolic and diastolic blood pressure** and **height** from baseline to endpoint. There was a statistically significant, but not clinically relevant, difference between raloxifene-treated and placebo-treated patients in change from baseline in **sitting heart rate**.

There was minimal **weight gain** associated with raloxifene, predominately seen in the lowest tertile of weight at baseline. An overall statistically significant difference was observed for the change from baseline to endpoint in weight ($p<0.001$, ANOVA with unranked data) (Table GGGK.12.31). There was a 0.20-kg increase in mean weight in the raloxifene 60-mg group which was significantly different from the 0.36-kg decrease in mean weight observed in the placebo group ($p<0.001$). This within-group increase from baseline to endpoint in mean weight observed in the raloxifene 60-mg group was statistically significant ($p<0.018$). There was a 0.15-kg increase in mean weight observed in the raloxifene 120-mg group which was significantly different from the decrease observed in the placebo group ($p<0.001$). This within-group increase from baseline to endpoint in mean weight observed in the raloxifene 120-mg group was not statistically significant ($p=0.059$). There was no statistically significant difference between the raloxifene 60-mg and the raloxifene 120-mg groups with respect to the change in weight.

An overall statistically significant difference was observed in change from baseline to endpoint for sitting heart rate ($p<0.001$, ANOVA with unranked data) (Table GGGK.12.31). The change from baseline to endpoint was -0.652 bpm for the placebo group, 0.601 bpm for the raloxifene 60-mg group, and 0.114 bpm for the raloxifene 120-mg group and was significantly greater for both the raloxifene 60-mg and the raloxifene 120-mg groups compared with the placebo group ($p<0.001$ and $p=0.009$, respectively). There was no statistically significant difference between the raloxifene 60-mg and the raloxifene 120-mg groups with respect to the change in sitting heart rate.
Sitting heart rate increased by less than one beat per minute from baseline to endpoint for both raloxifene groups. This increase in sitting heart rate observed among raloxifene treated patients was not considered clinically relevant.

Weight, heart rate, and systolic and diastolic blood pressure were measured at each regularly scheduled visit. Height was measured only at baseline, 6 months, 12 months, and annually thereafter. Since serial height measurement was not a primary outcome of this study, specific height measurement with a wall-mounted stadio-meter was not required, although recommended when available. Standardization of wall-mounted stadio-meters also was not performed throughout the study. Vital sign results are summarized in (Table GGGK.12.31).

Table GGGK.12.31. Summary of Vital Signs (Mean Change from Baseline to Endpoint, All Randomly Assigned Patients, 48-Month Data)

	Unit		Treatment Group: Placebo	RLX060	RLX120	Overall p-value*
Height	cm	Mean Baseline	158.95	158.95	159.38ad	0.017
		Mean Change	-0.589	-0.723	-0.494	0.317
		Mean Percentage Change	-0.368	-0.454	-0.309	0.214
Weight	kg	Mean Baseline	63.735	63.709	64.095	0.349
		Mean Change	-0.359	0.195c	0.147c	<0.001
		Mean Percentage Change	-0.508	0.365c	0.284c	<0.001
Systolic Blood Pressure	mm Hg	Mean Baseline	133.57	133.57	133.07	0.544
		Mean Change	1.885	1.356	1.391	0.531
		Mean Percentage Change	2.328	1.913	1.945	0.506
Diastolic Blood Pressure	mm Hg	Mean Baseline	78.642	78.194	78.211	0.208
		Mean Change	-0.616	-0.400	-0.469	0.765
		Mean Percentage Change	0.187	0.453	0.323	0.796
Heart Rate	bpm	Mean Baseline	72.643	72.146a	72.486	0.123
		Mean Change	-0.652	0.601c	0.114b	<0.001
		Mean Percentage Change	0.138	1.830c	1.225b	<0.001

* Using ANOVA with Unranked data
%qcmpres(a - pairwise comparison statistically significantly (p < 0.05) different from placebo)
%qcmpres(b - pairwise comparison statistically significantly (p < 0.01) different from placebo)
%qcmpres(c - pairwise comparison statistically significantly (p < 0.001) different from placebo)
%qcmpres(d - pairwise comparison of RLX060 statistically significantly (p < 0.05) different from R
DATA FROM RMP.SAS.H3SN.MCGGGKSC.FINAL
RMP.H3SSX4YR.SASPGM(VITLPIST) 95761

12.5.1.1. Height

There were no statistically significant differences among the three treatment groups in overall or pair-wise comparisons (using ANOVA with unranked data) for the change from baseline to endpoint in height.

12.5.1.2. Weight

An overall statistically significant difference was observed for the change from baseline to endpoint in weight ($p<0.001$, ANOVA with unranked data) (Table GGGK.12.33).
There was a 0.20-kg increase in mean weight in the raloxifene 60-mg group that was significantly different from the 0.36-kg decrease in mean weight observed in the placebo group ($p<0.001$). This within-group increase from baseline to endpoint in mean weight observed in the raloxifene 60-mg group was statistically significant ($p=0.018$). There was a 0.15-kg increase in mean weight observed in the raloxifene 120-mg group which was significantly different from the decrease observed in the placebo group ($p<0.001$).
This within-group increase from baseline to endpoint in mean weight observed in the raloxifene 120-mg group was not statistically significant ($p=0.059$). There was no statistically significant difference between the raloxifene 60-mg and the raloxifene 120-mg groups with respect to the change in weight.

Table GGGK.12.33. Weight (Change from Baseline to Endpoint, All Randomly Assigned Patients, 48-Month Data, Data)

ANALYSIS VARIABLE: CHANGE FROM BASELINE OF WEIGHT (KG)

	VISIT*	DESCRIPTIVE STATISTICS						
THERAPY	BASELINE+	Visit4	Visit5	Visit7	Visit9	Visit10	Visit11	ENDPOINT
PLACEBO								
N	2516	2516	2516	2516	2516	2516	2516	2516
MEAN	63.735	-0.183	-0.139	-0.273	-0.200	-0.091	-0.348	-0.359
STD	10.460	2.074	2.614	3.307	3.694	3.891	4.506	4.609
T-TEST		<0.0001	0.0076	<0.0001	0.0066	0.2409	0.0001	<0.0001
RLX060								
N	2502	2500	2502	2502	2502	2502	2502	2502
MEAN	63.709	0.088	0.185	0.131	0.236	0.350	0.216	0.195
STD	10.398	2.214	2.681	3.321	3.797	3.926	4.031	4.100
T-TEST		0.0480	0.0006	0.0479	0.0019	<0.0001	0.0075	0.0172
RLX120								
N	2519	2519	2519	2519	2519	2519	2519	2519
MEAN	64.095	-0.009	0.109	0.137	0.273	0.364	0.148	0.147
STD	10.707	2.080	2.563	3.187	3.566	3.689	3.865	3.894
T-TEST		0.8285	0.0326	0.0305	0.0001	<0.0001	0.0554	0.0589

+ BASELINE STATISTICS CALCULATED ON ACTUAL ANALYSIS VARIABLE
* STATISTICS CALCULATED ON THOSE PATIENTS WITH POST BASELINE MEASUREMENTS

RMP.H3S8K4YR.SASPGM(VITLMTB5) (RMP.H3SO.GGGK.FINAL(VITLMTB2)) X7164 17:04 11DEC00

ANALYSIS VARIABLE: CHANGE FROM BASELINE OF WEIGHT (KG)

	VISIT*	GENERAL LINEAR MODEL						
GLM	BASELINE+	Visit4	Visit5	Visit7	Visit9	Visit10	Visit11	ENDPOINT
TYPE III SS (P-VALUES)								
THERAPY	0.3490	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
GROCODE	<0.0001	<0.0001	<0.0001	<0.0001	0.0083	<0.0001	0.0001	<0.0001
CONTRAST (P-VALUES)								
PLACEBO-RLX060	0.9903	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
PLACEBO-RLX120	0.2109	0.0034	0.0008	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
RLX060-RLX120	0.2072	0.1133	0.2996	0.9427	0.7089	0.8817	0.5507	0.6708

+ BASELINE STATISTICS CALCULATED ON ACTUAL ANALYSIS VARIABLE
* STATISTICS CALCULATED ON THOSE PATIENTS WITH POST BASELINE MEASUREMENTS
GLM OUTPUT FROM MODEL:
CHANGE(WEIGHTKG) = THERAPY GROCODE

RMP.H3S8K4YR.SASPGM(VITLMTB5) (RMP.H3SO.GGGK.FINAL(VITLMTB2)) X7164 17:04 11DEC00

For change in weight, a subgroup analysis was performed to assess if a **treatment-by-baseline weight interaction effect** was present (Table GGGK.12.34).

The baseline weight variable was categorized into upper (>67 kg), middle (>59 and ≤ 67 kg), and lower (≤ 59 kg) tertiles. The treatment-by-baseline weight tertile interaction effect was not significant. However, there was a statistically significant within-group increase in weight from baseline to endpoint for both the raloxifene 60-mg and the raloxifene 120-mg groups (p=0.001 and p=0.011, respectively) in the lower weight tertile and in the raloxifene 120-mg group (p=0.017) for the middle weight tertile. There were no significant within-group changes for the raloxifene 60-mg group in the middle weight

tertile or for either raloxifene group in the upper weight tertile.
This analysis demonstrated that the raloxifene patients in the lowest weight tertile had the greatest mean increase in weight. The magnitude of this weight gain was relatively small considering the 48-month duration over which these patients were followed. The higher weight tertile demonstrated an insignificant increase in weight with raloxifene, which was not considered to be clinically relevant.

Table GGGK.12.34. Analysis of Mean Change in Weight by Baseline Weight Tertiles (All Randomly Assigned Patients, 48-Month Data)

			LOWER 33%			MIDDLE 33%			UPPER 33%		
Subgroup Variables	Subgroup Interaction Effect	Treatment	Mean change	Within Group p-value	Between Group P-Value *	Mean change	Within Group p-value	Between Group P-Value *	Mean change	Within Group p-value	Between Group P-Value *
Patients Weight	0.560	PLACEBO	-.037	0.746	-	-.297	0.059	-	-.750	0.000	-
		RLX060	0.434	0.001	0.006	0.110	0.409	0.039	0.030	0.849	0.002
		RLX120	0.298	0.011	0.048	0.306	0.017	0.004	-.142	0.350	0.015

* Compared to Placebo Group
DATA FROM RMP.SAS.H3SM.MCGGGK8C.FINAL
RMP.H3SSK4YR.SASPGM(MEIGHTTB) 95761

12.5.1.3. Blood Pressure

There were no statistically significant differences among the three treatment groups in overall or pair-wise comparisons (using ANOVA with unranked data) for the change from baseline to endpoint in systolic or diastolic blood pressure measurements (Table GGGK.12.35 and Table GGGK.12.36, respectively).

Table GGGK.12.35. Systolic Blood Pressure Change From Baseline to Endpoint (All Randomly Assigned Patients, 48-Month Data, Unranked Data)

ANALYSIS VARIABLE: CHANGE FROM BASELINE OF SYSTOLIC BLOOD PRESSURE

	VISIT*	DESCRIPTIVE STATISTICS						
THERAPY	BASELINE+	Visit4	Visit5	Visit7	Visit9	Visit10	Visit11	ENDPOINT
PLACEBO								
N	2522	2521	2522	2522	2522	2522	2522	2522
MEAN	133.571	-0.322	-0.195	1.274	1.672	1.783	2.036	1.885
STD	19.259	16.438	16.756	18.128	18.299	18.338	18.738	18.681
T-TEST		0.3253	0.5588	0.0004	<0.0001	<0.0001	<0.0001	<0.0001
RLX060								
N	2502	2501	2502	2502	2502	2502	2502	2502
MEAN	133.571	-0.507	-0.488	0.361	0.890	1.430	1.315	1.356
STD	18.919	16.766	17.049	17.522	17.971	18.400	18.412	18.308
T-TEST		0.1306	0.1527	0.3024	0.0133	0.0001	0.0004	0.0002
RLX120								
N	2519	2519	2519	2519	2519	2519	2519	2519
MEAN	133.066	-0.507	0.006	1.269	1.168	1.461	1.713	1.391
STD	18.917	16.669	17.224	18.269	18.492	18.499	18.703	18.714
T-TEST		0.1273	0.9871	0.0005	0.0015	<0.0001	<0.0001	0.0002

+ BASELINE STATISTICS CALCULATED ON ACTUAL ANALYSIS VARIABLE
* STATISTICS CALCULATED ON THOSE PATIENTS WITH POST BASELINE MEASUREMENTS

RMP.H3SSK4YR.SASPGM(VITLMTB3) (RMP.H3SO.GGGK.FINAL(VITLMTB3)) X7164 17:04 11DEC00

ANALYSIS VARIABLE: CHANGE FROM BASELINE OF SYSTOLIC BLOOD PRESSURE

	VISIT*	GENERAL LINEAR MODEL						
GLM	BASELINE+	Visit4	Visit5	Visit7	Visit9	Visit10	Visit11	ENDPOINT
TYPE III SS (P-VALUES)								
THERAPY	0.5443	0.8875	0.6072	0.1150	0.2937	0.7457	0.3917	0.5310
GEOCODE	<0.0001	0.0343	0.0012	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CONTRAST (P-VALUES)								
PLACEBO-RLX060	0.9608	0.6814	0.5385	0.0717	0.1242	0.4851	0.1718	0.3147
PLACEBO-RLX120	0.3522	0.6640	0.7073	0.9973	0.3063	0.5344	0.5432	0.3476
RLX060-RLX120	0.3282	0.9815	0.3224	0.0713	0.6059	0.9379	0.4477	0.9459

+ BASELINE STATISTICS CALCULATED ON ACTUAL ANALYSIS VARIABLE
* STATISTICS CALCULATED ON THOSE PATIENTS WITH POST BASELINE MEASUREMENTS
GLM OUTPUT FROM MODEL:
CHANGE(SYSBP) = THERAPY GEOCODE

RMP.H3SSK4YR.SASPGM(VITLMTB3) (RMP.H3SO.GGGK.FINAL(VITLMTB3)) X7164 17:04 11DEC00

Table GGGK.12.36. Diastolic Blood Pressure Change From Baseline to Endpoint (All Randomly Assigned Patients, 48-Month Data, Unranked Data)

ANALYSIS VARIABLE: CHANGE FROM BASELINE OF DIASTOLIC BLOOD PRESSURE

VISIT* — DESCRIPTIVE STATISTICS

THERAPY	BASELINE+	Visit4	Visit5	Visit7	Visit9	Visit10	Visit11	ENDPOINT
PLACEBO								
N	2522	2521	2522	2522	2522	2522	2522	2522
MEAN	78.642	-0.397	-0.257	-0.690	-0.492	-0.489	-0.470	-0.616
STD	10.431	9.511	9.650	10.089	10.124	10.378	10.509	10.530
T-TEST		0.0360	0.1820	0.0006	0.0147	0.0180	0.0247	0.0033
RLX060								
N	2502	2501	2502	2502	2502	2502	2502	2502
MEAN	78.194	-0.155	-0.056	-0.226	-0.067	-0.093	-0.347	-0.400
STD	10.090	9.542	9.833	10.075	10.512	10.592	10.682	10.635
T-TEST		0.4163	0.7775	0.2623	0.7508	0.6615	0.1048	0.0602
RLX120								
N	2519	2519	2519	2519	2519	2519	2519	2519
MEAN	78.211	-0.250	0.099	-0.231	-0.054	-0.108	-0.294	-0.469
STD	9.941	9.317	9.774	9.995	10.468	10.513	10.626	10.591
T-TEST		0.1780	0.6118	0.2469	0.7943	0.6076	0.1648	0.0263

+ BASELINE STATISTICS CALCULATED ON ACTUAL ANALYSIS VARIABLE
* STATISTICS CALCULATED ON THOSE PATIENTS WITH POST BASELINE MEASUREMENTS

RMP.H3SSK4YR.SASPGM(VITLMTB3) (RMP.H3SO.GGGK.FINAL(VITLMTB4)) X7164 17:04 11DEC00

ANALYSIS VARIABLE: CHANGE FROM BASELINE OF DIASTOLIC BLOOD PRESSURE

VISIT* — GENERAL LINEAR MODEL

GLM	BASELINE+	Visit4	Visit5	Visit7	Visit9	Visit10	Visit11	ENDPOINT
TYPE III SS (P-VALUES)								
THERAPY	0.2084	0.6497	0.4457	0.1782	0.2614	0.3330	0.8505	0.7652
GEOCODE	<0.0001	0.0002	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CONTRAST (P-VALUES)								
PLACEBO-RLX060	0.1133	0.3548	0.4546	0.1037	0.1529	0.1880	0.6784	0.4685
PLACEBO-RLX120	0.1396	0.5958	0.2062	0.1123	0.1595	0.2118	0.5861	0.6546
RLX060-RLX120	0.9135	0.6924	0.6071	0.9669	0.9803	0.9442	0.8974	0.7809

+ BASELINE STATISTICS CALCULATED ON ACTUAL ANALYSIS VARIABLE
* STATISTICS CALCULATED ON THOSE PATIENTS WITH POST BASELINE MEASUREMENTS
GLM OUTPUT FROM MODEL:
CHANGE(DIABP) = THERAPY GEOCODE

RMP.H3SSK4YR.SASPGM(VITLMTB3) (RMP.H3SO.GGGK.FINAL(VITLMTB4)) X7164 17:04 11DEC00

12.5.1.4. Heart Rate

An overall statistically significant difference among the three treatment groups was observed in change from baseline to endpoint for sitting heart rate ($p<0.001$, ANOVA with unranked data). The change from baseline to endpoint was 0.65 bpm for the placebo group, 0.60 bpm for the raloxifene 60-mg group, and 0.11 bpm for the raloxifene 120-mg group and was significantly greater for both the raloxifene 60-mg and the raloxifene 120-mg groups compared with the placebo group ($p<0.001$ and $p=0.009$, respectively) (Table GGGK.12.37). There was no statistically significant difference between the raloxifene 60-mg and the raloxifene 120-mg groups with respect to the change in sitting heart rate.

Table GGGK.12.37. Heart Rate (Change from Baseline to Endpoint, All Randomly Assigned Patients, 48-Month Data, Unranked Data)

ANALYSIS VARIABLE: CHANGE FROM BASELINE OF HEART RATE

	VISIT*	DESCRIPTIVE STATISTICS						
THERAPY	BASELINE+	Visit4	Visit5	Visit7	Visit9	Visit10	Visit11	ENDPOINT
PLACEBO								
N	2521	2521	2521	2521	2521	2521	2521	2521
MEAN	72.643	0.027	0.107	-0.401	-0.229	0.045	-0.647	-0.652
STD	9.330	9.657	9.992	10.237	10.303	10.248	10.593	10.574
T-TEST		0.8901	0.5905	0.0495	0.2640	0.8247	0.0022	0.0020
RLX060								
N	2501	2500	2501	2501	2501	2501	2501	2501
MEAN	72.146	0.551	0.896	0.465	0.998	1.252	0.513	0.601
STD	9.137	9.904	10.107	10.061	10.106	10.164	10.214	10.199
T-TEST		0.0055	<0.0001	0.0208	<0.0001	<0.0001	0.0120	0.0032
RLX120								
N	2516	2516	2516	2516	2516	2516	2516	2516
MEAN	72.486	0.405	0.535	0.205	0.692	1.153	0.069	0.114
STD	9.460	9.724	10.070	10.126	10.381	10.407	10.566	10.545
T-TEST		0.0370	0.0078	0.3107	0.0008	<0.0001	0.7441	0.5887

+ BASELINE STATISTICS CALCULATED ON ACTUAL ANALYSIS VARIABLE
* STATISTICS CALCULATED ON THOSE PATIENTS WITH POST BASELINE MEASUREMENTS

RMP.H3SSK4YR.SASPGM(VITLMTB5) (RMP.H3SO.GGGK.FINAL(VITLMTB5)) X7164 17:04 11DEC00

ANALYSIS VARIABLE: CHANGE FROM BASELINE OF HEART RATE

	VISIT*	GENERAL LINEAR MODEL						
GLM	BASELINE+	Visit4	Visit5	Visit7	Visit9	Visit10	Visit11	ENDPOINT
TYPE III SS (P-VALUES)								
THERAPY	0.1332	0.1388	0.0176	0.0075	<0.0001	<0.0001	0.0003	<0.0001
GEOCODE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CONTRAST (P-VALUES)								
PLACEBO-RLX060	0.0500	0.0536	0.0045	0.0022	<0.0001	<0.0001	<0.0001	<0.0001
PLACEBO-RLX120	0.5482	0.1695	0.1287	0.0351	0.0014	0.0001	0.0152	0.0092
RLX060-RLX120	0.1738	0.5771	0.1857	0.3409	0.2892	0.7451	0.1250	0.0915

+ BASELINE STATISTICS CALCULATED ON ACTUAL ANALYSIS VARIABLE
* STATISTICS CALCULATED ON THOSE PATIENTS WITH POST BASELINE MEASUREMENTS
GLM OUTPUT FROM MODEL:
CHANGE(PULSE) = THERAPY GEOCODE

RMP.H3SSK4YR.SASPGM(VITLMTB5) (RMP.H3SO.GGGK.FINAL(VITLMTB5)) X7164 17:04 11DEC00

12.6. Safety Conclusions

- Venous thromboembolism was the only serious adverse event of clinical significance associated with raloxifene.
- Raloxifene treatment was not associated with a greater risk of death, serious adverse events, >1 TESS or secondary conditions.
    - Of the TESS events, a significant, >2% incidence with raloxifene treatment was observed for flu syndrome, vasodilatation, leg cramps, peripheral edema, and uterine disorder (uterine disorder was the COSTART term used to describe endometrial fluid in the majority of cases).
- The increased reporting of diabetes mellitus among patients on raloxifene is of uncertain clinical relevance, and there is no evidence that raloxifene causes diabetes mellitus.
- A number of changes in safety laboratories were seen, but were assessed not to be of clinical significance, either because the changes were small or because the changes were known to be associated with estrogen or SERM treatment.

- Raloxifene decreased the risk of breast cancer and did not have a stimulatory effect on breast tissue as indicated by several surrogate markers of breast stimulation, including breast pain, breast enlargement, and breast engorgement. Breast engorgement was actually seen less frequently in the raloxifene patients compared with the placebo patients. Although there was an increase in female lactation with raloxifene, this could be attributed to the small number of total cases (n=13) and to the fact that a number of various types of breast discharge were assigned to the COSTART term "female lactation". A mechanism for the increased lactation is not apparent because raloxifene has no clinically significant effects on prolactin.

- The 48-month data confirmed the existing preclinical and clinical data showing that raloxifene has no stimulatory effects on the uterus. Raloxifene was not associated with any increase in the risk of any uterine or endometrial malignancy. The incidence of vaginal or uterine-related bleeding was no different from that observed in the placebo group and was rare, seen in approximately 4% of patients. At the conclusion of an assessment of postmenopausal bleeding, the finding of benign endometrial polyp was seen with higher frequency in patients on raloxifene, but this was not associated with any serious gynecological pathology (specifically endometrial hyperplasia or carcinoma).

- Raloxifene was associated with a transient and minute average increase (<0.3 mm) in endometrial thickness from baseline to endpoint, which resolved completely by 36 months in patients whose endometrial thickness was measured over time. No other significant malignant or benign changes were observed in the uterus after 48 months of raloxifene treatment. In addition, there was no adverse effect on the vulva, vagina, or the ovaries. There was an increase in benign cervical polyps observed at 36 months that continued through 48 months of treatment. Because the medical literature generally does not attach clinical significance to the finding of cervical polyps (Kurman 1994), and

because no action was mandated by the protocol for cervical polyps, no conclusions are possible regarding the presence of cervical polyps.

- Adverse event reporting and electrocardiographic data indicated no adverse effects of raloxifene on myocardial infarction/ischemia, cerebrovascular accident/ischemia, or peripheral vascular events.
- There were no clinically relevant changes in vital signs.
- Raloxifene reduced total cholesterol, LDL-C, LDL-C/HDL-C ratio, and fibrinogen, and did not affect HDL-C, or HbA1c. An analysis of triglyceride changes revealed no clinically relevant changes.
- Raloxifene treatment was associated with a significant increase in the occurrence of VTE. At the end of the study, the incidence of VTE, which was defined as deep thrombophlebitis (or DVT), RVT, and PE, was increased in the pooled raloxifene group compared with the placebo group. There was an increased incidence of deep thrombophlebitis overall and in the pooled raloxifene group compared with the placebo group, as previously reported in the 36-month clinical study report. Similarly, higher incidences of deep thrombophlebitis occurred in both the raloxifene 60-mg group and the raloxifene 120-mg group compared with the placebo group. The risk of VTE was highest in the first year and by the fourth year returned to placebo levels for the raloxifene 60-mg dose.
- There was no evidence that 48 months of treatment with raloxifene was associated with an increased risk of retinal vein occlusion.

- In conclusion, treatment with raloxifene was not associated with stimulation of the breast tissue, endometrial cancer, or clinically relevant effects on the endometrium.
- Raloxifene treatment was associated with beneficial or neutral effects on biochemical markers of cardiovascular risk and did not increase the risk of major cardiovascular events.
- There were no clinically relevant vital signs or safety laboratory changes or effects on cognition.

- Therefore, the sponsor concludes that 48 months of raloxifene treatment is well tolerated in postmenopausal women with osteoporosis.

13. Discussion and Overall Conclusions

Raloxifene treatment for 48 months decreased the incidence of all breast cancers, invasive breast cancers, and invasive estrogen receptor-positive (ER+) breast cancers by 62%, 73%, and 83%, respectively. A decrease in the relative risk of invasive breast cancer was evident by the second year of treatment ($p<.001$).
Overall, 93 patients would need to receive raloxifene to prevent one new case of invasive breast cancer.
Raloxifene did not decrease the rate of estrogen receptor negative (ER-) breast cancers, thus suggesting that raloxifene binds to the estrogen receptor in the breast to competitively inhibit estrogen-induced DNA transcription (Grese et al. 1997; Brzozowski et al. 1997). The estrogen-binding ability of raloxifene is further supported by its lack of stimulatory effect on breast tissue, as measured by surrogate markers of breast stimulation: neither breast pain nor breast enlargement was increased in raloxifene treated patients compared with placebo, and breast engorgement was decreased. In contrast, an increase in female lactation was observed in raloxifene-treated patients, but this was, at least in part, an artifact of various types of breast discharge being assigned to the Coding Symbol and Thesaurus for Adverse Reaction Terms (COSTART) term "female lactation".

The protocol-specified primary endpoints of this study support the use of raloxifene to treat osteoporosis in postmenopausal women. In raloxifene-treated women, the rate of new vertebral fractures decreased in both subsets (women with and without prevalent vertebral fractures) and BMD at the lumbar spine and femoral neck increased. In addition to the primary endpoints, significant reductions in biochemical markers of bone turnover were detected. However, raloxifene did not have an effect on new nonvertebral fractures.

Raloxifene had an excellent safety profile. Venous thromboembolism was the only serious adverse event of clinical significance associated with raloxifene. Raloxifene treatment was not associated with a greater risk of death, serious adverse events, >1 treatment-emergent adverse events (TESS) or secondary conditions. Of the TESS events, a significant, >2% incidence with raloxifene treatment was observed for flu syndrome, vasodilatation, leg cramps, peripheral edema, and uterine disorder (uterine disorder was the COSTART term used to describe endometrial fluid in the majority of cases). The increased reporting of diabetes mellitus as a TESS among raloxifene-treated patients was considered to be due, in part, to the baseline imbalance among treatment groups in the prevalence of diabetes mellitus, as indicated by the baseline imbalances in fasting glucose and use of hypoglycemic agents. Since completion of this study, a separate investigation in a cohort of postmenopausal women with osteopenia has supported that there is no negative effect of raloxifene on glyco-insulinemic metabolism (Cagnacci et al. 2002; Cucinelli et al. 2002).
Data from this study confirmed the existing preclinical and clinical data showing that raloxifene has no stimulatory effects on the uterus. Raloxifene was not associated with any increase in the risk of any uterine or endometrial malignancy. The incidence of vaginal or uterine-related bleeding was no different from that observed in the placebo group and was rare, seen in approximately 4% of patients. At the conclusion of an assessment of postmenopausal bleeding,

the finding of benign endometrial polyp was seen with higher frequency in patients on raloxifene, but this was not associated with any serious gynecological pathology (specifically endometrial hyperplasia or carcinoma).
Raloxifene was associated with a transient and minute average increase (<0.3 mm) in endometrial thickness from baseline to endpoint, which resolved completely by 36 months in patients whose endometrial thickness was measured over time. No other significant malignant or benign changes were observed in the uterus after 48 months of raloxifene treatment.
In addition, there was no adverse effect on the vulva, vagina, or the ovaries.
There was an increase in benign cervical polyps observed at 36 months that continued through 48 months of treatment. Because the medical literature generally does not attach clinical significance to the finding of cervical polyps (Kurman 1994), and because no action was mandated by the protocol for cervical polyps, no conclusions are possible regarding the presence of cervical polyps.

Raloxifene had an excellent cardiovascular profile. Adverse event reporting and electrocardiographic data indicated no adverse effects of raloxifene on myocardial infarction/ischemia, cerebrovascular accident/ischemia, or peripheral vascular events.
There were no clinically relevant changes in vital signs. In addition, raloxifene reduced total cholesterol, low-density lipoprotein cholesterol (LDL-C), LDL-C/high-density lipoprotein cholesterol (HDL-C) ratio, and fibrinogen, while not affecting HDL-C or hemoglobin A1c (HbA1c). An analysis of triglyceride changes revealed no clinically relevant changes.
However, raloxifene treatment was associated with a significant increase in the occurrence of venous thromboembolic events (VTE). At the end of the study, the incidence of VTE, which was defined as deep thrombophlebitis (or deep vein thrombosis [DVT]), retinal vein thrombosis (RVT), and pulmonary embolism (PE), was increased in the pooled raloxifene group compared with the placebo group. There was an increased incidence of deep thrombophlebitis overall and in the pooled raloxifene group compared with the placebo group, as previously reported in the 36-month clinical study report. Similarly, higher incidences of deep thrombophlebitis occurred in both the raloxifene 60-mg group and the raloxifene 120-mg group compared with the placebo group. The risk of VTE was highest in the first year and by the fourth year returned to placebo levels for the raloxifene HCl 60-mg dose.
Raloxifene did not appear to have a significant effect on cognitive or neuro-psychomotor function after 48 months of treatment. Statistically significant beneficial findings were limited to selected analyses for only a few of the various cognitive and neuro-psychomotor tests. For the subset of patients who underwent the dementia diagnostic evaluation, there was no effect of raloxifene on dementia.

The sponsor concludes that 48 months of raloxifene is an effective treatment for osteoporosis that significantly reduces the risk of breast cancer in postmenopausal women with osteoporosis. It was well tolerated and had an excellent safety profile for the uterus. Furthermore, raloxifene treatment did not increase the risk of cardiovascular events and improved several cardiovascular risk factors.

Summary 3 CORE Clinical Study Report

Clinical Study Report: Continuing Outcomes Relevant to Evista® (CORE): A Study of Raloxifene HCl and Placebo in the Prevention of Invasive Breast Cancer in Postmenopausal Women with Osteoporosis (H3S-MC-GGJY Study Report)

This is a multicenter, double-blind, parallel, placebo-controlled Phase 3 study using a continued follow-up of the Study H3S-MC-GGGK (also known as Multiple Outcomes of Raloxifene Evaluation [MORE]) cohort.

First patient enrolled (assigned to therapy): 25 October 1999
Last patient completed: 29 August 2003
Date report approved by Lilly Medical: 18 March 2004

Clinical Study Synopsis:

Title of Study: Continuing Outcomes Relevant to Evista® (CORE): A Study of Raloxifene HCl and Placebo in the Prevention of Invasive Breast Cancer in Postmenopausal Women with Osteoporosis

Investigator(s): This multicenter study included 130 principal investigators.

Study Center(s): This study was conducted at 130 study center(s).

Publication(s) Based on the Study: Martino S, Costantino J, McNabb M, Mershon J, Bryant K, Powles T, Secrest RJ. In press 2004. The role of selective estrogen receptor modulators in the prevention of breast cancer: comparison of the clinical trials. Oncologist.

Length of Study: 3.5 years
Date of first patient enrolled: 25 October 1999
Date of last patient completed: 29 August 2003

Phase of Development: Phase 3

Objectives:

Primary: To compare long-term raloxifene 60 mg/day versus placebo to reduce the incidence of invasive breast cancer in postmenopausal women with osteoporosis

Secondary: To compare long-term raloxifene 60 mg/day versus placebo to reduce the incidence of a) invasive, estrogen receptor-positive (ER[+]) breast cancer and b) nonvertebral fractures in postmenopausal women with osteoporosis.

Methodology: This is a multicenter, double-blind, parallel, placebo-controlled study using a follow-up of the Study H3S-MC-GGGK (Multiple Outcomes of Raloxifene Evaluation [MORE] cohort).

Number of Patients: 4011 females

Planned: 3000 patients, minimum
Enrolled: 2725 raloxifene HCl 60 mg/day, 1286 placebo
Completed: 2336 raloxifene HCl 60 mg/day, 1106 placebo

Diagnosis and Main Criteria for Inclusion: Patient must have been randomized in the Lilly clinical Study H3S-MC-GGGK.

Test Product, Dose and Mode of Administration, Batch Number: Raloxifene HCl 60 mg tablets, given daily

Duration of Treatment: 3.5 years (Including treatment during Study GGGK, total patient treatment/observation duration is approximately 8 years. Patients were allowed to participate in Study GGJY even if they did not take study drug.)

Reference Therapy, Dose and Mode of Administration, Batch Number: Placebo tablets, given daily

Criteria for Evaluation:

Efficacy: Mammograms; breast examinations; data collected on nonvertebral fractures.
Safety: Clinical adverse events.

Statistical Methods:

The protocol-specified primary analysis of invasive breast cancer incidence rates was replaced by survival analysis.
The log-rank test was used to compare the two survival curves, and a test for treatment effect was based on a 100(1-α) % confidence interval for the relative hazard (hazard ratio).
The period of observation was from 1 January 1999 through the end of Study GGJY, and the population included all patients who were at investigative sites that participated in Study GGJY.
Other secondary and sensitivity analyses were also conducted.
Time-to-event analysis was used to compare nonvertebral fracture rates between groups for all Study GGJY patients from Study GGGK baseline through Study GGJY termination.
Confidence intervals using a Bonferroni adjustment were added to account for multiplicity when analyzing fractures by location. Adverse events were analyzed using Fisher's Exact test.

Summary and Conclusions:

Study GGJY was designed to evaluate the long-term efficacy of raloxifene compared with placebo on the reduction in risk of invasive breast cancer as seen by the end of 4 years of raloxifene treatment in Study H3S-MC-GGGK (Comparison of Raloxifene Hydrochloride and Placebo in the Treatment of Postmenopausal Women with Osteoporosis, commonly known as Multiple Outcomes of Raloxifene Evaluation [MORE or Study GGGK] throughout peer-reviewed literature).
All patients randomly assigned in Study GGGK were eligible for enrollment in Study GGJY if their investigator elected to participate in Study GGJY.
Sixty-three percent of eligible patients in Study GGGK (n=6511) elected to enroll in Study GGJY (n=4011). The two treatment groups in Study GGJY were well balanced with respect to breast cancer risk; however, the treatment groups differed in severity of osteoporosis.

During Study GGJY, 576 (14.4%) of the 4011 enrolled patients discontinued the study: 182 patients (14.2%) in the placebo group and 394 patients (14.4%) in the raloxifene group. The number of patients who completed the protocol was similar between treatment groups and no differences were observed in individual reasons for discontinuation (for example, adverse event, patient decision, death, etcetera) between the two treatment groups. Eighty-four patients (2.1%) discontinued Study GGJY due to an adverse event. Discontinuations due to an adverse event were similar between groups. There were no remarkable findings concerning any of these events.

Raloxifene treatment resulted in a significant reduction of adjudicated invasive breast cancer (59% risk reduction, hazard ratio 0.41 [95%CI 0.24, 0.71] [p<0.001]) and invasive estrogen receptor positive ER(+) breast cancer (66% risk reduction, hazard ratio 0.34 [95%CI 0.18, 0.66] [p<0.001]) in the PAD from 1 January 1999 through study termination. Also, there were statistically significant reductions in adjudicated invasive breast cancer and invasive ER(+) breast cancer in every population at every treatment duration studied. There was no difference between the treatment groups in the risk of estrogen receptor negative (ER [-]) breast cancer or in the risk of noninvasive breast cancer.

Time-to-event analyses demonstrated a continuous separation between the placebo and raloxifene groups for invasive and invasive ER (+) breast cancer cases over 4.5 and 8 years of treatment.
Every sensitivity analysis conducted confirmed that the result of the primary analysis on adjudicated invasive breast cancer was robust.
Subgroup analyses demonstrated that patients at increased risk of invasive breast cancer had an overall decrease in the incidence of breast cancer with raloxifene treatment.
Raloxifene-treated patients with lower risk factors for developing invasive breast cancer generally had a lower incidence of invasive breast cancer than placebo-treated patients, although the difference may not have been significant.

Raloxifene treatment had a neutral effect on nonvertebral fractures (hazard ratio 1.000 [95%CI 0.870, 1.149]) and on nonvertebral-six fractures (hazard ratio 1.007 [95%CI 0.859, 1.180]). There was an imbalance between raloxifene- and placebo-treated arms of the Study GGJY population in the severity of osteoporosis by prevalent vertebral fracture and SQ score (semi-quantitative visual assessment [Genant et al. 1993] by a radiologist for presence of fractures in the T4-L4 vertebral bodies; scoring includes 0 [no fracture], 1 [mild], 2 [moderate], or 3 [severe] at baseline of Study GGGK). Moreover, patients in the placebo group received more bone-active agents than patients in the raloxifene group. The likelihood of determining an effect of raloxifene on nonvertebral fractures was also diminished by the safety provision that allowed patients to use other bone-active agents after the 3rd year of Study GGGK and through
Study GGJY. Also, patients were allowed to remain in Study GGJY even if they never took study drug.

Post-hoc analyses demonstrated that proportionally fewer raloxifene-treated women sustained ≥ 2 nonvertebral fractures and multiple nonvertebral-six fractures than placebo-treated women from baseline of Study GGGK through Study GGJY termination. In patients with more severe osteoporosis, defined as patients with baseline prevalent vertebral fractures or with a vertebral fracture scored as SQ=3, proportionally fewer raloxifene patients sustained ≥ 2 nonvertebral or nonvertebral-six fractures than placebo patients, even given the imbalance of these treatment groups as noted previously. Thus, raloxifene may have had an effect on nonvertebral fractures although multiple confounders did not make definitive determination possible.

During Study GGJY, 3207 (80%) of patients reported at least one treatment-emergent adverse event (TEAE). Among all TEAEs reported in ≥ 2% of patients, only 2 events, both at the preferred-term level, were statistically significantly different between groups. "Pneumonia NOS" was reported more frequently in placebo-treated patients than in raloxifene-treated patients (p=0.046). "Depression" was reported more frequently in patients in the raloxifene group than in those in the placebo group (p=0.015). It is unlikely that these events were related to study drug. Evaluation of the Study GGJY cohort from Study GGGK baseline through the termination of Study GGJY showed no adverse events not already previously evaluated and was consistent with events observed through 3 years of treatment in Study GGGK.

At least one serious adverse event (SAE) was reported in 939 patients (23.4%), with similar reporting between groups. Three SAEs were reported more frequently in the raloxifene-treated patients: spinal fractures and dislocations, osteoarthropathies, and breathing abnormalities. It is unlikely that any of these events was related to raloxifene treatment. There were 76 deaths (1.9%) in Study GGJY and, as previously observed through 3 years of treatment in Study GGGK, there were fewer deaths in the raloxifene group compared with the placebo group. Two deaths in raloxifene-treated patients were considered by the investigator to be possibly related to study drug.

Evaluation of SAEs previously associated with raloxifene treatment (venous thromboembolism) or with estrogen or tamoxifen treatment (ovarian cancer, endometrial cancer, and cardiovascular-related events) resulted in no new findings. During Study GGJY there was an increased risk of venous thromboembolism with raloxifene treatment. There was no increased risk of ovarian cancer, endometrial cancer, or cardiovascular-related events with raloxifene treatment compared with placebo treatment.

Thus, raloxifene treatment reduced the risk of invasive breast cancer from Study GGGK baseline through Study GGJY termination (approximately 8 years). Raloxifene was generally safe and well-tolerated during the approximately 8 years of follow-up, and the safety profile for raloxifene remains consistent with what was previously known for the drug. Specifically, raloxifene is associated with one SAE: venous thromboembolism. Non-serious adverse events associated with raloxifene treatment are muscle cramps, flushing, and likely peripheral edema.

List of Abbreviations and Definitions of Terms

ACE inhibitor	angiotensin converting enzyme inhibitor
AE	adverse event
ANCOVA	analysis of Covariance
ANOVA	analysis of Variance
BMD	bone mineral density
BMI	body mass index
CCD	Continuing in CORE Dataset
CI	confidence interval
Clinical Global Impression of Improvement CGI-Improvement	Clinical Global Impression of Improvement (CGI-Improvement) (NIMH 1976) was administered by the clinician to measure the degree of improvement at the time of assessment. The score ranges from 1 (very much improved) to a score of 4 (no change) to a score of 7 (very much worse).
Clintrace	Clintrace is the database used by Pharmacovigilance to collect adverse event reports worldwide, report adverse events to regulatory authorities worldwide, and provide safety information to both Lilly and non-Lilly customers.
CORE	Continuing Outcomes Relevant to Evista
Coding Symbol and Thesaurus for Adverse Reaction Terms COSTART	A dictionary developed by the US Food and Drug Administration (FDA) that is used to describe, catalog, analyze, and report all adverse events.
CRF	case report form
CRO	contract Research Organization
CRP	clinical research physician
CV	cardiovascular
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
Early D/C	early discontinuation
ECG	electrocardiogram

Enroll/Randomize	The act of assigning a patient to a treatment. Patients who were enrolled in the trial are those who had been assigned to a treatment.
Enter/Consent	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible to participate in the clinical trial. Patients entered into a trial were those who signed the informed consent document directly or through their legal representatives.
ER	estrogen receptor
ER(+)	estrogen receptor positive
ER(-)	estrogen receptor negative
Ethical review board ERB	A board or committee (institutional, regional, or national) composed of medical professionals and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects or patients participating in a clinical trial are protected. Sometimes called institutional review board (IRB) or independent ethics committee (IEC).
GCP	Good Clinical Practices
HCl	hydrochloride
HERS	Heart and Estrogen/Progestin Replacement Study
HRT	hormone replacement therapy
Informed consent document ICD	An official document that is used to obtain informed consent for a clinical study from potential study participants.
ICH	International Conference on Harmonization
ITT	intent-to-treat
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities: a standard coding terminology for adverse events used globally in compliance with the International Conference for Harmonization (ICH) guidelines.
Medical quality assurance MQA	A part of the corporate quality assurance component, which provides corporate and research management with ongoing evaluation of the quality of processes used and data generated to support worldwide registration of drugs.
MI	myocardial infarction
MMRM	mixed model repeated measures
MOID	MORE-Only Investigators Dataset
MOPCID	MORE-Only Patients of CORE Investigators Dataset

MORE	Multiple Outcomes of Raloxifene Evaluation
NEC	not elsewhere classified
NOS	not otherwise specified
PAD	primary analysis dataset
PE	pulmonary embolism
PI	Principal investigator
Pmol/L	picomole per liter
Reporting Database	Data from the sites are entered into the collection database. These data are then transferred and validated. A database quality review (DBQR) is the process performed prior to a datalock to ensure the data received from the investigator sites (including any corrections) matches the data output from the reporting database with the exclusion of data that are derived or calculated through programming. The reporting database contains unblinded treatment group identification, which allows for statistical analysis to compare the treatment groups.
RVT	retinal vein thrombosis
SAP	statistical analysis plan
SAE	serious adverse event
Screen	The act of determining if an individual met minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involved interviews of patients previously enrolled in Study H3S-MC-GGGK. For this type of screening, informed consent for these screening procedures and/or tests was obtained; this consent may have been separate from obtaining consent for the study.
SERMs	selective estrogen receptor modulators
SQ	semiquantitative
TEAE	treatment-emergent adverse event
VTE	venous thromboembolism
WHI	Women's Health Initiative

Ethics (5)

Ethical Review Boards (ERBs)

Ethical Review Boards (ERBs) provided written approval of the study protocol and the informed consent document (ICD). The study was initiated after the principal investigator (PI) at each site obtained approval documents from their respective ERBs and copies were received by Lilly. Reports on the progress of the study were made by the PIs to the ERBs in accordance with the applicable government regulations and in agreement with policy established by Lilly.

Ethical Conduct of the Study

This study was conducted in accordance with applicable laws and regulations, good clinical practices, and the ethical principles that have their origin in the Declaration of Helsinki. The principal investigator or designee promptly submitted the protocol to applicable ethical review board(s) for approval.

Patient Information and Consent

A properly executed, signed ICD, in compliance with the International Conference on Harmonization (ICH) guideline on Good Clinical Practices (GCP), was obtained from each patient.
Lilly provided a protocol-specific ICD to each investigative site. The PI at each site was allowed to modify this template in order to meet applicable ERB guidelines at that site.
Lilly approved all site-specific ICDs prior to their use at the site.
The PI was responsible for obtaining informed consent from each patient or legal representative and for obtaining the appropriate signatures on the ICD prior to the performance of any protocol procedures and prior to the administration of study drug.
The PI provided a copy of the signed informed consent to the patient and a copy was maintained at the investigative site. Appendix 16.1.9 contains a copy of the protocol-specific ICD used in this study.

Investigators and Study Administrative Structure (6)

This multicenter study was conducted by 130 investigators at 130 study sites.
Appendix 16.1.3 contains information on the qualifications of these investigators.
The table below lists all vendors, laboratories, and contract research organizations used by Eli Lilly and Company during the conduct of this study. All statistical analyses were performed by Eli Lilly and Company.
The sponsor's medical officer responsible for the content of this clinical study report is Per Cantor, MD/PhD, Eli Lilly and Company.
The coordinating investigator for this study is Silvana Martino, DO of the John Wayne

Cancer Institute, Santa Monica, CA, USA. Appendix 16.1.4 lists the authors of this clinical study report.

Table Contracted Services

Organization	Role

b(4)

Introduction (7)

CORE (Study H3S-MC-GGJY or Study GGJY) was designed to evaluate the efficacy of long-term administration of raloxifene hydrochloride (HCl) to reduce the incidence of invasive breast cancer in women with osteoporosis—by continued study of women randomized in the clinical study MORE (Multiple Outcomes of Raloxifene Evaluation or H3S-MC-GGGK or Study GGGK).

Study GGGK was designed to establish the effect of long-term treatment with raloxifene, compared with placebo, on the rate of new vertebral fractures in osteoporotic postmenopausal women with and without prevalent vertebral fractures. After 4 years of treatment in Study GGGK, a significant 62% reduction in breast cancer incidence was observed in raloxifene-treated women compared with those who received placebo.
Considering invasive and invasive ER (+) tumors, the percent reductions were 73% and 83%, respectively (H3S-MC-GGGK 4-Year Study Report).

Patients were enrolled in MORE based on a diagnosis of osteoporosis rather than an increased risk of breast cancer.

At Visit 1 of Study GGJY (CORE), patients were asked questions from the Gail criteria to evaluate individual breast cancer risk over a 5-year period. Answers to these questions were used to quantify the risk of breast cancer in this cohort of postmenopausal women with osteoporosis by estimating the 5-year risk of breast cancer using the Gail method for each patient.

Study GGGK (MORE) had compared three treatment groups: raloxifene HCl 60 mg/day, raloxifene HCl 120 mg/day, and placebo.
However, in Study GGJY, only two treatment groups were compared: raloxifene HCl 60 mg/day and placebo. The selection of raloxifene HCl 60 mg/day as the only active treatment dosage for Study GGJY was based on similar breast cancer reduction efficacy in the two raloxifene treatment groups in Study GGGK and because raloxifene HCl 60 mg/day is the approved, marketed dose for the prevention and treatment of osteoporosis in postmenopausal women.

In addition to breast cancer data, long-term data (approximately 8 years from the date of randomization in Study GGGK) were solicited to analyze the occurrence of nonvertebral fractures and specific adverse events, including death, vaginal bleeding, uterine cancer, endometrial hyperplasia, deep venous thrombosis, pulmonary embolus, and retinal vein thrombosis. Data on the occurrence of other adverse events were followed in Study GGJY through spontaneous adverse reports (both serious and non-serious) and were also analyzed for the 8-year time period.

The original design of Study GGGK was a 3-year placebo-controlled study in postmenopausal women with osteoporosis. Subsequently, a 1-year extension phase was added, followed by approximately 4 years of additional treatment for women who participated in Study GGJY (CORE).

The primary objective of the GGGK extension phase and Study GGJY was to obtain long-term data on breast cancer risk reduction with raloxifene usage.
Secondarily, additional long-term fracture nonvertebral data were collected. However, the sponsor determined that allowing bone-active drugs during the GGGK extension phase and Study GGJY was ethically necessary given disease state of the cohort, and many patients chose to receive bone-active therapy during this time.

Thus, the fracture data obtained during Study GGJY is of limited value and must be interpreted in the context of confounding concomitant medications that were allowed after the 3rd year of Study GGGK.

Study Objectives (8)

Primary Objective

The primary objective of this Phase 3 study was to test the hypothesis that a statistically significant reduction in the incidence of invasive breast cancer will occur in postmenopausal women with osteoporosis treated with raloxifene HCl 60 mg/day compared with placebo over a long-term period of observation.

The long-term observation period was defined by relationship to the patients' enrollment in Study GGGK. The period of interest began 1 January 1999 (the date of the last breast cancer data analysis to support the osteoporosis treatment indication for marketing authorizations). Thus, the beginning of this period of observation in Study GGJY corresponded to at least 3 years after the randomization of patients into Study GGGK; this period of observation continued for approximately 8 years after the randomization of patients into Study GGGK.

The figure below illustrates time periods for the Study GGJY (CORE) analyses for the primary and secondary objectives.

Secondary Objectives

A secondary objective of this study was to test the hypothesis that a statistically significant reduction in the incidence of invasive estrogen receptor-positive breast cancer will occur in postmenopausal women with osteoporosis treated with raloxifene HCl 60 mg/day compared with placebo over a long-term period of observation.

The period of interest for this objective was the same as that stated for the primary objective.

An additional secondary objective of this study was to test the hypothesis that raloxifene HCl 60 mg/day will have an effect of reducing the incidence of nonvertebral fractures in postmenopausal women with osteoporosis, compared with placebo, over a long-term period of observation.

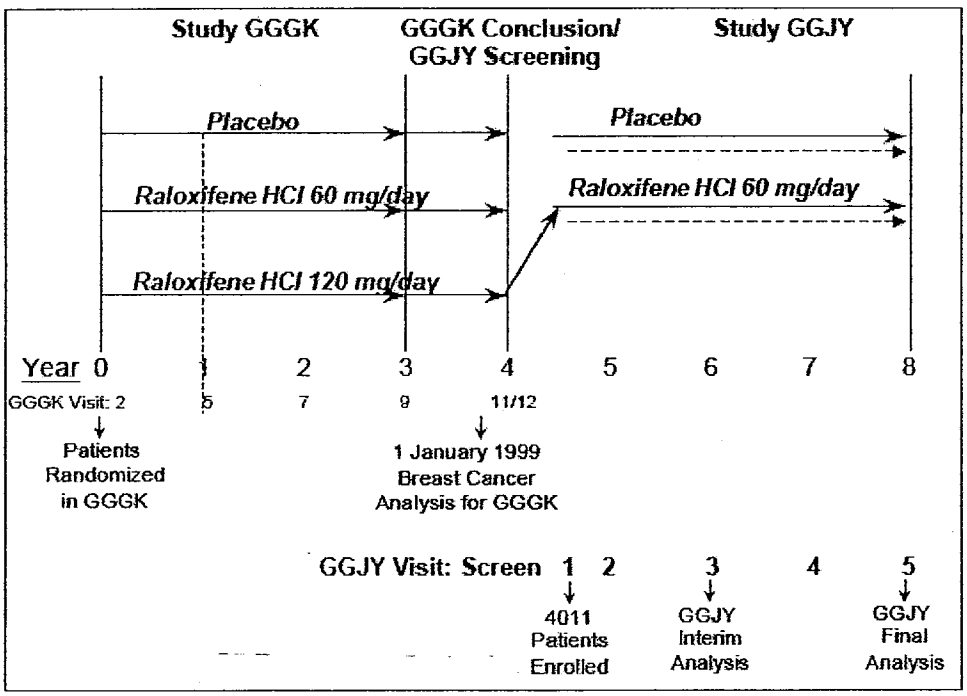
The period of interest for this objective began with the patients' randomization in Study GGGK rather than the 1 January 1999 baseline defined for the breast cancer observations.

Investigational Plan (9)

Overall Study Design and Plan: Description

This was a multicenter, double-blind, parallel, placebo-controlled investigation of the long-term efficacy of raloxifene HCl 60 mg/day in reducing the incidence of invasive breast cancer in postmenopausal women with osteoporosis, using continued treatment of a cohort from the Study GGGK (MORE).

The figure below shows the study design and the relationship of Study GGJY to Study GGGK. Of note, Visits 2, 3, 4, and 5 were timed to occur on the 5-, 6-, 7-, and 8-year anniversaries of enrollment in Study GGGK, respectively. If the date a patient enrolled in Study GGJY (Visit 1) was sufficiently near the 5-year anniversary of their enrollment in Study GGGK, the patient would not have a Visit 2 in Study GGJY.



Solid line indicates subjects completing Study GGGK through Visit 11 or 12.
Broken line indicates subjects entering Study GGJY after early termination from Study GGGK.

Figure. Illustration of study design for Study GGJY.

Discussion of Study Design, Including the Choice of Control Groups (9.2)

This study was designed to collect long-term breast cancer and nonvertebral fracture data from the Study GGGK cohort.
The double-blind, placebo-controlled, parallel-group design of Study GGJY began at Visit 1 of Study GGJY. In order to preserve the randomization established in Study GGGK, Study GGJY participants continued to have the same patient number that was assigned to them for Study GGGK.
Participants who were randomized to placebo or raloxifene HCl 60 mg/day during Study GGGK received the same treatment in Study GGJY. Participants who were randomized to raloxifene HCl 120 mg/day during Study GGGK received raloxifene HCl 60 mg/day in Study GGJY. In addition, all participants were provided with an elemental calcium supplement (500 mg/day) and vitamin D (400 to 600 IU).

For most patients, there was a period of time between their termination from Study GGGK and their enrollment in Study GGJY during which they were not enrolled in either clinical trial and did not receive study drug.
The mean time off therapy during this interim period was approximately 12 months.
For patients who consented to participate in Study GGJY, it was specified in the Informed Consent Document (ICD) that any known events that occurred during the interim period could be used in Study GGJY analyses.
Because Study GGJY was designed based on intention-to-treat principles (see Section 9.7.1.1), all patients, including those who either were excluded from or who refused to take study medication (approximately 20% of patients; see Section 11.3) during Study GGGK, were encouraged to participate.

Selection of Study Population (9.3)

Participants randomized in Study GGGK and who were at investigative sites that chose to participate in Study GGJY were invited to participate in Study GGJY after their completion or discontinuation from Study GGGK.
Participants who discontinued from Study GGGK, including those who were randomized but became ineligible for study drug, were eligible for screening and follow-up in Study GGJY.
Participating investigators attempted to contact all GGGK participants, including those who were lost to follow-up during Study GGGK.
Entry into Study GGJY had to occur after termination from Study GGGK. The total observation period was approximately 8 years from the time of randomization in Study
GGGK (for patients who required further breast evaluation on the basis of a suspicious breast examination or mammogram at the Study GGJY Visit 5, the observation period continued until appropriate follow-up occurred).

Screening Window (9.3.1)

Screening contact with a patient who was previously randomized in Study GGGK occurred after the Study GGJY protocol was approved by the appropriate ethical review board. The screening period for each investigative site continued approximately 5 months after protocol approval was obtained. This screening window definition encouraged the quick enrollment of patients who were easily contacted without excluding those patients who were more difficult to locate.

Inclusion Criteria (9.3.2)

Patients were eligible for Study GGJY (CORE) only if they were randomized in Study GGGK (MORE).
Participants who discontinued from Study GGGK, even those who were randomized but became *ineligible for study drug* at a later date, were eligible for participation in Study GGJY.
These participants were *eligible for study medication* administration unless they met any of the following criteria:

- Diagnosed cancer of the breast or uterus, or other malignancy considered to be estrogen-dependent.
- History of venous thromboembolism (VTE), including deep vein thrombophlebitis, pulmonary embolus, retinal vein thrombosis, or other serious vein thrombosis.
- Patients who were unblinded to study medication for safety reasons during Study GGGK, or for whom unblinding became necessary for safety reasons during Study GGJY.
- Required treatment with prescribed raloxifene, tamoxifen, cholestyramine, systemic hormone replacement therapy, or other reproductive hormone products that would have been ongoing during Study GGJY. Patients treated with these compounds prior to entry in Study GGJY were not excluded from study medication if they chose to discontinue their use. A washout period was not required. (Occasional concurrent symptomatic use of topical estrogens up to 3 times/week, use of estrogen vaginal ring, or oral estriol up to 2 mg/day was permitted with study medication administration.)
- Patients experiencing clinically severe postmenopausal symptoms at Study GGJY Visit 1 that required estrogen therapy.
- Patients with known, clinically significant acute or chronic liver disease.
- Patients with known, clinically significant impaired kidney function.
- Patients with known, severe, untreated malabsorption syndromes.
- Patients who, in the opinion of the investigator, were poor medical or psychiatric risks (including known alcohol or drug abuse) for treatment with an investigational drug.
- Treatment with a drug that has not received regulatory approval (that is, an investigational drug other than raloxifene HCl).

Appropriateness of assignment (or exclusion from study drug administration in participants who terminated from Study GGGK for adverse events other than those specifically noted) was determined by the investigator.

Exclusion Criteria (9.3.3)

- Patients were excluded from entry into Study GGJY if they were unblinded to their study medication in Study GGGK for any reason other than safety.

Due to the necessity for a blinded study population during Study GGGK, the GGGK blinding code was not broken at the site level at the time of initiation of Study GGJY. The informed consent document addressed this issue and informed patients that a decision to enter into Study GGJY required agreement to defer the participant's eligibility to be informed of her GGGK/GGJY treatment assignment, for any reason other than safety, until the final GGJY analyses were completed.

Removal of Patients from Therapy or Assessment (9.3.4)

Patients were removed from study drug if any of the criteria that precluded administration of study medication at baseline Study GGJY became true at any point during the study (see Section 9.3.2). Unless a patient was unblinded to her therapy for any reason other than a safety concern, any patient who discontinued study drug was encouraged to continue through the end of Study GGJY for *follow-up*.

Treatments (9.4)

9.4.1. Treatments Administered

- No study drug was administered during the time between the last visit of Study GGGK and Visit 1 of Study GGJY.
- Starting at Visit 1, patients were instructed to take open-label supplements of approximately 500 mg/day calcium and approximately 400 to 600 IU/day of vitamin D. (If a patient was unable to tolerate either of these supplements, the investigator could decide to reduce or discontinue the supplementation. However, the patient continued to participate in the study.)

Identity of Investigational Product(s) (9.4.2)

Study material (raloxifene HCl and placebo) for the Study GGJY double-blind treatment phase was provided as oral tablets and packaged according to a random-number table in numbered bottles. At each visit, the patient was asked to return the unused study medication so that the remaining tablets could be counted and recorded. (If, at any visit, the patient forgot to return her medication to the investigative site, she could return it to be counted and recorded at her next regularly scheduled visit.)

- Each 60-mg dose of **raloxifene HCl** was equivalent to 55.71 mg of raloxifene.
- **Placebo** tablets were identical in appearance to those of raloxifene.
- Approximately 500 mg/day **elemental calcium** was provided as open-label calcium tablets containing approximately 250 or 500 mg of elemental calcium per tablet. A **vitamin D** supplement containing approximately 400 to 600 IU of vitamin D was also provided.

Method of Assigning Patients to Treatment Groups

- Patients who were randomized to placebo or raloxifene HCl 60 mg/day during Study GGGK received the same treatment in Study GGJY.
- Patients who were randomized to raloxifene HCl 120 mg/day during Study GGGK received raloxifene HCl 60 mg/day in Study GGJY.
- This reassignment occurred at Visit 1 of Study GGJY.

Selection of Doses in the Study

Patients enrolled in Study GGJY received either raloxifene HCl 60 mg/day or placebo. The raloxifene HCl 60 mg/day dosage was chosen based on similar breast cancer reduction efficacy in the two raloxifene treatment groups in Study GGGK and because raloxifene HCl 60 mg/day is the approved, marketed dose for the prevention and treatment of osteoporosis in postmenopausal women.

Selection and Timing of Dose for Each Patient

Patients eligible for study drug administration were instructed to take one blinded study medication tablet each morning.

Blinding (9.4.6)

This was a double-blind study. Patients, investigators, and all other personnel involved with the conduct of the study were blinded to individual treatment assignments for the duration of the study. This double-blinded arrangement for Study GGGK was not to have been broken for patients who participated in Study GGJY.

- Patients enrolled in Study GGGK who entered Study GGJY were not re-randomized. Reassignment to raloxifene HCl 60 mg/day for patients who were randomized to raloxifene HCl 120 mg/day in Study GGGK was accomplished by conversion of the GGGK study drug kit numbers to GGJY study drug bottle numbers or kit numbers.
- Emergency codes, generated by a computer drug-labeling system, were available to the principal investigator (PI) at each site. These codes, which reveal the patient's treatment group when opened, could be opened during the study only if the choice of follow-up treatment depended on the patient's therapy assignment. The patient's agreement, in the informed consent document, to defer their eligibility to be informed of the GGGK/GGJY therapy assignment did not apply in the event of a safety issue that required unblinding.
- The PI was instructed to make every effort to contact the Lilly clinical research physician (CRP) prior to unblinding a patient's treatment assignment. If a patient's treatment assignment was unblinded, the Lilly CRP was to be notified immediately by telephone.
- After the study, the PI was to return all sealed and any opened codes.
- If a PI, site personnel performing assessments, or patient was unblinded, the patient was to be discontinued from the study unless there were ethical reasons to have the patient

remain in the study. In these special cases, the PI was to obtain specific approval from Lilly's CRP for the patient to continue in the study.
- Patients who were unblinded for safety reasons did not have to be discontinued from the study, but were required to discontinue study drug administration.
- Blinding status and the date of the final dose of study medication were documented in the case report form.
- The most common reason for unblinding of patients was diagnosis of breast cancer. Patients were unblinded after their diagnosis because treatment assignment during the study could affect treatment decisions made to manage their disease.

9.4.7. Prior and Concomitant Therapy

Although the primary objective in Study GGJY pertained to breast cancer, the cohort was selected for Study GGGK based on a history of osteoporosis. Therefore, concomitant treatment with specific bone-active agents including bisphosphonates, calcitonin, or fluoride was permitted. However, dose and therapy duration were not collected.
The use of the following specified concomitant medications were solicited at each visit:
Bone-active agents including, but not limited to, bisphosphonates (alendronate, etidronate, residronate), calcitonin, and fluoride;
- Lipid-lowering agents including, but not limited to, statins (for example, lovastatin, simvastatin, atorvastatin), fibrinolytic agents (for example, gemfibrozil), nicotinic acid, and clofibrate;
- Hormones or selective estrogen receptor modulators (SERMs) including, but not limited to, estrogen (oral, transdermal, and vaginal), tamoxifen, toremifene, and tibolone;
- Nitrates for angina, including, but not limited to, nitroglycerine (sublingual, aerosol, oral, and transdermal) and isosorbide.

Other medications (other than study medication) taken during the study may have been recorded on the case report form (CRF), per the judgment of the investigator. Any use of excluded medication was a violation of the protocol and was documented. Section 10.2 provides a discussion of significant protocol violations

Treatment Compliance (9.4.8)

- Investigators assessed compliance with study medication at each visit or other study interval by direct questioning and by counting returned medication. All unused medication was returned to Lilly.
- Compliance across the study was computed.

Efficacy and Safety Variables (9.5)

9.5.1. Efficacy and Safety Measurements Assessed and Study Schedule

The following efficacy measures were collected at the times shown in the Study Schedule. Specific efficacy measures included mammograms, breast examinations, and data collected on nonvertebral fractures.

Breast Cancer

Although breast cancer cases were adjudicated in Study GGGK by review of mammographic films to determine whether there was evidence to suggest that lesions were pre-existing, all lesions in Study GGJY were considered as new-onset, based on a 4-year history of routine mammographic screening that occurred in Study GGGK.

At Visit 1 of Study GGJY, patients were asked to answer questions to evaluate breast cancer risk over a 5-year period using the **Gail** method. Answers to these questions were used to quantify the risk of breast cancer in this cohort of postmenopausal women with osteoporosis by calculating the 5-year risk of breast cancer using the Gail method for each patient.

Bilateral mammograms were performed at Visits 1, 3, and 5 (which corresponded approximately to Years 4.5 to 5, 6, and 8 after randomization into Study GGGK).
A mammogram was performed at early termination from Study GGJY if at least 1 year had passed since the previous mammogram (or at least 2 years from the previous mammogram in countries where the performance of mammograms at this time was in conflict with national guidelines of accepted standards of care).
Although mammographic films were not required to be submitted to the sponsor, the investigator was required to ensure that these images were retained at the institution where performed and were available for central review if requested.
Written reports of all mammograms considered abnormal were supplied to the sponsor.
Mammograms were defined as abnormal in any of the following circumstances:

- The written report suggested that follow-up imaging procedures were required,
- A lesion that required sampling was identified, or
- Reasons other than those described, which the investigator deemed to be clinically significant.

In the event that a mammogram identified the need for **follow-up breast imaging**, documentation of follow-up breast imaging was also supplied to the sponsor. If this occurred at the patient's last visit (either Early Termination or Visit 5), all additional information available prior to data-lock was used for analyses.

Histopathological reports were requested for all site-reported cases of breast cancer.

Written reports for all sampling methods performed (including, but not limited to, fine-needle aspiration cytology, core biopsy histopathology, and surgical pathology) were to be submitted to the sponsor. Although histopathology specimens were not required to be submitted to the sponsor, the investigator was required to ensure that these specimens were retained at the institution where performed and were available for central review if requested. In all cases of site-reported breast cancer, a local report of estrogen receptor status was requested.

Breast examinations were performed at Visits 1 through 5 (corresponding approximately to Years 4.5, 5, 6, 7, and 8 after randomization into Study GGGK) and at early termination. In the event that a breast exam identified the need for follow-up tissue sample(s) or breast imaging, written reports of the follow-up procedures were also supplied to the sponsor. If this occurred at the patient's last visit (either Early Termination or Visit 5), submission of this data to the sponsor was still required.

If a patient had **an abnormal mammogram associated with her last visit** as specified by the protocol (for Study GGJY this was either at the Early Termination Visit or Visit 5), the breast cancer data from follow-up procedures was included in the primary analysis if both of the following circumstances occurred:
1) The woman underwent invasive diagnostic procedures as a direct result of the abnormal mammogram, and
2) A diagnosis of invasive breast cancer was adjudicated by the blinded central reader.

If the **last-visit mammogram** was abnormal, but did not lead directly to invasive diagnostic procedures, the patient was considered to have provided complete efficacy data at the time of the last-visit mammogram. Specifically, if an abnormal mammogram associated with the last visit was not investigated by either further diagnostic imaging or an invasive procedure within 12 weeks of the original last-visit mammogram, no further follow-up from that patient was included in the efficacy analyses. If a medical recommendation was made for a follow-up mammogram at a time longer than 12 weeks after the last protocol-scheduled mammogram and this follow-up eventually led to a diagnosis of breast cancer, this information was to be communicated to the sponsor for inclusion in the sponsor's pharmacovigilance data. Such data are not included in the primary statistical analysis.

Nonvertebral Fractures (9.5.1.2)

Nonvertebral fractures reported by subjects were recorded in the CRF at all visits. These events were confirmed by local radiology reports to document the date and anatomical location of the fracture.

Safety (9.5.1.3)

The following safety measurements were collected at the times shown in the Study Schedule.

- If **death** was reported, the investigator was required to obtain information about the cause. Expected documentation included a copy of the death certificate and either a hospital summary at the time of death or a witness report if the death occurred outside of

a hospital setting. The investigator also attempted to determine whether an autopsy was performed; if performed, a written autopsy report should have been obtained.

- A questionnaire was administered at all visits to evaluate the occurrence of **deep venous thrombosis, pulmonary embolus, retinal vein thrombosis, vaginal bleeding, and diagnosis of uterine cancer** or **hyperplasia**. These events, except for vaginal bleeding, required written documentation to support the diagnoses. Serious adverse events were reported to Lilly Pharmacovigilance.
    - Patients who develop vaginal bleeding, spotting, or staining regardless of duration or severity were referred to a gynecologist for an endometrial evaluation that was appropriate to the local standard of care. The investigator was required to follow up to ascertain whether the final diagnosis was uterine cancer or endometrial hyperplasia.
    - Written documentation of the diagnosis was retained at the site.

- Adverse events were recorded at Visits 1 through 5 and at early termination.

Study medication should have been **temporarily discontinued** by the patient, the primary physician, or the study physician (as appropriate) immediately **in the event of an illness or condition leading to a prolonged period of immobilization** and should not have been restarted until the inciting condition or illness was resolved and the patient was fully mobile (see the following points).

- Whenever a patient was hospitalized, study medication should have been temporarily discontinued until the patient was discharged and had resumed her previous level of mobility.
- A patient who was planning to undergo an elective surgical procedure or was planning to be immobile for a long period of time (such as a long plane flight) should have temporarily discontinued her study medication approximately 72 hours prior to admittance to the hospital or to the start of travel, and should not have restarted it until she had resumed her previous level of mobility.
- A patient suffering an illness or trauma for which she was confined to bed (though not hospitalized) should have temporarily discontinued her study medication and should not have restarted it until she had resumed her previous level of mobility.

Table Study Schedule

Activity	Visit: / Month:	1 / Baseline	Double-Blind Treatment[d] 2 / 12	3 / 24	4 / 36	5 / 48 or early termination
Sign informed consent document		X				
Clinical Assessments						
Complete Gail Criteria Questionnaire		X				
Height		X	X	X	X	X
Weight		X	X	X	X	X
Breast examination		X	X	X	X	X
Record of adverse event reporting		X	X	X	X	X
Record of specific concomitant medications		X	X	X	X	X
Technical assessments						
Mammogram[a]		X		X		X[e]
Miscellaneous						
Patient number assigned[b]		X				
Randomization[c]		X				
Study drug administration			<----------			---------->

[a] Baseline mammogram requirement could have been met with either 1) CORE baseline mammogram, 2) mammogram performed as Visit 11 or 12 procedure from MORE, or 3) local healthcare facility written report of the mammogram performed within 12 months of baseline.

[b] Patient numbers assigned were identical to those assigned during MORE.

[c] Participants in MORE who were randomized to placebo or to raloxifene HCl 60 mg/day received the same treatment. Participants in MORE who were randomized to raloxifene HCl 120 mg/day received raloxifene HCl 60 mg/day in this study (Study GGJY).

[d] All participants were provided with an elemental calcium supplement (500 mg/day) and vitamin D (400 to 600 IU).

[e] At early termination, participants who had not had a mammogram for 1 year (2 years in countries where the performance of mammograms at this visit were in conflict with national guidelines or accepted standards of care) or longer were requested to have a bilateral mammogram.

Appropriateness of Measurements

All efficacy and safety assessments have been well documented and are generally regarded as reliable, accurate, and relevant.

Primary Efficacy Variable (9.5.3)

The primary efficacy variable was the date of diagnosis of invasive breast cancer, as diagnosed via mammograms, breast examinations, and breast biopsies or the date the patient left the study without having experienced a diagnosis of breast cancer.

Drug Concentration Measurements

Drug concentration measurements were not assessed in this study.

Data Quality Assurance (9.6)

To ensure accurate, complete, and reliable data, Lilly or its representatives did the following:

- Provided instructional material to the study sites, as appropriate;
- Sponsored a start-up training session to instruct the investigators and study coordinators;
- Made periodic visits to the study site;
- Were available for consultation and stayed in contact with the study site personnel by mail, telephone, and/or fax;
- Reviewed and evaluated CRF data and used standard computer edits to detect errors in data collection;
- Conducted quality review of reporting database.

- To assure the safety of participants in the study and to assure accurate, complete, and reliable data, the investigator kept records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study.
- Lilly or its representative periodically checked a sample of the patient data recorded against source documents at the study site.
- Lilly Medical Quality Assurance (MQA) and one regulatory agency audited the study