Statistical Methods and Determination of Sample Size (9.7)

Statistical and Analytical Plans

- The protocol for Study GGJY was approved on 28 July 1999.
- The final statistical analysis plan (SAP) was approved on 25 September 2003.
- This section addresses the planned statistical analyses prior to unblinding as described in the protocol and SAP and Section 9.8 addresses changes made to the planned statistical analyses after unblinding.
- The analyses presented in this report are based on data contained in the reporting database, an archived production database used for analysis purposes that contains data collected on case report forms. The reporting database was validated and locked for analysis on 30 September 2003.
- An interim safety and efficacy analysis was performed; the data cutoff point was Visit 3 (6 years post-randomization in Study GGGK), and the reporting database for this analysis was validated and locked on 9 November 2001.
- The adjudicated breast cancer database was validated and locked 25 November 2003.

General Considerations (9.7.1.1)

Study GGJY (CORE) was designed to provide follow-up data for as many women as possible who were enrolled in Study GGGK (MORE). Data from Study GGJY includes information about the patients contained in the final GGGK reporting database.

- The **primary analysis dataset (PAD) population** is comprised of all patients at sites that participated in Study GGJY who were eligible for participation in Study GGJY.
  - For patients who gave informed consent for Study GGJY, all data from Studies GGGK and GGJY were used in analyses.
  - For patients who did not consent to participate in Study GGJY, data from their participation in Study GGGK through their discontinuation were used in analyses.
- If a procedure at the last visit of either Study GGGK or Study GGJY led to follow-up procedures to determine the presence or absence of any type of cancer for any patient, all **additional information** available prior to data lock was used for analyses.
- **Follow-up information** regarding any serious adverse event (SAE) that was reported at the last visit was used in reporting.
- The cases of **invasive breast cancer** were **adjudicated** by a group of experts external to the sponsor, and the adjudicated results are the basis of the breast cancer analyses.

- The **primary analysis** was based on **survival analysis**. Survival analyses for invasive breast cancer and invasive ER + breast cancer were used in place of the *protocol-specified primary analysis* and *secondary breast cancer analysis*.
  - The log-rank test, equivalent to the score test in the Cox proportional hazards model, with therapy as the only covariate was used to compare the two survival curves.

- The **protocol-specified, primary analyses** of the primary and secondary breast cancer endpoints were based on **confidence intervals of the risk ratios**. These analyses were conducted as secondary analyses and compared **incidence rates of invasive breast cancer** and invasive ER(+) breast cancer using a Mantel-Haenszel 100(1-α) % confidence interval for relative risk. The statistical test of the null hypothesis of no treatment effect was considered statistically significant if the confidence interval did not contain the value 1.0.

- The primary analysis used intention-to-treat (ITT) principles. An ITT analysis is an analysis of data by the groups to which patients were assigned by random allocation, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol.
- Unless otherwise stated, all hypotheses were tested at the $\alpha = 0.05$ (two-sided) level of significance. No adjustments for multiple comparisons were made. The interim analysis for the primary efficacy endpoint used $\alpha = 0.001$ as the level of significance. Because the trial was not terminated due to outstanding efficacy, the final efficacy analysis used $\alpha = 0.0495$ as the level of significance to maintain an overall Type I error rate of $\alpha = 0.05$.
- Categorical data (for example, comparison of adverse event rates) were analyzed using Fisher's Exact test. If computational resources did not permit the use of Fisher's Exact test, Pearson's chi-square test was substituted, but only if the number of events across all treatment groups was at least 10. Statistical inference was not performed when fewer than 5 events occurred.

Adjustments for Covariates

No adjustments for covariates were planned for the primary analysis.

Handling of Dropouts or Missing Data

Analysis of Study GGJY (CORE) data was based on ITT principles, so that the entire patient population as enrolled was included in the analyses.

- The primary analysis was based on time-to-event, and patients who dropped out of the study were censored at the time of their last contact with the study site.
- For analyses of risk rates, the denominator of total woman-years included, for each woman, the time from the start of observation until either an event or final contact with the study site occurred.

Multicenter Studies

Due to the large number of sites in Study GGJY (130), including investigator in the model was impractical. Instead of investigator, region code was used to investigate possible systematic bias in the data. The proportional hazards model for time-to-event data included a term for treatment and region as fixed effects. Initially, a term for the treatment-by-region interaction was included and tested at the $\alpha = 0.10$ significance level.

Table Assignment of Countries to Region for Treatment-By-Region Interaction in Study GGJY (CORE)

Region	Country
North America	Canada, United States
Latin America	Argentina, Mexico
Eastern Europe	Czech Republic, Hungary, Poland, Slovenia, Slovakia
Western Europe	Austria, Belgium, Denmark, Spain, Finland, France, Great Britain, Israel, Italy, Netherlands, Norway, Sweden, Germany
Asia Pacific	Australia, New Zealand, Singapore

Multiple Comparisons/Multiplicity

- A single analysis of the primary endpoint was conducted; thus, no adjustment for multiple comparisons or multiplicity was necessary.
- Analyses of nonvertebral fracture incidence by site were conducted using the Bonferroni correction for multiplicity.

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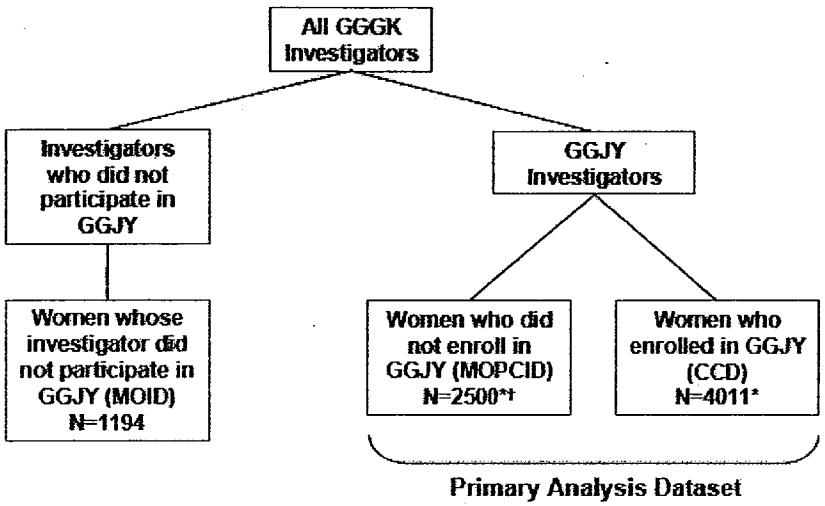
Use of an Efficacy Subset of Patients

Datasets

See the diagram of datasets used in analyses:



*Patients in the primary analysis dataset who were diagnosed with breast cancer before 1 January 1999 will not be included in the primary efficacy analysis. Also, patients in the primary analysis dataset who ended participation in Study GGGK (MORE) before 1 January 1999 and did not enroll in Study GGJY (CORE) will not be included in the primary efficacy analysis.

†The MOPCID population includes all 2500 women at Study GGJY (CORE) investigative sites who did not enroll in Study GGJY (CORE). However, only 1217 of these patients were still enrolled in Study GGGK (MORE) as of 1 January 1999, which was the cutoff date for inclusion in Study GGJY (CORE). Thus, the PAD consists of 5228 patients. For the primary analysis of invasive breast cancer, an additional 15 patients in the PAD are excluded based on a diagnosis of breast cancer prior to 1 January 1999.

Abbreviations: CCD = Continuing in CORE (GGJY) Dataset; GGGK = Study H3S-MC-GGGK (MORE); GGJY = Study H3S-MC-GGJY (CORE); MOID = MORE (GGGK)-Only Investigators Dataset; MOPCID = MORE (GGGK)-Only Patients of CORE (GGJY) Investigators Dataset.

Figure GGJY.9.2. Datasets defined for Study GGJY analyses.

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Primary Analysis Dataset (PAD)

Two subpopulations comprise the PAD:

1) Patients who continued in CORE (Study GGJY) and,
2) Patients from MORE (Study GGGK) who were at an investigative site that participated in CORE but who did not participate in CORE (see descriptions in the following text).

- Thus, the PAD population consists of all eligible patients who were at sites that participated in CORE.
- For patients who gave informed consent for CORE, all data from MORE and CORE were used in the analyses (including data after discontinuation from MORE and prior to Visit 1 of CORE).
- For patients who did not give informed consent for CORE, data from their participation in MORE through their discontinuation from MORE were used in the analyses.
- The primary efficacy analysis necessarily excluded patients who were diagnosed with breast cancer prior to 1 January 1999 and patients who ended participation in MORE prior to 1 January 1999 without enrolling in CORE.

Continuing in CORE Dataset (CCD): Patients who participated in CORE (GGJY)

The population of patients who consented to participate in CORE was included in the PAD. Some secondary analyses, safety analyses, and sensitivity analyses included only those patients who participated in CORE (the CCD).

MORE Only Patients of CORE Investigators Dataset (MOPCID): Nonparticipating Patients of CORE Investigators

The population of MORE patients who declined participation in CORE (or were otherwise not qualified for participation in CORE) although the investigative sites participated in CORE was included in the PAD.

MORE (GGGK)-Only Investigators Dataset (MOID)

The population of MORE patients who were at investigative sites that declined participation in CORE was not eligible to participate in CORE and was not included in the PAD. The primary analysis does not include these patients because the investigators for these patients never provided data during CORE. Because the investigator effect over 8 years could not be measured for these investigators, their data were excluded by design in the protocol.

MORE (GGGK) Patients Dataset

Secondary analyses of the breast cancer and fracture endpoints were conducted that included all patients who enrolled in MORE (N=7705).

Analyses

Both the primary efficacy analysis and the secondary efficacy analyses were ITT analyses. The primary analysis considered all invasive breast cancer cases diagnosed on or after 1 January 1999, as stated in the protocol. The period of observation for the primary analysis for patients in the PAD was the following:

- 1 January 1999 through time of discontinuation from CORE for women who participated in CORE (CCD population).
- 1 January 1999 through time of ending participation in MORE for women at CORE investigative sites who did not participate in CORE (MOPCID population).

If a patient had an abnormal mammogram associated with her last visit as specified by the protocol (for CORE, this is 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 communicated to the sponsor for inclusion in the sponsor's pharmacovigilance data. Such data was not part of the primary statistical analysis.

Adjudication of breast cancer was performed by a group of physicians external to Lilly and blinded to therapy. Results of estrogen receptor (ER) status were communicated to the adjudicators as those data became available. Results of adjudication for all breast cancer data were stored in an ongoing database maintained by Lilly for that purpose. The clinical database was locked after all patients who had a protocol-specified mammogram associated with her last visit either had a normal mammogram, received a diagnosis of breast cancer resulting from the mammogram associated with the last visit, or was recommended to have a follow-up mammogram more than 12 weeks after the protocol-mandated mammogram.

Likewise, the efficacy analysis of the secondary variable, incidence of invasive ER (+) breast cancer, considered the same population (PAD patients) and the same time period (from 1 January 1999 through the end of participation in Studies MORE or CORE as described in the preceding text) as the primary analysis of all invasive breast cancers.

The protocol specified that patients were excluded from the PAD if they had already experienced a breast cancer. This exclusion was applicable only to the analysis of breast cancer and was not necessary for analyses of other events such as nonvertebral fractures.

The secondary efficacy analyses of the incidence of nonvertebral fracture considered all patients enrolled in CORE (the CCD) for the following periods of observation:

- Randomization in MORE through the end of participation in CORE for women who participated in CORE (the CCD population).
- Randomization in MORE through the end of participation in MORE for women at CORE investigative sites who did not participate in CORE (the MOPCID population).

The pre-specified safety analyses were ITT analyses on all CORE patients (that is, the CCD population) over the entire 8 years of the combined trials, MORE and CORE. Additional safety analyses that encompassed only the time of the CORE trial were also completed.

Patient Disposition

The reasons for discontinuation were coded in a manner similar to that in Study GGGK (for example, "adverse event", "patient moved", etcetera). The results are summarized by therapy and compared using a chi-squared test.

Patient Characteristics

Most patient characteristics were collected in MORE. These demographics data were analyzed according to the same methodology used in MORE, but restricted to patients in the PAD. Exploratory analyses were carried out to examine the comparability of patients included in the PAD versus patients not included, as well as the comparability of patients who participated in CORE versus patients included in the PAD who did not participate in the study. For continuous measurements, the summary statistics included the number of patients with mean, median, standard deviation, and minimum and maximum values given for each group being compared. For categorical measurements, the summary statistics will include the total number of patients and the number of patients in each category for each group being compared. Each patient's 5-year risk of breast cancer (using the Gail method) and information on previous use of estrogens and bisphosphonates were assessed at Visit 1 of CORE.
In addition, use of bone-actives was assessed at annual visits throughout CORE, as was use of lipid lowering agents, hormones or SERMs, and nitrates for angina.

Treatment Compliance (9.7.1.9)

- By design, some patients in CORE did not actively take study drug (for example, they may have experienced an exclusionary adverse event during MORE).
- Noncompliance was not defined in the protocol and was not a factor in the primary analysis.

- For purposes of additional efficacy analyses, noncompliance with study medication was defined as follows: a patient was considered noncompliant if her overall percentage compliance throughout the trial was less than 80%. (Percentage compliance for a patient was defined as the number of pills dispensed minus the number of pills returned and then divided by the number of days from the first visit through the last visit. Some patients did not return their pills at the appropriate visit and may have brought them in to be counted at a later visit. Because some patients did not return pills until a later visit, by-visit compliance could not be reliably computed. Also, cumulative compliance through any visit prior to the last visit could not be reliably computed. However, because patients were assumed to have returned all remaining medication at the last visit, the cumulative compliance through the last visit was assumed reliable.)

- Patients who experienced breast cancer during CORE were instructed to stop study drug. Thus, study drug compliance during CORE for women diagnosed with breast cancer was computed as the total number of tablets taken divided by the number of days from Visit 1 through the date of breast cancer diagnosis.

Concomitant Therapy

- Although the primary objective in CORE pertains to breast cancer, the cohort was selected for MORE based on a history of osteoporosis. Therefore, concomitant treatment with specific bone-active agents including bisphosphonates, calcitonin, or fluoride was permitted during CORE.
- The use of specified concomitant medications was collected at Visit 1 and at each annual visit thereafter. The patient was asked if she had taken certain medications that may influence the efficacy or safety of raloxifene since her last visit (see Section 9.4.7 for details).

Efficacy Analyses (9.7.1.11)

Breast Cancer Analyses

The primary analysis considered the incidence of adjudicated, invasive breast cancers occurring after 1 January 1999 in women assigned to placebo compared with that in women assigned to raloxifene.

- A survival analysis was used in lieu of the protocol-specified primary analysis (Section 9.7.1.1 and Section 9.8.2).
- The log-rank test, equivalent to the score test in the Cox proportional hazards model with therapy as the only covariate was used to compare the two survival curves. A $100(1-\alpha)$ % confidence interval was computed for the relative hazard (hazard ratio).
- The same survival analysis replaced the protocol-specified analysis for the secondary endpoint of invasive ER (+) breast cancer.

Sensitivity Analyses

The sensitivity of the primary analysis to the choice of population and time period was explored:

- A sensitivity analysis using the Cox proportional hazards model was conducted on the primary outcome as the single term in the model by analyzing all patients in the PAD from their start of participation in CORE.
- Another sensitivity analysis was conducted using only patients who participated in CORE (that is, the CCD) beginning 1 January 1999 and excluding any patient who had a breast cancer prior to that date.
- A third sensitivity analysis was conducted using only patients who participated in CORE (that is, the CCD) from the start of their CORE participation through the last contact during the study (this excluded any patients who had a breast cancer prior to Visit 1 of CORE).
- A fourth sensitivity analysis was conducted on all patients randomized in MORE from the start of their participation in MORE through their final contact in either MORE or CORE.
- A final sensitivity analysis repeated the primary analysis on the investigator-reported breast cancer results, ignoring any adjudication, for patients who participated in CORE (that is, the CCD) from Visit 1 of CORE. This final sensitivity analysis determined the sensitivity of the primary analysis to the adjudication process.

Subgroup Analyses

Exploratory subgroup analyses used the Cox proportional hazards model on patients in the PAD without a breast cancer prior to 1 January 1999. The time period for each patient was from 1 January 1999 through the end of participation in MORE or CORE.

Potential subgroups are listed as follows:

- Region
- 5-year risk of breast cancer as assessed using Gail criteria at CORE baseline (5-year risk $\geq 1.67\%$ versus $< 1.67\%$);
- Baseline estradiol (<5.0 pmol/L versus ε5.0 pmol/L);
- Baseline age (both tertiles of baseline age and $\geq$ 60 years versus <60 years);
- Baseline bone mineral density (BMD) (tertiles of baseline BMD);
- Previous use of hormone replacement therapy;
- Family history of breast cancer;
- Patients taking a specific proportion of assigned study medication (for example, 80% compliance with assigned study medication).

For subgroups defined by baseline demographics, baseline data from MORE was used.

Secondary Analysis

As a secondary analysis of the primary endpoint, the protocol-specified analysis was performed. This analysis compared incidence ratios of invasive breast cancer using Mantel-Haenzsel techniques for a statistical test and to compute a 95%, large-sample, test-based confidence interval. The incidence rates were compared using an exact 95% confidence interval for relative rates. The denominator for the analyses of invasive breast cancer included woman-years for

women in the PAD population who did not experience breast cancer prior to 1 January 1999. The total woman-years were computed as the time from 1 January 1999 until either the woman discontinued from MORE (for women at CORE investigative sites who did not participate in CORE [the MOPCID population]) or from CORE (for women who participated in CORE [the CCD population]). An additional analysis of invasive ER (+) breast cancer was also conducted in this manner.

Nonvertebral Fracture Analyses

A secondary objective of the study was to test whether raloxifene would reduce the incidence of nonvertebral fractures in postmenopausal women with osteoporosis over a long-term period of observation. The period of interest for this objective began with the patient's randomization in MORE.

Two patient populations were analyzed for osteoporotic nonvertebral fractures:
1) All patients enrolled in Study GGJY (the CCD), and
2) All patients in the protocol-specified PAD population

Two nonvertebral endpoints were considered for each of the two populations.

- The **primary nonvertebral endpoint** included osteoporotic nonvertebral fractures of the *clavicle, scapula, ribs, sacrum, humerus, forearm, wrist, carpus, pelvis, hip, femur, lower leg, patella, ankle, calcaneus, tarsus, metatarsus, sternum,* and *coccyx* (hereafter referred to as "any" nonvertebral fractures).
- The **secondary nonvertebral fracture endpoint** was performed on **a subgroup** including osteoporotic nonvertebral fractures of the *clavicle, humerus, wrist, pelvis, hip,* and *leg* (hereafter referred to as the "nonvertebral-six").

The nonvertebral fractures included in each of the two endpoints were analyzed collectively for each of the two populations. In addition, in the population of women who participated in CORE (the CCD) each of the fracture sites included in the nonvertebral-six was analyzed separately. A multiple comparisons procedure was used to simultaneously estimate the response at these six sites. All nonvertebral fractures reported between randomization in MORE and the end of CORE were considered.

- For the **primary nonvertebral endpoint** of any nonvertebral fracture, time to first nonvertebral fracture from any included site was analyzed.
- For the **secondary nonvertebral endpoint**, the nonvertebral-six was analyzed.

The survival analysis method was used to analyze nonvertebral fractures:

- Kaplan-Meier curves were generated for any nonvertebral fracture and the nonvertebral-six, and the placebo and raloxifene groups were compared using a log-rank test.
- A Cox proportional hazards regression model was used to estimate relative hazard and 95% confidence interval for the raloxifene group compared with placebo on the basis of time to first nonvertebral fracture. When a baseline imbalance between treatment groups was observed for baseline covariates, a Cox proportional hazards regression analysis was performed. Treatment and the imbalanced baseline covariates were included in the model.

Subset Analyses of Nonvertebral Fractures

The following three subsets of the population of women who participated in CORE (the CCD) were considered:
1) Patients who did not use other bone-active agents after the 3rd year of MORE;
2) Patients who took at least one dose of study drug during CORE;
3) Patients who did not use other bone-active agents after the 3rd year of MORE and who took at least one dose of study drug during CORE.

All subset analyses were conducted for any nonvertebral fracture and for the nonvertebral-six.

Subgroup Analyses of Nonvertebral Fractures

Exploratory subgroup analyses using the following subgroup variables were performed for any nonvertebral fracture and for the nonvertebral-six in the population of women who participated in CORE (the CCD):

- Age tertiles at MORE baseline;
- BMD tertiles at MORE baseline;
- Semi-quantitative visual assessment status (SQ) of vertebral fractures at MORE baseline (SQ3 Versus SQ0, SQ1, and SQ2);
- Prevalent vertebral fracture status at MORE baseline (yes versus no);
- Prevalent nonvertebral fracture at MORE baseline (yes versus no);
- Treatment compliance (80% compliance, yes versus no).

Other subgroup analyses may also have been performed. Interaction between subgroup and treatment was tested at the 10% level of significance.

Safety Analyses (9.7.1.12)

All reported serious adverse events (SAEs) were summarized and analyzed. Primary safety analyses were performed for patients who participated in CORE (the CCD).
In addition, the analysis of specific events that were analyzed in MORE (uterine cancer, ovarian cancer, venous thromboembolism [VTE], and mortality) was analyzed for patients who participated in CORE (that is, construction of an exact 95% confidence interval of the risk ratio).
1) An analysis was performed to assess treatment-emergent adverse events (TEAEs) for patients enrolled in CORE. This analysis considered the highest severity before entry into CORE as the baseline severity and compared the proportion of new or worsening events (since enrollment in CORE) across treatment groups.
2) An analysis was performed to assess serious TEAEs for patients enrolled in CORE from baseline in MORE through the end of CORE (that is, 0 through 8 years).
3) An analysis was performed on adverse events from randomization in MORE (usually Visit 2 of MORE) through the end of CORE.

Interim Analyses and Data Monitoring (9.7.1.13)

- Only the data monitoring board was authorized to review completely unblinded interim efficacy and safety analyses and to disseminate those results. The role of the data monitoring board was to disseminate interim results in a manner that minimized bias.
- Investigators did not receive interim analysis information specific to their site.
- One planned interim analysis occurred after all participants had their 6-year visit and after sufficient time (approximately 3 months) had been allowed for the follow-up of suspicious mammograms. All cases reported from 1 January 1999 to the data cutoff date were included in the interim analysis. The denominator for the interim analysis was the same as for the final analysis of invasive breast cancer (primary objective). The interim analysis used ≤ 0.001 as the level of significance. Results from the interim analysis did not meet the predefined stopping criteria for outstanding efficacy (participants assigned to raloxifene did not have a statistically significantly reduced incidence of invasive breast cancer [$p<0.001$]). The data monitoring board recommended the study continue as planned, with the exception that the observation period for patients in the PAD who did not enroll in CORE be changed to 1 January 1999 until the time of final follow-up contact in MORE (Section 9.8.2.1). The final analysis took place after the 8th year of follow-up, with ≤ 0.0495 as the level of significance.
- Members of the data monitoring board, including Lilly employees who served on the board, were unblinded at the time of the interim analysis. Any Lilly employee on the data monitoring board who was also a study team member was replaced. In particular, the lead statistician was replaced prior to the development of the statistical analysis plan of CORE and only Lilly employees who remain blinded to CORE data were responsible for the development of the statistical analysis plan of final CORE data.

Determination of Sample Size (9.7.2)

Study GGJY (CORE) was designed to provide follow-up data for as many women as possible who were enrolled in Study GGGK (MORE). Power calculations were performed using various permutations of assumptions regarding the number of protocol completers, the relative risk of invasive breast cancer in raloxifene patients, and the true annual placebo rate of invasive breast cancer.

It was estimated that a minimum of 2610 patients were needed to complete the study. This calculation assumed a true relative risk of invasive breast cancer of 0.24 in patients assigned to study medication, and that 3000 patients would enroll in the study, with 390 patients not on study medication.

Changes in the Conduct of the Study or Planned Analyses (9.8)

Changes in the Conduct of the Study

- No changes to the conduct of the study were made.

Changes in the Planned Analyses (9.8.2)

A significant change to the primary analysis was submitted to a regulatory agency in a letter dated 23 March 2001. The change was approved by the regulatory agency as indicated in a fax to the sponsor dated 17 July 2001. Also, a minor change from the statistical analysis plan (SAP) reflecting the data monitoring board's recommendation emerging from the interim analysis has been implemented in this report.

Changes in Period of Observation for Primary Efficacy Endpoints (9.8.2.1)

For patients who enrolled in CORE, the period of observation for invasive breast cancer was defined as 1 January 1999 until time to discontinuation from the study.
However, for patients in the PAD who did not enroll in CORE, the end of the period of observation was changed to the time of unblinding or the last contact during MORE.

- These recommendations were implemented by making the period of observation for women in the PAD who did not participate in CORE (the MOPCID population) 1 January 1999 until final MORE follow-up contact. This change was described in a letter to the regulatory agency dated 23 March 2001 with a faxed response dated 17 July 2001.
- The change was intended to reflect the vastly unequal follow-up between the two patient groups in the PAD (those patients who participated in CORE [the CCD population] versus those patients at CORE investigative sites who did not participate [the MOPCID population]). Later, the data monitoring board recommended that once a woman had refused to participate in CORE, no data regarding her obtained thereafter, by any means, should be used in any CORE analysis because she did not consent to participate in CORE.

Changes in Primary Efficacy Analysis (9.8.2.2)

The **primary objective** of this study was to test whether a statistically significant **reduction in the incidence of invasive breast cancer** would occur in postmenopausal women with osteoporosis, treated with raloxifene HCl 60 mg/day compared with placebo, over a long period of observation. The primary objective considered all invasive breast cancer cases diagnosed on or after 1 January 1999. The protocol specified a comparison of breast cancer incidence rates using a 100(1-α) % confidence interval for **relative risk**. By design, women in the PAD were followed for vastly unequal time periods dependent upon their participation status in CORE.

- A more appropriate methodology, given the unequal periods of observation, is **survival analysis**, which was used in place of the protocol-specified primary analysis.
- The **log-rank test**, equivalent to the score test in the Cox proportional hazards model with therapy as the only covariate, 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).
- Finally, implementation of **Cox proportional hazards** analysis became available since the protocol was originally written. This analysis method allowed inclusion of covariates in addition to therapy.

- Additional analyses of breast cancer not prespecified in the statistical analysis plan (SAP) were conducted on all patients who participated in MORE. The period of observation was the beginning of MORE through the end of CORE.

Changes in Secondary Efficacy Analyses (9.8.2.3)

A secondary objective of this study was to test whether a statistically significant reduction in the incidence of **invasive *ER* + breast cancer** would occur in postmenopausal women with osteoporosis treated with raloxifene HCl 60 mg/day compared with placebo over a long-term period of observation.

- The change from categorical analysis to survival analysis and from relative risk to relative hazard was implemented in the same manner as for the primary endpoint.

An additional secondary objective of this study was to test whether raloxifene, compared with placebo, reduced the **incidence of nonvertebral fractures** from the time of randomization in MORE through the end of CORE in postmenopausal women with osteoporosis.

- The **population** for main analysis was changed from all patients in the PAD, which is relevant only to the breast cancer endpoint, to only patients who enrolled in CORE (the CCD population).
- The **analysis method** was changed to a survival (time-to-event) analysis. The original population of all patients in the PAD was run as an additional analysis as was the population of all patients randomized in to MORE. Confidence intervals using a Bonferroni adjustment were added based on consideration of multiplicity for analyses of different location fractures.

Several **potential confounders** were taken into consideration when evaluating the efficacy of raloxifene on nonvertebral fractures. There may have been a difference in severity of vertebral fractures in patients who chose to participate in CORE, thus vertebral SQ score at the end of MORE was evaluated as a confounder. Furthermore, patients were permitted to use other bone-active agents after completion of the 3rd year of MORE and use could continue throughout CORE. It would be expected that more placebo-treated patients would use a bone-active drug than raloxifene-treated patients.
Finally, the presence of an osteoporosis-related fracture like vertebral fractures puts a patient at increased risk of any additional osteoporosis-related fracture, including nonvertebral fractures. The occurrence of at least one new vertebral fracture during MORE could be a possible confounder to the efficacy results of raloxifene on nonvertebral fractures.
The original proposed method to evaluate the efficacy of raloxifene on nonvertebral fractures and nonvertebral-six fractures over the duration of MORE and CORE for the patients enrolled in CORE was to use survival analysis to compare the cumulative incidence of nonvertebral fractures and nonvertebral-six fractures between the raloxifene group and placebo group on the basis of time to first nonvertebral fracture event. During the period from randomization into Study GGGK through termination of CORE (over 8 years), many patients may have developed more than one nonvertebral fracture. Therefore, whether the rate of occurrence of nonvertebral fracture events per patient during the total follow up period was different between treatments was tested. Post hoc Poisson analysis comparing the incidence rate of nonvertebral fractures in the

raloxifene group and placebo group using all nonvertebral fracture events occurring from randomization into MORE through study termination of CORE was conducted for patients enrolled in CORE (CCD population), the PAD population, and for all patients enrolled in MORE. Furthermore, Poisson analyses were conducted for the subgroups based on SQ score and on prevalent vertebral fractures at MORE baseline for each of the populations.

Changes in Safety Analyses (9.8.2.4)

The **population studied** for all safety analyses was changed from patients in the PAD to patients enrolled in CORE (the CCD population). This is in agreement with recommendations from the data monitoring board and correspondence with a regulatory agency.
Categorical data were analyzed:

- Using Pearson's chi-square test when the number of events across all treatment groups was at least 10,
- Fisher's Exact test when the number of events across all treatment groups was between five and nine.

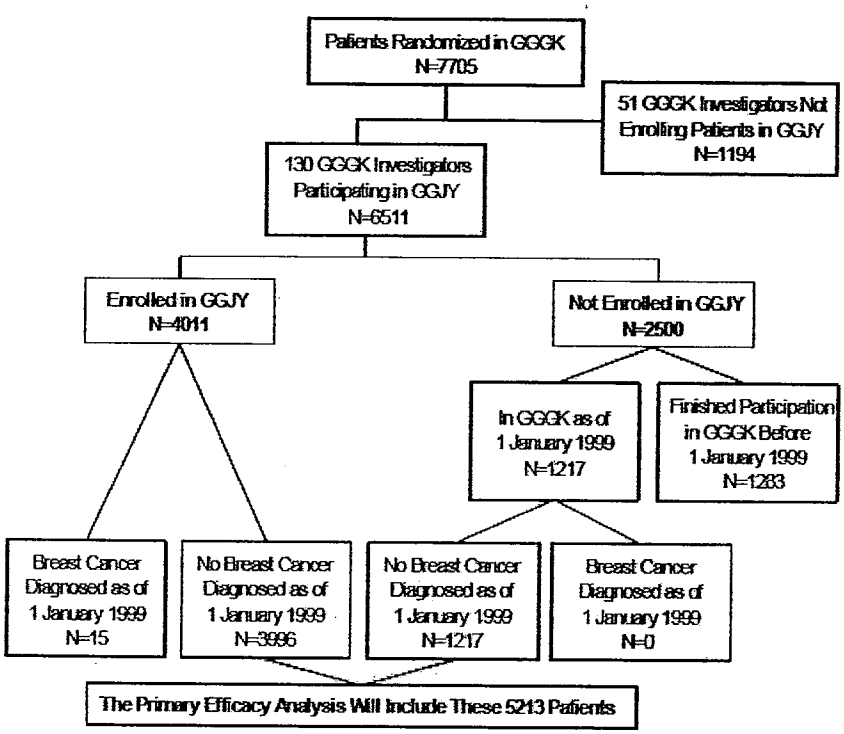
Statistical inference was not performed when fewer than five events occur. When computational resources permitted, all testing of incidence rates for adverse events was done using Fisher's Exact test.

In the protocol, three analyses were pre-specified to assess treatment-emergent adverse events (TEAEs):
1) An analysis considering the highest severity before entry into CORE as the baseline severity and comparing the proportion of new or worsening events (since enrollment in CORE) across treatment groups,
2) An analysis considering the highest severity before entry into MORE as the baseline severity and comparing the proportion of new events (since enrollment in CORE) across treatment groups, and
3) An analysis of all TEAEs from baseline in MORE through the end of CORE (that is, 0 through 8 years).
Events that started in MORE were not followed systematically into CORE for changes in severity or for end dates. However, a computer program was developed to link the databases from the two studies to allow for analysis of TEAEs. Analyses of both TEAEs and adverse events from baseline in MORE through the end of CORE are provided in this report. The analysis of the TEAEs was made possible by the computer program combining data from the two databases and the analysis of all AEs (3 above) was specified in the SAP. The second analysis was not possible and therefore omitted from the SAP and this study report because it was decided by the sponsor that the data would not be meaningful due to the large period of time between MORE baseline and CORE. Instead, an analysis was performed to assess serious TEAEs for patients enrolled in CORE from baseline in MORE through the end of CORE (that is, 0 through 8 years).
Additional analyses of several cardiovascular events were also performed.

Study Patients (10)

10.1. Disposition of Patients

All patients randomly assigned into MORE were eligible for enrollment into CORE if their investigator elected to participate in CORE. The figure below illustrates the succession of patients from MORE into CORE.
Sixty-three percent of eligible patients in MORE (n = 6511) elected to enroll into CORE (n = 4011).



Abbreviations: GGGK = Study H3S-MC-GGGK; GGJY = Study H3S-MC-GGJY; N=Number of patients

Figure GGJY.10.1. Patient succession from Study GGGK into Study GGJY.

The primary analysis dataset (PAD) for CORE breast cancer analyses is comprised of all MORE patients who were at investigative sites that participated in CORE. To reduce bias, data from all women at CORE sites, regardless of whether they enrolled in CORE, are included in the PAD. Patients in the PAD diagnosed with invasive breast cancer before 1 January 1999 (15 patients enrolled in CORE) are excluded from the primary analysis, which considers the time to first invasive breast cancer after this date. Thus, the primary analysis includes 5213 patients, 3996 (77%) of who enrolled in CORE.

Comparability of Patient Populations (10.1.1)

The baseline differences between PAD patients and the non-PAD patients (MORE-Only Investigators Dataset [MOID]) and the differences between PAD patients who enrolled in CORE (Continuing in CORE Dataset [CCD]) versus PAD patients who did not enroll in CORE (MORE-Only Patients of CORE Investigators Dataset [MOPCID] dataset) are examined in this study report. Because CORE was an extended follow-up of patients previously enrolled in MORE, the baseline characteristics described in this section refer to baseline of MORE.

Table GGJY.14.2, Table GGJY.14.3, Table GGJY.14.4, and Table GGJY.14.5 summarize the comparisons of PAD patients versus non-PAD patients, as well as therapy group comparisons within the PAD. Table GGJY.14.6, Table GGJY.14.7, Table GGJY.14.8, and Table GGJY.14.9 summarize the comparisons of PAD patients enrolled in Study GGJY versus PAD patients not enrolled in Study GGJY, as well as therapy group comparisons within the population of PAD patients who enrolled in Study GGJY.
Frequencies are analyzed using a chi-square test. Means are analyzed using a two-sample t-test.

PAD versus Non-PAD Patients (10.1.1.1)

Baseline characteristics were similar between the placebo-treated and raloxifene HCl treated patients in CORE who were included in the PAD. However, there were differences at baseline between PAD patients and non-PAD patients. Raloxifene-treated patients in the PAD tended to be slightly older and more were smokers than raloxifene treated patients not in the PAD. Furthermore, fewer raloxifene patients in the PAD used alcohol, had family history of breast cancer, had a hysterectomy, or previously used hormone replacement therapy (HRT) than raloxifene-treated patients not in the PAD.
Placebo-treated patients in the PAD tended to be slightly older and had a greater body mass index (BMI) than placebo-treated patients not in the PAD. Also, fewer placebo patients in the PAD used alcohol, had a family history of breast cancer, or previously used hormone replacement therapy compared with placebo patients not in the PAD.

GGJY Participants versus Non-Participants in PAD (10.1.1.2)

Baseline differences were also present between the population of PAD patients who participated in Study GGJY versus those PAD patients who did not participate. Compared with PAD patients who did not enroll in CORE, PAD patients who participated in the study tended to be younger and fewer years postmenopausal.
Additionally, CORE participants were less likely to be smokers, have undergone hysterectomy, or have received previous hormone replacement therapy compared with non-participating patients. These results were fairly consistent within the raloxifene treated and placebo-treated groups of patients who participated in CORE compared with those patients who chose not to participate in CORE.

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Patient Disposition (10.1.2)

The figure below is an overview of patient disposition for all enrolled patients in CORE.

- 86% patients in each treatment group completed the protocol and only 14% in each group discontinued the study.

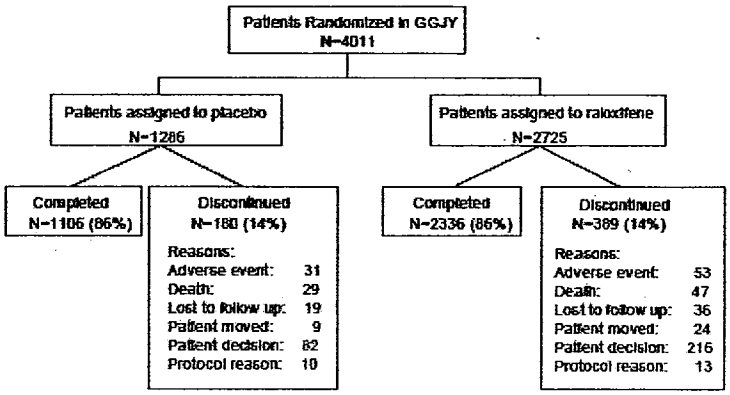

Figure GGJY.10.2. Patient disposition.

Source is RMP.HESP.SASMACRO (RDS1A) PS002 000

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Discontinuation of All Patients Enrolled in CORE

During CORE, 569 (14.2%) of the 4,011 enrolled patients discontinued the study:

- 180 patients (14.0%) in the placebo group
- 389 patients (14.3%) in the raloxifene group

The number of patients who completed the protocol was similar between the treatment groups and no differences were observed in individual reasons for discontinuation (for example, adverse event, patient decision, death, etc.) between the two treatment groups.

Table GGJY.10.1. Reasons for Discontinuation (Comparison of Treatment Groups, All Patients Enrolled in CORE)

Primary Reason for Discontinuation	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Protocol completed	1104 (85.8)	2331 (85.5)	3435 (85.6)	.796
Patient completed the protocol, but had an adverse event	2 (0.2)	5 (0.2)	7 (0.2)	.843
Adverse event	31 (2.4)	53 (1.9)	84 (2.1)	.336
Death	29 (2.3)	47 (1.7)	76 (1.9)	.250
Unable to contact patient (lost to follow-up)	19 (1.5)	36 (1.3)	55 (1.4)	.691
Patient moved	9 (0.7)	24 (0.9)	33 (0.8)	.554
Personal conflict or other patient decision	82 (6.4)	216 (7.9)	298 (7.4)	.081
Protocol entry criteria not met	3 (0.2)	4 (0.1)	7 (0.2)	.540
Protocol variance	7 (0.5)	9 (0.3)	16 (0.4)	.316

SOURCE IS RMP.H3SP.SASMACRO(RDS1A) PS002 000
DATA FROM RMP.SAS.H3SM.MCGGJY8C.FINAL
* Frequencies are analyzed using a Chi-Square test.
XRDS0001

Reasons for discontinuation were also summarized by country and by visit:

- There was no unusual distribution of reasons for discontinuation by country
- Reasons for discontinuation were fairly well balanced across the visits

More patients discontinued the study due to personal conflict or patient decision after Visit 2 than at Visit 2 for both treatment groups.

Protocol Violations (10.2)

A summary of protocol violations is presented in this section. Clinically relevant protocol violations:

- Missed breast examinations or mammograms;
- Patients not meeting inclusion/exclusion criteria;
- Patients continuing in the study when criteria to discontinue the study were met;
- Patients not signing and dating the original and the updated informed consent document (ICD);
- Patients with a study visit outside the visit window by 45 days for Visit 3 and/or Visit 5; patients taking an expired drug, incorrect drug, or exceeded the study drug dosage; Patients having serious adverse events not reported in a timely manner;
- Other site, sponsor, or investigator issues.

It is unlikely that these violations affected the conclusions and inferences indicated in this report.

Patients Missing Breast Exams or Mammograms

Patients were considered missing a breast exam or mammogram if the procedures were not performed at the study visit or reported with the clinical trial data for Visit 1, Visit 3, and Visit 5.

- There were 109 patients with missing breast exams or mammograms (40 in the placebo group, 69 in the raloxifene HCl 60-mg group).
- Patients who missed the breast exams or mammograms due to early termination from the study were not included in this group of protocol violations.

Discontinuation from Study Violation

Patients who continued in CORE after enrolling in another study violated the protocol.

- Four patients enrolled in another study while also enrolled in CORE. All of these patients were in the raloxifene group. One patient discontinued from the other study; 2 patients were discontinued from CORE; and 1 patient completed CORE while she was enrolled in the other study because the site was not aware of the situation until the final visit.

ICD Not Administered Properly

Patients who did not sign and date the appropriate ICD were included in this category.

- There were a total of 136 violations related to the ICD, (78 raloxifene, 51 placebo, 3 patients' treatment not known [patient numbers not recorded by investigative site], and 4 site-related violations).
- Most violations revolved around updated ICDs.
- Many patients had their bone mineral density (BMD) or deoxyribonucleic acid (DNA) lab draws without signing the updated ICD before the procedure, although most subsequently signed the ICD at a later date.

Incorrect Study Drug or Dose

There were a total of 37 violations (21 raloxifene, 15 placebo, and 1 case of treatment group not identified [patient number not recorded by investigative site]):

- Patients taking study drug when there was a contraindication (eg, deep vein thrombosis: 7 patients)
- Taking the incorrect treatment (6 patients)
- Patients exceeding the dose of study drug (11 patients)
- Patients taking expired study drug (10 patients)

Out of Visit Window

Patients were considered to be within the allowable visit window for Visit 3 and Visit 5 if the visit was conducted within the 30 days prior to the 6- and 8-year anniversary of the MORE patient randomization date. Violations for these visits are reported because the mammograms were performed at these visits. Any visits that did not occur within this period of time and exceeded 45 days were considered significant protocol violations.

- There were 285 such violations, (98 in the placebo group and 187 in the raloxifene HCl group).

10.2.6. Serious Adverse Events

Not reporting serious adverse events within the time period specified within the protocol was considered a protocol violation.

- There were 73 violations in this category: 19 placebo patients, 50 raloxifene HCl patients and 4 patients whose treatment group was not identified (patient number was not recorded by the investigative site).

Other

Protocol violations in the "Other" category included legibility, appropriateness and availability of source documents, documentation of training of site personnel, availability of documentation of ethical review board (ERB) renewal of study, and documentation of investigator's involvement.

- There were a total of 24 violations, 12 patient specific violations (6 placebo patients and 6 raloxifene HCl patients) and 12 site-related issues.

Table GGJY.10.2. Summary of Significant Protocol Violations (Patient Numbers by Investigative Site, All Patients Enrolled in CORE)

Site	Inclusion/ Exclusion Criteria	Original and Updated ICD Not Administered Properly	Study Assessments Not Done	Incorrect Drug or Dose	Visit Interval Exceeded	SAEs Not Reported Timely	Other (ERB, Training, Source Documents, Excluded Concomitant Medications, etc.)
3					3		
6			1		6		
8		2			2		
32		9	1	2	5		
38					5		
41		5		1	1		
42					2		
44					1		
45				2			
46		3					
47					2		
48		1			1		
52					3		
53			1		5		
55		3	1		4		
56			1		6		1
58					2		
60					1		
61					4		
64			2	1	3		
66			1		1		
67					3	1	
68		3					
70		1			1		
71		5			9		
72			2	1	2		
73		4			11		
75				1	5		
77		1		2	11		4
78					1	1	
81					3		
83		13			2		
85					5		
88		1			2		
89			2		1		5
91						1	
141		2			3		
142					1		
143			1	1	1		
145					1	2	
146					1		
147					2		
148				1	2	2	

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Site	Inclusion/ Exclusion Criteria	Original and Updated ICD Not Administered Properly	Study Assessments Not Done	Incorrect Drug or Dose	Visit Interval Exceeded	SAEs Not Reported Timely	Other (ERB, Training, Source Documents, Excluded Concomitant Medications, etc.)
151					2		
153			3		7	2	
154			1				
155						3	
200		4		2	1	1	
202	1		2	3	2		1
204				1	2	4	2
205		1			1		
207		23	2	1	3		
243					2		
244		13	8		10	1	
245			3		5		
281		1		6	3	1	
282		1		6	16		
291		3			1	1	
292					2		
300							1
303			1				
304							
305		1				1	
308		1	1		2	1	
310							1
502			5				
504			1				
506			1				
510			4				
511			2			1	
603						2	1
604		1	1		6	2	1
605			1				
606						1	
607		2	2		2		
700	1	2	2		6	8	
701		8					
702	1						
721				2		1	
722			10			3	1
723						3	
724						1	
725					1	1	
742		6	23	2	41	13	
743		1	1		2		
744		2				8	
753					1		

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Site	Inclusion/ Exclusion Criteria	Original and Updated ICD Not Administered Properly	Study Assessments Not Done	Incorrect Drug or Dose	Visit Interval Exceeded	SAEs Not Reported Timely	Other (ERB, Training, Source Documents, Excluded Concomitant Medications, etc.)
800							1
802					1		1
803			4				
804		1			1		
805		2		1	1	1	
807		1	1			1	
808			1		3		
850			2		4		
851					1		
852					1		
853			1				
855					1		
858							1
859							
860	1				3		
864					1		1
865					5		
866					2		
867		10	10		8		2
961					2	2	
963					2		
964			1		4		
966			1	1	1	1	
968					1	1	
993			1		1	1	
Total	4	136	109	37	285	73	24

Abbreviations: ERB = ethical review board, ICD = informed consent document, SAEs = serious adverse events.

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Efficacy Evaluation (11)

Data Sets Analyzed (11.1)

Primary and secondary analyses were performed on an intention-to-treat (ITT) basis.

- For the **primary efficacy analysis** of **invasive breast cancer** and the **secondary efficacy analysis** of **invasive *ER* + breast cancer**, all patients in the **primary analysis dataset** (**PAD** population) were included.
- For the **secondary efficacy analysis** of nonvertebral fractures, patients who participated in CORE (the Continuing in CORE Dataset [**CCD**] population) were included in analyses, but the period of analysis includes the duration of both MORE and CORE, or approximately 8 years.

- An interim analysis was conducted on 3 December 2001 under the auspices of a data monitoring board according to the specifications set forth in the protocol.
- On 30 September 2003, the final reporting database was validated and locked.
- The adjudicated breast cancer database was locked on 25 November 2003.

Appendix 16.2.4 contains a list of patients and observations excluded from the breast cancer efficacy analyses due to a breast cancer diagnosis before 1 January 1999.

- 46 patients in the PAD were excluded from the breast cancer efficacy analyses due to a breast cancer diagnosis before 1 January 1999.
- 15 excluded patients were enrolled in CORE
- 31 excluded patients were in MORE who did not participate in CORE.

Thus, of the 6511 patients in the primary analysis dataset, 5213 patients contributed data after 1 January 1999 and had not been diagnosed with breast cancer at that time. The primary breast cancer analysis includes these 5213 patients, 3996 of whom enrolled in CORE.

Demographic and Other Baseline Characteristics (11.2)

The demographics of the following populations are presented below:

- The demographics at CORE baseline of all patients who enrolled in CORE (CCD population);
- The demographics at MORE baseline of all patients who enrolled in CORE;
  - Comparison of demographics at MORE baseline of patients who enrolled in CORE with those who did not enroll in CORE;
- The demographics at MORE baseline of all patients included in the PAD population (patients whose investigator enrolled patients in CORE, including patients at that site who did not enroll in CORE);

- Comparison of the demographics at MORE baseline of all patients included in the PAD population with those not included in the PAD population.

The two treatment groups in CORE (CCD population) were well balanced with no significant differences indicative of breast cancer risk between the groups, however there were differences in osteoporosis severity and in cardiovascular risk.

- The mean baseline 5-year predicted risk of breast cancer score for patients was 1.94% in both CORE treatment groups, which is considered an elevated risk for breast cancer according to the Gail model (a 5-year predicted risk of breast cancer > 1.67 was considered at elevated risk according to the Gail model).

Comparison of MORE baseline characteristics of patients who subsequently enrolled in CORE (4011 patients) with those of patients who did not enroll in CORE (3694 patients) showed several differences.

- Patients who enrolled in CORE tended to be younger, fewer years postmenopausal, had less severe osteoporosis and fewer used cardiovascular disease-related therapies than patients who did not enroll in CORE. However, there was a similar family history of breast cancer (mother, daughter or sister) in the two patient populations.

The treatment groups within the PAD population were well balanced. The patients included in the PAD population tended to be older, more years postmenopausal, less representative of North America, more smoked, consumed less alcohol, fewer had a family history of breast cancer, fewer had undergone hysterectomy, and fewer had prior use of HRT than patients not in the PAD population.

All Patients Enrolled in Study GGJY at Start of Study GGJY (11.2.1)

The following table summarizes the baseline characteristics for all patients in CORE at the baseline.

- The two treatment groups in CORE were well balanced with respect to breast cancer risk.
- Most of the patients were from North America or Europe.
- The median age of the patients was 71 years
- 22% of the patients had undergone a hysterectomy.

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Table GGJY.11.1. Patient Demographics at the Start of CORE (All Patients Enrolled in CORE)

Variable	PLACEBO (N=1286)	RLX060 (N=2725)	Total (N=4011)	p-Value
ORIGIN				
No. Patients	1286	2725	4011	.060*
African Descent	1 (0.1)	2 (0.1)	3 (0.1)	
Western Asian	4 (0.3)	1 (0.0)	5 (0.1)	
Caucasian	1235 (96.0)	2622 (96.2)	3857 (96.2)	
East/Southeast A	26 (2.0)	39 (1.4)	65 (1.6)	
Hispanic	19 (1.5)	51 (1.9)	70 (1.7)	
Other	1 (0.1)	10 (0.4)	11 (0.3)	
AGE: (yrs)				
No. Patients	1286	2725	4011	.441**
Mean	70.91	70.73	70.79	
Median	71.01	70.95	70.97	
Standard Dev.	6.72	6.76	6.75	
Minimum	40.90	49.85	40.90	
Maximum	86.00	85.95	86.00	
HEIGHT: (cm) (VISIT: 1)				
No. Patients	1271	2708	3979	.962**
Mean	158.26	158.25	158.25	
Median	158.10	158.40	158.20	
Standard Dev.	6.66	6.68	6.67	
Minimum	138.00	137.50	137.50	
Maximum	177.40	190.90	190.90	
Unspecified	15	17	32	
SOURCE IS RMP.H3SP.SASMACRO(DESM1) DE005 000				
WEIGHT: (kg) (VISIT: 1)				
No. Patients	1273	2710	3983	.408**
Mean	63.95	64.24	64.15	
Median	63.00	63.11	63.11	
Standard Dev.	10.61	10.55	10.57	
Minimum	29.74	34.50	29.74	
Maximum	108.40	132.00	132.00	
Unspecified	13	15	28	
BMI: (kg/m2) (VISIT: 1)				
No. Patients	1268	2707	3975	.357**
Mean	25.54	25.67	25.63	
Median	25.10	25.39	25.24	
Standard Dev.	4.10	4.04	4.06	
Minimum	14.52	15.13	14.52	
Maximum	44.29	50.42	50.42	
Unspecified	18	18	36	

SOURCE IS RMP.H3SP.SASMACRO(DESM1) DE005 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
* Frequencies are analyzed using a Chi-Square test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
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Variable	PLACEBO (N=1286)	RLX060 (N=2725)	Total (N=4011)	p-Value
COUNTRY (VISIT: 1)				
No. Patients	1286	2725	4011	1.00*
Argentina	95 (7.4)	200 (7.3)	295 (7.4)	
Austria	3 (0.2)	9 (0.3)	12 (0.3)	
Australia	43 (3.3)	94 (3.4)	137 (3.4)	
Belgium	36 (2.8)	81 (3.0)	117 (2.9)	
Canada	78 (6.1)	162 (5.9)	240 (6.0)	
Czech Republic	12 (0.9)	29 (1.1)	41 (1.0)	
Denmark	59 (4.6)	119 (4.4)	178 (4.4)	
Spain	36 (2.8)	70 (2.6)	106 (2.6)	
Finland	30 (2.3)	71 (2.6)	101 (2.5)	
France	7 (0.5)	21 (0.8)	28 (0.7)	
United Kingdom	40 (3.1)	77 (2.8)	117 (2.9)	
Hungary	21 (1.6)	61 (2.2)	82 (2.0)	
Israel	15 (1.2)	28 (1.0)	43 (1.1)	
Italy	40 (3.1)	90 (3.3)	130 (3.2)	
Mexico	17 (1.3)	40 (1.5)	57 (1.4)	
The Netherlands	59 (4.6)	135 (5.0)	194 (4.8)	
Norway	198 (15.4)	396 (14.5)	594 (14.8)	
New Zealand	20 (1.6)	32 (1.2)	52 (1.3)	
Poland	40 (3.1)	91 (3.3)	131 (3.3)	
Sweden	20 (1.6)	48 (1.8)	68 (1.7)	
Singapore	10 (0.8)	18 (0.7)	28 (0.7)	
Slovenia	7 (0.5)	18 (0.7)	25 (0.6)	
Slovakia	5 (0.4)	10 (0.4)	15 (0.4)	
United States	395 (30.7)	825 (30.3)	1220 (30.4)	
SOURCE IS RMP.H3SP.SASMACRO(DESM1) DE005 000				
HYSTERECTOMY (VISIT: 1)				
No. Patients	1286	2725	4011	.956*
Yes	278 (21.6)	587 (21.5)	865 (21.6)	
No	1008 (78.4)	2138 (78.5)	3146 (78.4)	
TYPE OF HYSTERECTOMY (VISIT: 1)				
No. Patients	1286	2725	4011	.756*
Uterus/1 ovary	138 (49.6)	295 (50.3)	433 (50.1)	
Uterus/2 ovaries	123 (44.2)	249 (42.4)	372 (43.0)	
Unknown	17 (6.1)	43 (7.3)	60 (6.9)	
Unspecified	1008	2138	3146	

SOURCE IS RMP.H3SP.SASMACRO(DESM1) DE005 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
* Frequencies are analyzed using a Chi-Square test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
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Treatment group comparisons were performed for the 5-year predicted risk of breast cancer (using the Gail model) at baseline in CORE. The Gail model is based on these historical factors:

- Age at menarche
- Age of first live birth
- First degree relatives with breast cancer
- Number of breast biopsies
- Any biopsy with atypical hyperplasia

Women with a 5-year predicted risk of breast cancer ≥ 1.67% are considered to be at high risk for developing breast cancer.

The 5-year predicted risk of breast cancer for patients in CORE ranged from 0.4 to 13.1 at baseline with the mean score of 1.94% for each of the two treatment groups:

- Overall, 54% of the patients had an elevated 5-year predicted risk of breast cancer according to the Gail model (53% for placebo patients and 54% for raloxifene patients). Thus, the treatment groups were well matched and had, on average, an elevated risk for breast cancer according to the Gail model.
- There was no statistical difference between the groups for each of the parameters measured in the Gail model.

Table GGJY.11.2. CORE Baseline Breast Cancer Risk Assessment (All Patients Enrolled in CORE)

Variable	PLACEBO (N=1286)	RLX060 (N=2725)	Total (N=4011)	p-Value
CORE Gail Score (VISIT: 1)				
No. Patients	1286	2725	4011	.903**
Mean	1.94	1.94	1.94	
Median	1.70	1.70	1.70	
Standard Dev.	0.93	0.98	0.96	
Minimum	0.40	0.70	0.40	
Maximum	11.10	13.10	13.10	
Age at Menarche (VISIT: 1)				
No. Patients	1286	2725	4011	.522*
6 - <12	145 (11.3)	313 (11.5)	458 (11.4)	
12 - <14	575 (44.7)	1166 (42.9)	1741 (43.5)	
14 - <99	565 (44.0)	1242 (45.6)	1807 (45.1)	
Unspecified	1	4	5	
Age at Menarche (VISIT: 1)				
No. Patients	1285	2721	4006	.631**
Mean	13.35	13.38	13.37	
Median	13.00	13.00	13.00	
Standard Dev.	1.56	1.63	1.61	
Minimum	9.00	8.00	8.00	
Maximum	19.00	19.00	19.00	
Unspecified	1	4	5	

SOURCE IS RMP.H3SP.SASMACRO(DESM1) DEC04 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
* Frequencies are analyzed using a Chi-Square test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
*** Chi-Square test is not performed for overlapping optional variable.
XDES0001

Variable	PLACEBO (N=1286)	RLX060 (N=2725)	Total (N=4011)	p-Value
Age of First Live Birth (VISIT: 1)				
No. Patients	1286	2725	4011	.635*
0	31 (2.8)	59 (2.5)	90 (2.6)	
>0 - <20	85 (7.6)	199 (8.3)	284 (8.1)	
20 - <25	494 (44.0)	1019 (42.5)	1513 (43.0)	
25 - <30	356 (31.7)	806 (33.7)	1162 (33.0)	
>=30	157 (14.0)	312 (13.0)	469 (13.3)	
Unspecified	163	330	493	
Age of First Live Birth (VISIT: 1)				
No. Patients	1123	2395	3518	.628**
Mean	24.53	24.40	24.44	
Median	24.00	24.00	24.00	
Standard Dev.	8.15	7.35	7.61	
Minimum	0.00	0.00	0.00	
Maximum	99.00	99.00	99.00	
Unspecified	163	330	493	
CONE First Degree Relatives with BC (VISIT: 1)				
No. Patients	1286	2725	4011	.175*
1 - <2	150 (90.9)	333 (89.5)	483 (89.9)	
2 - <3	14 (8.5)	33 (8.9)	47 (8.8)	
3 - <4	0	6 (1.6)	6 (1.1)	
>=4	1 (0.6)	0	1 (0.2)	
Unspecified	1121	2353	3474	
Number of Breast Biopsies (VISIT: 1)				
No. Patients	1286	2725	4011	.079*
1 - <2	157 (68.6)	343 (74.9)	500 (72.8)	
>=2	72 (31.4)	115 (25.1)	187 (27.2)	
Unspecified	1057	2267	3324	
Number of Breast Biopsies (VISIT: 1)				
No. Patients	229	458	687	.313**
Mean	1.77	1.57	1.64	
Median	1.00	1.00	1.00	
Standard Dev.	2.95	2.17	2.46	
Minimum	1.00	1.00	1.00	
Maximum	40.00	35.00	40.00	
Unspecified	1057	2267	3324	
Any Biopsies with Atypical Hyperplasia (VISIT: 1)				
No. Patients	1286	2725	4011	***
Yes	7 (3.1)	11 (2.4)	18 (2.6)	
No	203 (88.6)	416 (90.8)	619 (90.1)	
Unknown	19 (8.3)	31 (6.8)	50 (7.3)	
Unspecified	1057	2267	3324	

SOURCE IS RMP.H3SP.SASMACRO(DESM1) DEC04 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
* Frequencies are analyzed using a Chi-Square test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
*** Chi-Square test is not performed for overlapping optional variable.
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All Patients Enrolled in CORE at Start of MORE (11.2.2)

Evaluation of the demographics of the CORE population at MORE baseline demonstrated that the treatment groups were fairly well balanced with the exception of some bone-specific parameters.

- At MORE baseline, placebo patients who later enrolled in CORE appeared to have less severe osteoporosis compared with raloxifene patients who later enrolled in CORE, although the groups had comparable lumbar spine and femoral neck BMD values.
- At MORE baseline, significantly more raloxifene patients had prevalent vertebral fractures and higher SQ scores (semi-quantitative visual assessment by a radiologist for presence of fractures in the T4-L4 vertebral bodies, of which scoring includes 0 [no fracture], 1 [mild], 2 [moderate], or 3 [severe]) than placebo patients.
- The presence of any osteoporosis-related fracture predisposes a patient to future fractures independent of BMD values.

Comparison of Patients Who Enrolled in CORE with Those Who Did Not Enroll in CORE (11.2.2.1)

Comparison of MORE baseline characteristics of patients who subsequently enrolled in CORE (4011 patients) with those of patients who did not enroll in CORE (3694 patients) showed several differences:

- Patients who enrolled in CORE tended to be younger, were fewer years postmenopausal, fewer smoked, fewer had undergone a hysterectomy and fewer had previously used HRT than patients who did not enroll in CORE.
- However, there was a similar family history of breast cancer in the two patient populations.

There was a difference in the bone-specific parameters of SQ score and prevalence of vertebral fracture in patients who enrolled in CORE versus those who did not.
Thus, the population enrolled in CORE was not representative of MORE with respect to bone-specific parameters. In addition to differences between the population of patients who enrolled in CORE versus those who did not enroll in CORE, there were differences within each therapy group between these two populations:

- Patients in the placebo group who enrolled in CORE had fewer prevalent vertebral fractures and lower SQ scores than patients in the placebo group who did not enroll in CORE, and, thus, were considered to have less severe osteoporosis than placebo patients who did not enroll in CORE.
- Although patients in the raloxifene group who enrolled in CORE also tended to have less severe osteoporosis as indicated by prevalent vertebral fractures and SQ score than patients in the raloxifene group who did not enroll in CORE, the difference between the populations was less than that observed in the placebo population.

- Significantly fewer patients who later enrolled in CORE took anti-hypertensives, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, diuretics, anticoagulants, aspirin, coumadin, anti-platelet agents or any form of estrogen compared with patients who did not enroll in CORE.

- Also, fewer diabetic patients and more patients with hyperlipidemia enrolled in CORE than those who did not enroll in CORE.
- Patients who enrolled in CORE had higher total cholesterol, higher low-density lipoprotein (LDL) cholesterol, lower triglycerides, and lower estradiol levels than patients who did not enroll in CORE.
- These patients also had less history of myocardial infarction, coronary heart disease, and stroke (thus lower cardiovascular risk scores than patients who did not enroll in CORE.

All Patients Included in the PAD Population at Study GGGK Baseline (11.2.3)

Comparison of the treatment groups included in the PAD demonstrated that the groups were well balanced at MORE baseline.

- The MORE baseline characteristics of the entire PAD population, compared with patients not included in the PAD, showed that patients included in the PAD were generally older, more years postmenopausal, less representative of North America, more smoked, consumed less alcohol, fewer had a family history of breast cancer, fewer had undergone hysterectomy, and fewer had prior use of HRT than patients not in the PAD population.
- Compared with placebo patients not included in the PAD, the placebo patients included in the PAD were older; consumed less alcohol; fewer smoked; fewer had a family history of breast cancer; more had higher LDL cholesterol, fewer had undergone hysterectomy; and fewer had higher previous use of HRT than patients who were not included in the PAD.
- Compared with raloxifene patients not included in the PAD, the raloxifene patients included in the PAD were older, more years postmenopausal, fewer had a family history of breast cancer, more smoked; more had higher LDL cholesterol, consumed less alcohol, fewer had undergone hysterectomy, and fewer had previous use of HRT compared with patients not included in the PAD.

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Measurements of Treatment Compliance (11.3)

Percentage of treatment compliance for a patient was defined as the number of pills dispensed minus the number of pills returned divided by the number of days between the first (first dispensation) and last visit of CORE. If a patient developed breast cancer, the patient was to discontinue therapy. For these patients, compliance was evaluated from the start of CORE until diagnosis.

Patients in CORE were allowed to continue their *study participation* even if they had experienced an adverse event and/or were no longer taking study drug. Among those patients who took study drug during MORE and during CORE, the median time between MORE and CORE was 10 months regardless of treatment assignment.

The following table displays the median total percentage compliance within each treatment group. There were no differences in compliance between the two treatment groups.

Table GGJY.11.3. Patient Compliance during CORE (All Patients Enrolled in CORE)

	Placebo	Raloxifene	TOTAL	P-Value*
ALL CORE PATIENTS(N=)	1286	2725	4011	
Missing Compliance Data	352	724	1076	
Non-Missing Compliance	934	2001	2935	
Minimum	0.19	0.00	0.00	
Mean	84.68	83.96	84.19	0.4485
Median	94.03	93.95	93.96	
Maximum	134.98	134.10	134.98	
Standard Deviation	23.52	24.30	24.05	
** Compliance >=80%	717/1286(56%)	1497/2725(55%)	2214/4011(55%)	0.6267
RESUMED DRUG IN CORE(N=)	1018	2182	3200	
Compliance >=80%	717/1018(70%)	1497/2182(69%)	2214/3200(69%)	0.2977

* P-Value for the mean compliance is from a two-sample t-test.
P-Value for the percent compliance by therapy is from a Mantel-Haenszel Chi-Square

** Patient overall compliance is measured by (TOTAL PILLS TAKEN)/(TOTAL DAYS IN STUDY)

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- 4,011 patients enrolled in CORE, 56% placebo-treated patients and 55% raloxifene-treated patients were considered fully compliant as defined as taking at least 80% of the study drug.
- 811 (20.1%) patients enrolled in CORE never took any study drug throughout the duration of the study. If the 811 patients enrolled in Study GGJY who never took any study drug are not included in the compliance calculation, 70% of the placebo-treated

patients and 69% of the raloxifene treated patients were considered compliant in the study as defined by taking at least 80% of study drug throughout the study.

- Patients at many sites had drug accountability issues, the vast majority of which were failure to return study medication at the appropriate visit. Because study medication might have been returned at subsequent visits, a by-visit compliance analysis was not feasible. The Sponsor implemented corrective actions, including education with site personnel, stickers on drug packages, and recommended the use of verbal reminders from the site to patients. These drug accountability issues may have compromised the assessment of overall compliance.

Concomitant Medications (11.3.1)

Concomitant medications that might confound the interpretation of efficacy and safety analyses were grouped into four classes:

- Bone-active agents
- Lipid-lowering agents
- Hormones or selective estrogen receptor modulators (SERMs)
- Nitrates

- Concomitant use of other osteoporosis medications, including bisphosphonates, calcitonin, or fluorides was allowed during the 4th year of MORE and during CORE. Patients were allowed concomitant use of the double-blind study medication provided only specific bone-active agents were used.
    - There were significantly more patients in the placebo group taking bone-active agents at CORE baseline (Visit 1: the period between MORE termination and enrollment into CORE) ($p = 0.003$), and there continued to be proportionately more patients taking bone-active agents in the placebo group throughout the study.
- Patients who began taking sex hormones and related compounds (such as systemic estrogens, combined hormone replacement therapy, phytoestrogens, anabolic androgens, or SERMS, including marketed Evista®), other than estriol up to 2 mg/day or intravaginal estrogen up to 3 times per week, had to stop the double-blind study medication immediately. They could resume the double-blind study medication as soon as they discontinued treatment with the previously mentioned compounds.
- At baseline and throughout the study, significantly more placebo-treated patients took lipid-lowering agents compared to raloxifene-treated patients ($p<0.05$ for all comparisons).
- There were no differences between the treatment groups at any visit for the other concomitant medications: hormones or SERMs, or nitrates.

The following table lists each class and the proportion of patients in each treatment group who reported the use of any medication in that class at each visit.

Table GGJY.11.4. Use of Concomitant Medications during Study CORE (All Patients Enrolled in CORE)

	PLACEBO n (%)	Ralox n (%)	P-VALUE*
VISIT 1	N=1286	N=2725	
Bone-active agents	466 (36.2)	858 (31.5)	0.003
Lipid-lowering agents	190 (14.8)	317 (11.6)	0.005
Hormones or SERMs	228 (17.7)	501 (18.4)	0.629
Nitrates for angina	54 (4.2)	136 (5.0)	0.300
VISIT 2*	N= 648	N=1363	
Bone-active agents	197 (30.4)	365 (26.8)	0.099
Lipid-lowering agents	105 (16.2)	170 (12.5)	0.026
Hormones or SERMs	82 (12.7)	199 (14.6)	0.270
Nitrates for angina	28 (4.3)	78 (5.7)	0.201
VISIT 3	N=1281	N=2688	
Bone-active agents	506 (39.5)	956 (35.6)	0.016
Lipid-lowering agents	238 (18.6)	383 (14.2)	<0.001
Hormones or SERMs	221 (17.3)	462 (17.2)	0.964
Nitrates for angina	62 (4.8)	158 (5.9)	0.207
VISIT 4	N=1225	N=2572	
Bone-active agents	489 (39.9)	948 (36.9)	0.073
Lipid-lowering agents	259 (21.1)	409 (15.9)	<0.001
Hormones or SERMs	200 (16.3)	407 (15.8)	0.704
Nitrates for angina	64 (5.2)	158 (6.1)	0.268
VISIT 5	N=1160	N=2413	
Bone-active agents	486 (41.9)	935 (38.7)	0.073
Lipid-lowering agents	254 (21.9)	432 (17.9)	0.004
Hormones or SERMs	177 (15.3)	369 (15.3)	1.000
Nitrates for angina	63 (5.4)	154 (6.4)	0.295

* Frequencies are analyzed using a Fisher's Exact test.
* Visit 2 exclude those patients whose visit 2 date is same as visit 1 date.
Abbreviations: CORE=Continuing Outcomes Relevant to Evista; Ralox=raloxifene hydrocholoride; SERMs=Selective Estrogen Receptor Modelators

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Additionally, the number of patients who took another bone-active agent, and specifically a bisphosphonate, after the 3rd year of MORE, was analyzed:

- Nearly half of all the patients (49.1%) enrolled in CORE utilized some other bone active agent after the 3rd year of MORE.
- Significantly more patients in the placebo group than patients in the raloxifene group (p=0.0269 and p=0.0005, respectively) used either an additional bone-active agent or bisphosphonate.

Table GGJY.11.5. Bone-Active Agents Use after the 3rd Year of MORE (All Patients in CORE)

	Placebo (N=1286)	RLX (N=2725)	p-value*
Any Bone-Active Agents Use	664 (51.6%)	1305 (47.9%)	0.0269
Bisphosphonates Use	504 (39.2%)	914 (33.5%)	0.0005

* p-value is obtained from frequency analysis using a Pearson Chi-Square test.

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Efficacy Results and Tabulations of Individual Patient Data (11.4)

Analysis of Efficacy (11.4.1)

All primary and secondary breast cancer endpoints are presented in this section and the incidence of nonvertebral fractures, a secondary endpoint, is evaluated and discussed.

Statistical/Analytical Issues

Please refer to Section 9.7 for discussion of statistical/analytical issues.

Breast Cancer (11.4.3)

A total of 63 cases of breast cancer were reported from the patients whose investigators participated in CORE since 1 January 1999 (the primary analysis dataset [PAD]).

Two cases were excluded from the analyses:

- Case 244-2023 was excluded because the cancer could not be adjudicated as breast cancer; the pathology report was inconclusive (that is, the analysis could not exclude ductal hyperplasia)
- Case 742-3950 was excluded because the cancer was not a primary breast cancer but rather a metastasis from the lung (small-cell lung carcinoma) to the breast.

Although **the primary analyses** comprise of the incidence of invasive breast cancer that occurred after 1 January 1999 in women whose investigators participated in CORE (PAD population), several **other patient datasets** were also analyzed. The following list presents the order of the analyses:

Breast cancer incidence from 1 January 1999 through the end of CORE in women whose investigators participated in CORE (PAD population):

- Breast cancer incidence and patient exposure
- Breast cancer hazard ratio results by invasiveness and estrogen receptor (ER) status
- Time-to-event analyses of invasive breast cancer (primary objective analysis)
- Time-to-event analyses of invasive ER + breast cancer (secondary objective analysis)
- Sensitivity analyses
- Subgroup analyses
- Patient compliance
- Relative risk analyses of breast cancer

Breast cancer incidence from the beginning of MORE through the end of CORE in patients whose investigators participated in CORE (PAD population):

- Breast cancer hazard ratio results by invasiveness and ER status
- Time-to-event analyses of invasive breast cancer

- Time-to-event analyses of invasive ER + breast cancer

Breast cancer in all 7,705 patients in MORE through the end of CORE:

- Breast cancer hazard ratio results by invasiveness and ER status
- Time-to-event analyses of invasive breast cancer
- Time-to-event analyses of invasive ER + breast cancer
- Relative risk and relative rates of breast cancer by invasiveness and ER status

Breast Cancer Incidence from 1 January 1999 through the End of CORE in Women whose Investigators Participated In CORE (PAD Population) (11.4.3.1)

Breast Cancer Incidence and Patient Exposure (11.4.3.1.1)

The population for the analyses of all breast cancers and invasive breast cancers was defined as all patients who were eligible for participation in CORE and who had not been diagnosed with breast cancer as of 1 January 1999 (4,011 – 15 = 3,996) plus the patients who had not discontinued MORE prior to 1 January 1999 and did not enroll in CORE (1,217).

- This population (PAD population) includes 5213 patients.

The incidence of breast cancer and invasive breast cancer was lower in patients assigned to raloxifene than in patients assigned to placebo.

Table GGJY.11.6. Incidence of Breast Cancer and Invasive Breast Cancer in CORE (PAD Population)

Table GGJY.11.6. Incidence of Breast Cancer and Invasive Breast Cancer in Study H3S-MC-GGJY

Therapy	Number Enrolled	Invasive Breast Cancer	All Breast Cancer	Patient-Years Follow-up
Placebo	1703	28	30	5435
Raloxifene	3510	24	31	11438

Breast Cancer Hazard Ratio Results by Invasiveness and ER Status (11.4.3.1.2)

There were 61 cases of breast cancer (30 [1.76%] in placebo and 31 [0.88%] in raloxifene) since 1 January 1999 in patients whose investigators participated in CORE (PAD population): 52 cancers were invasive, 28 (1.64%) in the placebo group and 24 (0.68%) in the raloxifene group.

- Raloxifene treatment resulted in a significant reduction of 50% for **all breast cancers** compared with placebo treatment: hazard ratio of 0.50 (95% confidence interval [CI] 0.30, 0.82) (p=0.005).
- Considering only incidence of **invasive tumors**, which was the primary endpoint, raloxifene treatment resulted in a significant reduction of 59%: the hazard ratio 0.41 (95%CI 0.24, 0.71) (p<0.001).
- Raloxifene treatment reduced the risk of **invasive ER + tumors** by 66% compared with placebo: hazard ratio 0.34 (95%CI 0.18, 0.66) (p<0.001).

- Analysis of **ER – tumors** did not show a statistically significant difference between treatment groups: hazard ratio 1.13 (95%CI 0.29, 4.35).
- For cases of **unknown estrogen receptor** status, a non-significant reduction in risk was observed with raloxifene: hazard ratio 0.24 (95%CI 0.04, 1.30).
- Also there was no significant difference between the treatment groups for **noninvasive cases of breast cancer** (hazard ration 1.78 [95%CI 0.37, 8.61), although there were proportionately more cases of noninvasive breast cancer in the raloxifene group.

Table GGJY.11.7. Breast Cancer Hazard Ratio Results by Breast Cancer invasiveness and ER Status (From 1 January 1999, All PAD Patients, CORE)

Breast Cancer Category	PLACEBO (N=1703) n (%)	Ralox (N=3510) n (%)	Hazard Ratio (95% CI)	P-Value*
Invasive Cases	28 (1.64)	24 (0.68)	0.41 (0.24, 0.71)	<0.001
ER(+) Cases	21 (1.23)	15 (0.43)	0.34 (0.18, 0.66)	<0.001
ER(-) Cases	3 (0.18)	7 (0.20)	1.13 (0.29, 4.35)	0.864
ER Unknown Cases	4 (0.23)	1 (0.06)	0.24 (0.04, 1.30)	0.071
Noninvasive Cases	2 (0.12)	7 (0.20)	1.78 (0.37, 8.61)	0.466
All Cases	30 (1.76)	31 (0.88)	0.50 (0.30, 0.82)	0.005

* P-Value is obtained from a log-rank test.
Abbreviations: CI=confidence interval; Ralox=raloxifene; ER+=estrogen receptor-positive
ER-=estrogen receptor-negative

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Time-To-Event Analyses of Invasive Breast Cancer (11.4.3.1.3)

The primary analysis for incidence of invasive breast cancer was survival analyses for the PAD population. Survival curves for the two treatment groups were compared, where the p-value for the comparison was obtained from the ordinary log-rank test, and the hazard ratio between the two treatment groups resulted from the proportional hazards model with therapy as the only explanatory variable.

- Kaplan-Meier analyses of incidence rate per 1000 patients depict a continuous separation between placebo- and raloxifene-treated patients for **invasive** and **invasive ER +** breast cancer cases.
- The log-rank test p-value is less than 0.001, which is significant.

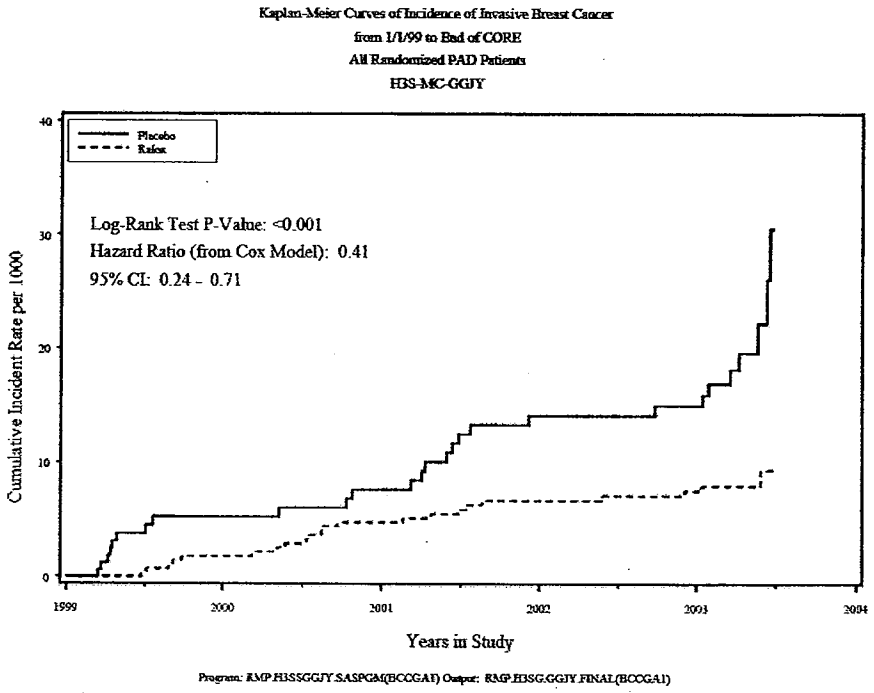

Figure GGJY.11.1. Kaplan-Meier curves of incidence of invasive breast cancer from 1 January 1999 to the end of CORE (All PAD patients contributing data from 1 January 1999, n = 5213)

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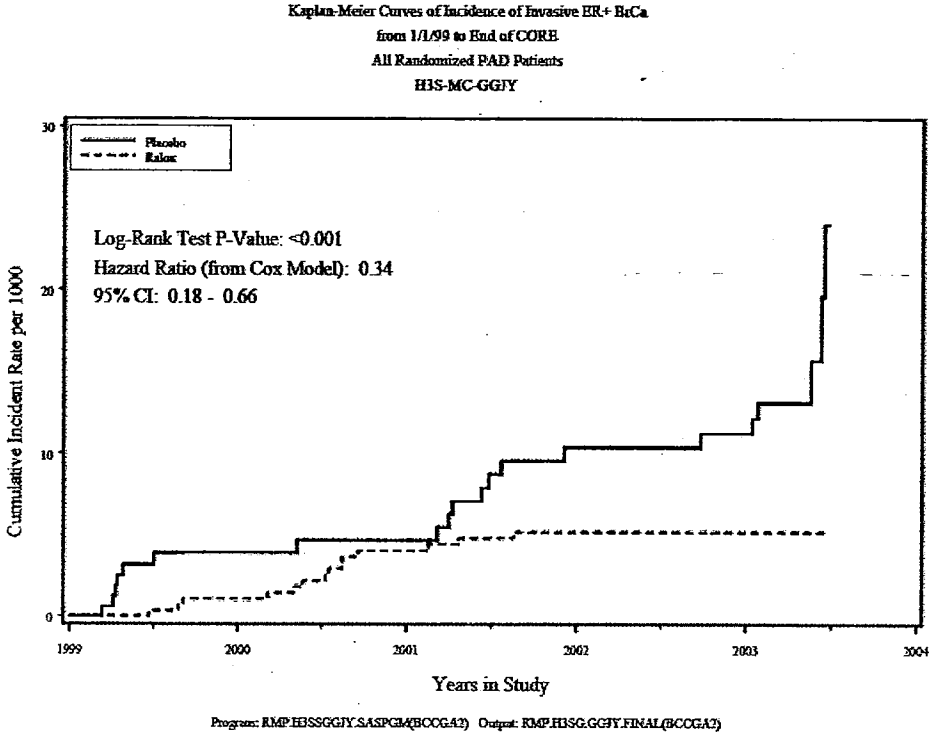

Figure GGJY.11.2. Kaplan-Meier curves of incidence of invasive ER + breast cancer from 1 January 1999 to the end of CORE (All PAD patients contributing data from 1 January 1999, n = 5213)

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Sensitivity Analyses (11.4.3.1.4)

The following sensitivity analyses were conducted to confirm that the primary analysis on adjudicated invasive breast cancer. Result was robust regardless of the particular time period or patient population selected:

- An analysis of all invasive breast cancer cases reported between randomization in MORE through the end of CORE in the PAD population (approximately 8 years).
- An analysis of all invasive breast cancer cases reported between 1 January 1999 and the end of CORE in the Continuing in CORE Dataset (CCD) population (which consists of patients who were enrolled in CORE) (approximately 4.5 years).
- An analysis of all invasive breast cancer cases reported between randomization into MORE and the end of CORE in the CCD population (those who enrolled in CORE, approximately 8 years).
- An analysis of all invasive breast cancer cases reported from Visit 1 in CORE (beginning of participation in CORE) through the end of CORE in the CCD population (approximately 3.4 years).

Sensitivity analyses of each population identified showed a significant reduction in the risk of invasive breast cancer with raloxifene treatment.

- The hazard ratio for the PAD population for the entire 8 years, which includes all 6,511 patients, was 0.35 (95% CI 0.23, 0.54).
- For patients who enrolled in CORE (the CCD population consisting of 4,011 patients), the hazard ratio was 0.42 (95% CI 0.23, 0.75) for cases reported between 1 January 1999 and the end of CORE.
- The hazard ratio was 0.37 (95%CI 0.22, 0.63) for cases reported between the randomization into MORE and the end of CORE
- The hazard ratio was 0.44 (95% CI 0.24, 0.83) for cases only occurring during CORE

Thus, each of these analyses demonstrated that raloxifene treatment reduces the risk of invasive breast cancer.

An additional sensitivity analysis was performed, which consisted of the investigator reported invasive breast cancers, regardless of adjudication status, in the PAD population from Visit 1 of CORE through the end of participation during CORE. The results of this analysis were comparable to the other sensitivity analyses and demonstrated that raloxifene therapy reduced the risk of invasive breast cancer by 56% compared to placebo (hazard ratio 0.44 [95%CI 0.24, 0.83]) (Table GGJY.14.18).

Subgroup Analyses

Three subgroup analyses evaluating the incidence of invasive breast cancer in the PAD population were conducted. The first analysis evaluated the incidence of invasive breast cancer by region of patient enrollment. The second analysis looked at the incidence of invasive breast cancer based on demographic parameters; the third analysis was based on patient compliance.

Subgroup Analyses by Region

Patients in the PAD were enrolled from five regions: North America, Latin America, Eastern Europe, Western Europe, and Asia Pacific. Estimates of regional effects within each of five regions are summarized in the table.

Most of the breast cancers occurred in North America and Western Europe, which were also the regions that enrolled the most patients. Although the overall interaction p-value is 0.005, when regions that did not report any events in a treatment group were excluded, the overall interaction p-value was 0.877 (based on a likelihood ratio test).

Table GGJY.11.8. Treatment Effect by Region (All Patients in the Primary Analysis Dataset, CORE)

Region	N	PLACEBO n (%)	Ralox n (%)	Hazard Ratio (95% CI)
North America	2138	13 (1.84)	14 (0.98)	0.52 (0.24, 1.11)
Latin America	413	6 (4.65)	0 (0.00)	N/A
Eastern Europe	345	0 (0.00)	3 (1.26)	N/A
Western Europe	2064	7 (1.03)	7 (0.50)	0.49 (0.17, 1.40)
Asia Pacific	253	2 (2.35)	0 (0.00)	N/A

Abbreviations: CI=confidence interval; Ralox=raloxifene

Overall interaction P-value is 0.005

For regions without zero event in any treatment group:
Overall interaction P-value is 0.877(based on likelihood ratio test)
Treatment main effect(without interaction) is 0.031

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Subgroup Analyses by Demographics (11.4.3.1.5.2)

Selected subpopulations based on demographics were analyzed primarily to confirm that there is a reduction in rate of invasive breast cancer within each of the subpopulations. The following subgroups were examined:

- Five-year risk of breast cancer using the Gail model determined at CORE baseline (5-year predicted risk > 1.67% versus < 1.67%)
- Baseline estradiol (< 5.0 pmol/L versus > 5.0 pmol/L) determined at MORE baseline
- Baseline age (age categorized by both division into tertiles of baseline age and division into > 60 years versus < 60 years) at MORE baseline
- Femoral neck baseline bone mineral density (BMD) (tertiles of baseline BMD) at MORE baseline
- Previous use of hormone replacement therapy as collected at MORE baseline
- Family history of breast cancer collected at MORE baseline

Generally, patients at increased risk of invasive breast cancer had an overall decrease in risk of developing invasive breast cancer with raloxifene treatment. However, raloxifene-treated patients with lower risk factors for developing invasive breast cancer also benefited from raloxifene treatment and generally had a lower risk of developing invasive breast cancer than placebo-treated patients, although the difference may not have been significant.

Breast Cancer Risk

The 5-year risk assessment of breast cancer estimates the chance that a woman will develop breast cancer over a specific interval and is based on risk factors and age. The level of breast cancer risk was calculated for each patient when she entered CORE (4,011 patients). Patients with a 5-year predicted risk of breast cancer of at least 1.67% at baseline were considered at elevated risk for developing breast cancer during the study.

- The incidence of invasive breast cancer was significantly reduced (66%) in this subset of patients with elevated breast cancer risk (5-year predicted risk from the Gail model > 1.67%) following raloxifene treatment (hazard ratio 0.33, 95%CI 0.16, 0.68) compared with placebo-treated patients at similar risk.
- For patients not at elevated risk for invasive breast cancer (5-year predicted risk from the Gail model < 1.67%), relatively fewer patients in the raloxifene-treated group developed invasive breast cancer than patients in the placebo group; however, there was no statistical difference.

Baseline Estradiol Levels

Estradiol levels above 5 pmol/L have been associated with an increased risk of breast cancer. Estradiol levels were measured at MORE baseline.

- Raloxifene-treated patients with baseline estradiol levels at least 5 pmol/L had a significant 62% reduction in risk of breast cancer (hazard ratio 0.38, 95% CI 0.20, 0.74) compared with placebo patients.

- For patients with baseline estradiol levels less than 5 pmol/L, raloxifene-treated patients had a lower incidence of invasive breast cancer compared with placebo-treated patients, although the difference was not significant.

Age

Advancing age has been associated with an increased risk of breast cancer. The subgroups based on age were evaluated by two different age groupings.

- In the first grouping, patient age at MORE baseline was divided into tertiles of less than 63.5 years, between 63.5 years and 69.9 years, and greater than 69.9 years.
- In the second grouping, women were classified as being under age 60 or ≥ 60 years old (being over 60 years of age is one criteria for elevated breast cancer risk.

- In the first grouping by tertiles, raloxifene-treated patients who were at least 69.9 years of age had a significant 72% reduction in risk of invasive breast cancer (hazard ratio 0.28, 95% CI 0.12, 0.67) compared with placebo-treated patients. There appeared to be too few patients who developed breast cancer in the other two tertiles for a significant difference to be observed.
- In the second grouping, significantly fewer raloxifene-treated patients developed invasive breast cancer in the ≥ 60 years group (hazard ratio 0.43, 95%CI 0.24, 0.77) compared with placebo treated patients. Too few patients in both treatment groups developed invasive breast cancer in the <60 years group for a determination to be made.

Femoral Neck BMD

Femoral neck BMD may be considered an indicator of lifetime endogenous estrogen exposure (Cauley et al. 1996; Zhang et al. 1997). Thus, patients with low femoral neck BMD or osteoporosis are hypothesized to have a lower risk of developing breast cancer.
All patients enrolled in MORE were considered to have osteoporosis either based on femoral neck or lumbar spine BMD or by presence of vertebral fractures at study enrollment. However, the degree of osteoporosis varied, as indicated by baseline BMD.
Patients with higher baseline femoral neck BMD could be considered to have higher lifetime estrogen exposure compared to patients with lower baseline femoral neck BMD.

- In this subgroup analysis, patients were placed in tertiles according to baseline femoral neck BMD: < 0.59, between 0.59 and 0.66, and > 0.66.
- Raloxifene treated patients in the highest BMD tertile had a 79% significantly lower risk of developing invasive breast cancer than placebo patients (hazard ratio 0.21, 95%CI 0.08, 0.54).
- Relatively fewer raloxifene treated patients in the other two lower BMD tertiles developed invasive breast cancer compared to placebo-treated patients; however, the difference was not significant.

Prior Hormone Use

Postmenopausal hormone replacement therapy use has been associated with an increased risk of breast cancer (Writing Group for the Women's Health Initiative Investigators 2002). Hormone use prior to enrollment into MORE was evaluated in women who developed breast cancer in CORE compared with those who did not use hormones prior to enrollment.

- 74% of the women enrolled in CORE did not have documented prior hormone use. In these patients, raloxifene-treated women had a 59% reduced risk of developing invasive breast cancer than placebo-treated patients (hazard ratio 0.41, 95%CI 0.22, 0.79).
- Fewer raloxifene-treated patients developed invasive breast cancer than placebo-treated patients in the prior hormone use group, but the difference was not significant.

Family History of Breast Cancer

A family history of breast cancer, defined as breast cancer occurring in a first-degree relative of the patient, is associated with an increased risk of later developing breast cancer.

- 12% of the patients who enrolled in CORE had a family history of breast cancer. In these patients, raloxifene treatment resulted in a significant 86% reduction in risk of invasive breast cancer compared with placebo-treated patients (hazard ratio 0.14, 95%CI 0.04, 0.53).
- Of the patients without a family history of breast cancer, relatively fewer raloxifene-treated patients developed breast cancer in CORE compared with the patients in the placebo group, although the difference between the therapies in this subgroup was not statistically significant.

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Table GGJY.11.9. Subgroup Analyses of Invasive Breast Cancer (From 1 January 1999 Through End of CORE, All Patients in the PAD)

Subgroups	PLACEBO (N=1703) n (%)	Ralox (N=2110) n (%)	Hazard Ratio (95% CI)
Gail risk score at CORE baseline*			
5-year risk >=1.67%	18 (1.41)	13 (0.48)	0.33 (0.16, 0.68)
5-year risk < 1.67%	6 (0.47)	8 (0.29)	0.66 (0.23, 1.89)
MORE baseline estradiol			
<5.0 pmol/L	9 (0.53)	8 (0.23)	0.45 (0.17, 1.16)
>=5.0 pmol/L	19 (1.12)	16 (0.46)	0.38 (0.20, 0.74)
MORE baseline age			
<63.5	7 (0.41)	9 (0.26)	0.62 (0.23, 1.66)
>=63.5 AND <69.9	7 (0.41)	7 (0.20)	0.46 (0.16, 1.31)
>=69.9	14 (0.82)	8 (0.23)	0.28 (0.12, 0.67)
<60	3 (0.18)	2 (0.06)	0.28 (0.05, 1.68)
>=60	25 (1.47)	22 (0.63)	0.43 (0.24, 0.77)
MORE baseline femoral neck			
<0.59	5 (0.29)	8 (0.23)	0.75 (0.24, 2.28)
>=0.59 AND <0.66	9 (0.53)	10 (0.28)	0.52 (0.21, 1.28)
>=0.66	14 (0.82)	6 (0.17)	0.21 (0.08, 0.54)
HRT use prior to MORE			
Yes	8 (0.47)	7 (0.20)	0.39 (0.14, 1.09)
No	20 (1.17)	17 (0.48)	0.41 (0.22, 0.79)
Family history of breast cancer prior to MORE			
Yes	9 (0.53)	3 (0.09)	0.16 (0.04, 0.53)
No	17 (1.00)	21 (0.60)	0.61 (0.32, 1.15)
Patients 80% compliant in both MORE and CORE	10 (0.59)	9 (0.26)	0.44 (0.18, 1.09)

Abbreviations: CI=confidence interval; HRT=hormone replacement therapy; MORE=Multiple Outcomes of Raloxifene Evaluation; CORE=Continuing Outcomes Relevant to Evista;PAD=primary analysis dataset; BMD=bone mineral density
* Only CORE Patients Have Gail Score, so Placebo N=1278, Ralox N=1710

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Patient Compliance (11.4.3.1.5.3)

Analyses of incident-invasive breast cancer for those patients who were at least 80% compliant for study drug administration were performed. The time gap between MORE and CORE was ignored for compliance computations. The following analyses were computed for the time-to-first-event of adjudicated invasive breast cancer:

- Patients in the PAD population who were at least 80% compliant in MORE and at least 80% compliant in CORE. The time period for analysis was from 1 January 1999 through the end of participation in MORE or CORE.
- Patients in the CCD population who were at least 80% compliant in CORE. The time period for analysis was from 1 January 1999 through the end of participation in CORE.
- Patients in the CCD population that were 80% compliant in CORE. The time period for analysis was from enrollment in CORE through the end of participation in CORE.

The compliance-related results for invasive breast cancer, based on 80% compliance, are presented in the last and the following table. Raloxifene-treated patients in the PAD population who were at least 80% compliant throughout MORE and CORE had a lower incidence of breast cancer than placebo-treated patients, although the difference was not statistically significant. Raloxifene-treated patients enrolled in CORE (the CCD population) who were at least 80% compliant either from 1 January 1999 or from Visit 1 of Study GGJY had a significantly lower risk of invasive breast cancer than placebo-treated patients (hazard ratio 0.40, 95%CI 0.17, 0.97 and hazard ratio 0.38, 95%CI 0.16, 0.93, respectively).

Table GGJY.11.10. Compliance-Related Analyses of Invasive Breast Cancer (All Patients Enrolled in CORE)

Compliance Status	Reporting Period	PLACEBO n/N (%)	Ralox n/N (%)	Hazard Ratio (95% CI)
80% Compliant in CORE	January 1, 1999 - End of CORE	11/ 723(1.52)	9/1508(0.60)	0.40(0.17, 0.97)
80% Compliant in CORE	Visit 1 of CORE - End of CORE	11/ 723(1.52)	9/1508(0.60)	0.38(0.16, 0.93)

Abbreviations: CI-confidence interval; RLX-raloxifene; CORE-Continuing Outcomes Relevant to Evista;

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Relative Risk Analyses of Breast Cancer (11.4.3.1.6)

Secondary analyses of invasive breast cancer in this PAD population from 1 January 1999 through CORE termination were conducted using **relative risk** *in place of* **hazard ratio** as the parameter to characterize the treatment effect; and **Mantel-Haenzel test p-value** was used in place of the **log-rank p-value** as the measure of statistical significance.

- Similar to the results based on the hazard ratio analyses, patients treated with raloxifene had a significantly reduced risk of developing any breast cancer (relative risk 0.50, 95%CI 0.30, 0.83), invasive breast cancer (relative risk 0.42, 95%CI 0.24, 0.72), and invasive ER + breast cancer (relative risk 0.35, 95%CI 0.18, 0.67).
- Using rate per 1000 women-years, incidence of breast cancer was significantly less with raloxifene treatment (relative risk 0.49, 95%CI 0.30, 0.81).
- Raloxifene treatment had no significant effect on risk or rate of ER - breast cancer, ER unknown breast cancer, or non-invasive breast cancer.

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Breast Cancer Incidence from Beginning of MORE through End of CORE in Patients whose Investigator Participated in CORE (11.4.3.2)

Breast Cancer Hazard Ratio Results by Invasiveness and ER Status (11.4.3.2.1)

Analyses of incidence of breast cancer by invasiveness and ER status from the beginning of MORE through completion of CORE for the 6,511 patients who were eligible for participation in CORE (patients of all investigators who chose to participate in CORE) were conducted.

- Raloxifene-treated patients had a significantly lower risk of developing all breast cancer (hazard ratio 0.46, 95% CI 0.32, 0.67), invasive breast cancer (hazard ratio 0.35, 95%CI 0.23, 0.54), invasive ER + breast cancer (hazard ratio 0.25, 95% CI 0.15, 0.43), or ER status unknown (hazard ratio 0.24, 95% CI 0.06, 0.98) compared with placebo-treated patients through the approximately 8-year treatment period.
- Raloxifene treatment had no significant effect on the relative risk of ER - or on noninvasive breast cancer, although the proportion of patients in the raloxifene group was higher than in the placebo group for these two categories.

Table GGJY.11.11. Breast Cancer Results by Breast Cancer Category from Beginning of MORE through End of CORE (All PAD Patients)

Breast Cancer Category	PLACEBO (N=2178) n (%)	Ralox (N=4333) n (%)	Hazard Ratio (95% CI)	P-Value*
Invasive Cases	51 (2.34)	37 (0.85)	0.35 (0.23, 0.54)	<0.001
ER(+) Cases	40 (1.84)	21 (0.48)	0.25 (0.15, 0.43)	<0.001
ER(-) Cases	5 (0.23)	13 (0.30)	1.28 (0.46, 3.60)	0.635
ER Unknown Cases	6 (0.28)	3 (0.07)	0.24 (0.06, 0.98)	0.030
Noninvasive Cases	4 (0.18)	15 (0.35)	1.85 (0.61, 5.58)	0.266
All Cases	55 (2.53)	52 (1.20)	0.46 (0.32, 0.67)	<0.001

* P-Value is obtained from a log-rank test.
Abbreviations: CI=confidence interval; Ralox=raloxifene; ER+=estrogen receptor-positive
ER-=estrogen receptor-negative

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Time-To-Event Analyses of Invasive Breast Cancer (11.4.3.2.2)

Kaplan-Meier analyses of incidence rate per 1000 patients depict a continuous separation between placebo- and raloxifene- treated patients for invasive and invasive ER + breast cancer cases. The step-wise pattern apparent in each of the figures is due to the performance of mammograms at regular intervals.
These figures show raloxifene treatment effect in reducing the risk of invasive breast cancer and invasive ER + breast cancer after the 1st year of treatment with sustained efficacy over 8 years.

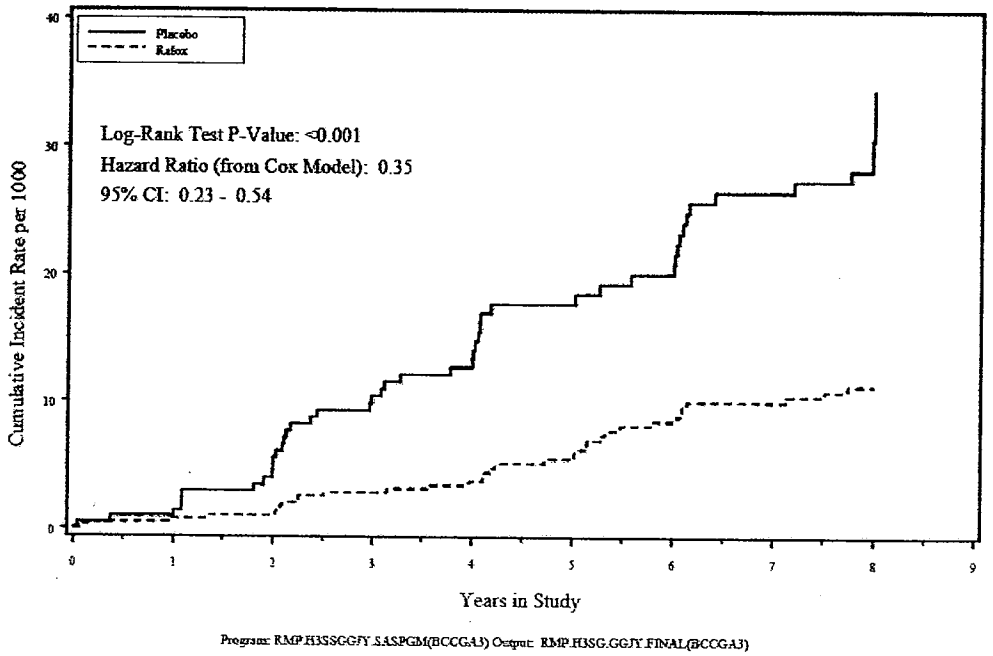

Figure GGJY.11.3. Kaplan-Meier curves of incidence of invasive breast cancer from randomization of MORE through end of CORE (All 6,511 PAD patients)

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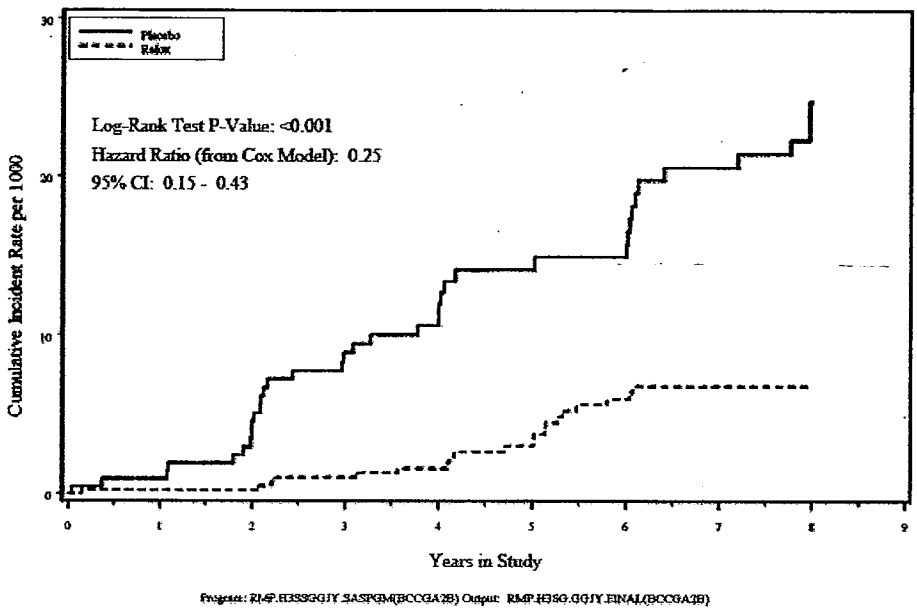

Figure GGJY.11.4. Kaplan-Meier curves of incidence of invasive ER + breast cancer from randomization of MORE through end of CORE (All 6,511 PAD patients)

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Breast Cancer in All 7,705 Patients in MORE through End of CORE (11.4.3.3)

Breast Cancer Hazard Ratio Results by Invasiveness and ER Status (11.4.3.3.1)

There were 121 cases of adjudicated breast cancer from the beginning of MORE through the end of CORE for all patients who enrolled in MORE (7,705 postmenopausal women with osteoporosis). Of those cases, 56 (1.09%) occurred in raloxifene-treated women and 65 (2.52%) in placebo-treated women. There was a significant reduction in hazard ratio for raloxifene-treated women for all breast cancer (hazard ratio 0.42, 95% CI 0.29, 0.60), invasive breast cancer (hazard ratio 0.34, 95% CI 0.22, 0.50), invasive ER + breast cancer (hazard ratio 0.24, 95% CI 0.15, 0.40), and ER status unknown breast cancer (hazard ratio 0.21, 95% CI 0.05, 0.81) over approximately 8 years of treatment. There was no difference between raloxifene treatment and placebo treatment for ER - breast cancer or noninvasive breast cancer.

Table GGJY.11.12. Breast Cancer Results by Breast Cancer Category from MORE to End of CORE (All 7,705 Randomized Patients in MORE)

Breast Cancer Category	PLACEBO (N=2576) n (%)	Ralox (N=5129) n (%)	Hazard Ratio (95% CI)	P-Value*
Invasive Cases	58 (2.25)	40 (0.78)	0.34 (0.22, 0.50)	<0.001
ER(+) Cases	44 (1.71)	22 (0.43)	0.24 (0.15, 0.40)	<0.001
ER(-) Cases	7 (0.27)	15 (0.29)	1.06 (0.43, 2.59)	0.903
ER Unknown Cases	7 (0.27)	3 (0.06)	0.21 (0.05, 0.81)	0.012
Noninvasive Cases	7 (0.27)	16 (0.31)	1.12 (0.46, 2.73)	0.797
All Cases	65 (2.52)	56 (1.09)	0.42 (0.29, 0.60)	<0.001

* P-Value is obtained from a log-rank test.
Abbreviations: CI=confidence interval; Ralox=raloxifene; ER+=estrogen receptor-positive
ER-=estrogen receptor-negative

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Time-To-Event Analyses of Invasive Breast Cancer (11.4.3.3.2)

Kaplan-Meier analyses of incidence rate per 1000 patients depict a continuous separation between placebo- and raloxifene-treated patients for invasive and invasive ER + breast cancer cases. These figures demonstrate that the treatment effect of raloxifene is apparent after the 1st year of treatment and that raloxifene has sustained efficacy to reduce the incidence of invasive and invasive ER + breast cancer in postmenopausal women with osteoporosis over 8 years.

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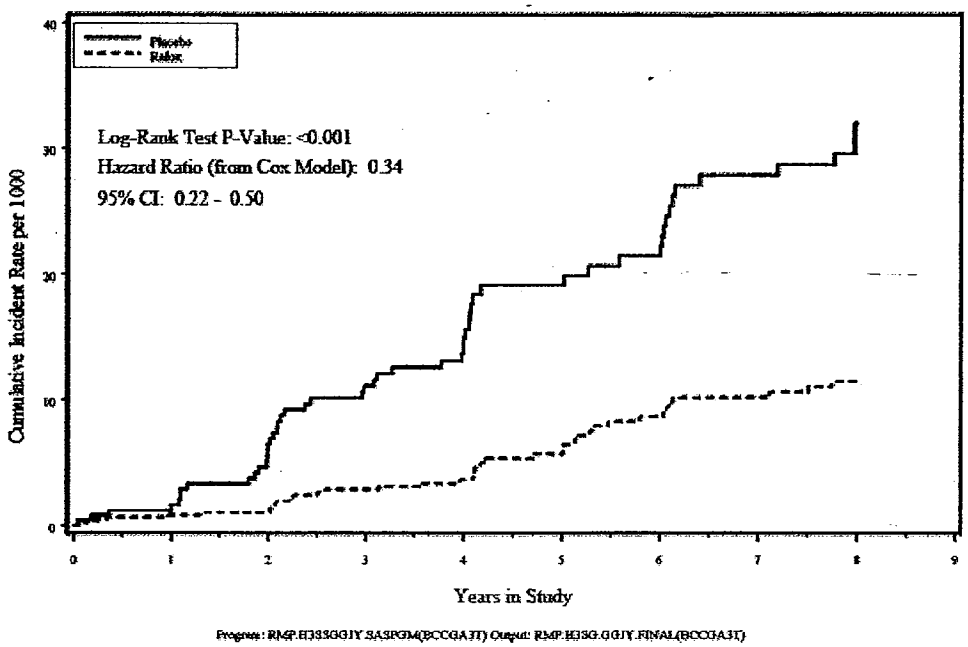

Figure GGJY.11.5. Kaplan-Meier curves of incidence of invasive breast cancer from randomization of MORE through end of CORE (All 7,705 patients)

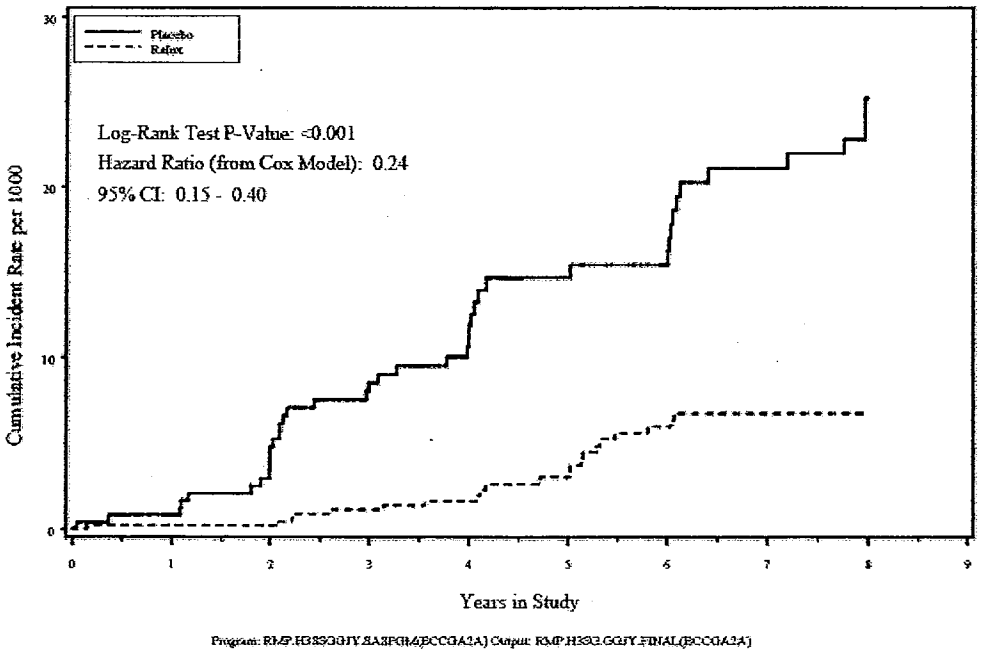

Figure GGJY.11.6. Kaplan-Meier curves of incidence of invasive breast cancer from randomization of MORE through end of CORE (All 7,705 patients)

Relative Risk and Relative Rates of Breast Cancer by Invasiveness and ER Status (11.4.3.3.3)

Secondary analyses of this population (all patients who enrolled in MORE through study end of CORE) were conducted using relative risk in place of the hazard ratio as the parameter to characterize the treatment effect. Similarly, the Mantel-Haenzel test p-value was used in place of the log-rank p-value as the measure of statistical significance.

Similar to the results based on the hazard ratio analyses, patients treated with raloxifene had a significantly reduced risk of developing any breast cancer (relative risk 0.43, 95% CI 0.30, 0.62), invasive breast cancer (relative risk 0.35, 95%CI 0.23, 0.52), and invasive ER + breast cancer (relative risk 0.25, 95%CI 0.15, 0.42), or ER unknown breast cancer (relative risk 0.22, 95%CI 0.06, 0.83).

Using rate per 1000 women years, incidence of breast cancer was significantly less with raloxifene treatment (relative risk 0.42, 95% CI 0.29, 0.60). Raloxifene treatment had no significant effect on risk or rate of ER (-) breast cancer or noninvasive breast cancer.

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Nonvertebral Fractures (11.4.4)

A secondary objective of CORE was incidence of osteoporotic nonvertebral fractures from enrollment in MORE through termination of CORE. Any osteoporotic nonvertebral fracture was defined as a fracture at any of the following sites: clavicle, scapula, ribs, sacrum, humerus, forearm, wrist, carpus, pelvis, hip, femur, lower leg, patella, ankle, calcaneus, tarsus, metatarsus, sternum, and coccyx. Nonvertebral-six fractures is a grouping of clavicle, humerus, wrist, pelvis, hip/femur, and leg fractures, which are typically associated as osteoporosis-related in patients with osteoporosis.

The survival analysis method was identified as the primary analysis method. The placebo and raloxifene groups were compared on the basis of time to first nonvertebral fracture.
A Cox proportional hazards regression model was used to estimate the relative hazard and 95% confidence interval (CI) for the raloxifene group compared with placebo.

Kaplan-Meier curves were generated from any nonvertebral fractures and non-vertebral six fractures, and a log-rank test was used to compare the two treatment groups.

Post-hoc Poisson analyses were also conducted for nonvertebral fractures. The Poisson regression analysis method, unlike the survival analysis method, accounts for the number of events adjusted by the time of exposure, and thus, takes into account more than one nonvertebral fracture.

The nonvertebral fracture results are presented in the following order:

All patients enrolled in CORE (CCD population) from MORE baseline to CORE termination;
- Any nonvertebral fracture and nonvertebral-six fracture;
- Time-to-event analyses for any nonvertebral fracture and nonvertebral-six fracture;
- Subgroup analyses by baseline characteristics and treatment compliance for any nonvertebral fracture and nonvertebral-six fracture;
    - Time-to-event analyses by baseline SQ = 3 score
    - Time-to-event analyses by baseline prevalent vertebral fracture
- Subset analyses based on concomitant bone-active agents and on whether a patient took at least one dose of study drug;
- Potential cofounders to nonvertebral fracture results including time-to-event analyses;

All patients in PAD from MORE baseline to CORE termination;
- Any nonvertebral fracture and nonvertebral-six fracture;

All patients in MORE from MORE baseline to CORE termination;
- Any nonvertebral fracture and nonvertebral-six fracture;

Poisson regression analyses for any nonvertebral fracture and nonvertebral-six fracture;
- Subgroup analyses for any nonvertebral fracture and nonvertebral-six fracture by baseline SQ score;
- Subgroup analyses for any nonvertebral fracture and nonvertebral-six fracture by baseline prevalent vertebral fracture.

Nonvertebral Fracture Results (11.4.4.1)

Overall, raloxifene had a neutral effect on any nonvertebral fracture and nonvertebral-six fracture. Confounders to the results were use of bone-active agents after the 3rd year of MORE and differences in baseline demographics for risk of nonvertebral fractures in patients in the placebo group and raloxifene group. Analyses of the subgroups at higher risk for nonvertebral-six fractures and accounting for multiple fractures demonstrated that fewer raloxifene-treated patients sustained nonvertebral-six fractures than placebo-treated patients.

All Patients Enrolled in CORE (11.4.4.2)

Nonvertebral Fracture Results by Location (11.4.4.2.1)

The following table summarizes the number and proportion of patients reporting any nonvertebral fracture, nonvertebral-six fractures collectively, and nonvertebral-six fractures by site for the primary nonvertebral fracture analysis population, which consists of all patients enrolled in CORE from the time of randomization into MORE through CORE termination, a period of more than 8 years.

- There was no significant effect of raloxifene on the incidence of all nonvertebral fractures or nonvertebral-six fractures. There was a significant reduction in wrist fractures in raloxifene-treated women; however, there was a significant increase in leg fractures in raloxifene-treated women. When a Bonferroni multiplicity adjustment was made, there was no significant effect on fractures observed. There was no difference between raloxifene treatment and placebo treatment at other fracture sites.

Table GGJY.11.13. Nonvertebral Fractures Results by Location (All Patients Enrolled in CORE)

Fracture Location	Placebo (N=1286)	RLX (N=2725)	Hazard Ratio (95% CI)	(Adjusted CI*)
Any nonvertebral fracture	295 (22.9%)	620 (22.8%)	0.997 (0.868, 1.145)	(0.821, 1.210)
Nonvertebral-six	225 (17.5%)	477 (17.5%)	1.007 (0.853, 1.180)	(0.807, 1.257)
Clavicle	4 (0.3%)	16 (0.6%)	1.897 (0.634, 5.673)	(0.411, 8.746)
Humerus	52 (4.0%)	97 (3.6%)	0.883 (0.631, 1.237)	(0.552, 1.413)
Wrist (forearm/carpus/wrist)	122 (9.5%)	204 (7.5%)	0.793 (0.633, 0.993)	(0.579, 1.085)
Pelvis	10 (0.8%)	27 (1.0%)	1.282 (0.620, 2.648)	(0.466, 3.527)
Hip/femur	35 (2.7%)	77 (2.8%)	1.043 (0.699, 1.555)	(0.597, 1.821)
Leg(Lower leg/ankle/tarsus/calcaneus)	36 (2.8%)	113 (4.1%)	1.497 (1.029, 2.179)	(0.887, 2.527)

* A Bonferroni multiplicity adjustment were made, where each of the above analyses is tested at the 0.00625 level to control the overall type I error at 0.05.

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Time-To-Event Analyses of Nonvertebral Fractures (11.4.4.2.2)

The time course of any osteoporotic nonvertebral fracture and nonvertebral-six fracture are presented using Kaplan-Meier analyses in the following figures. Both figures show no separation between placebo- and raloxifene-treated groups.

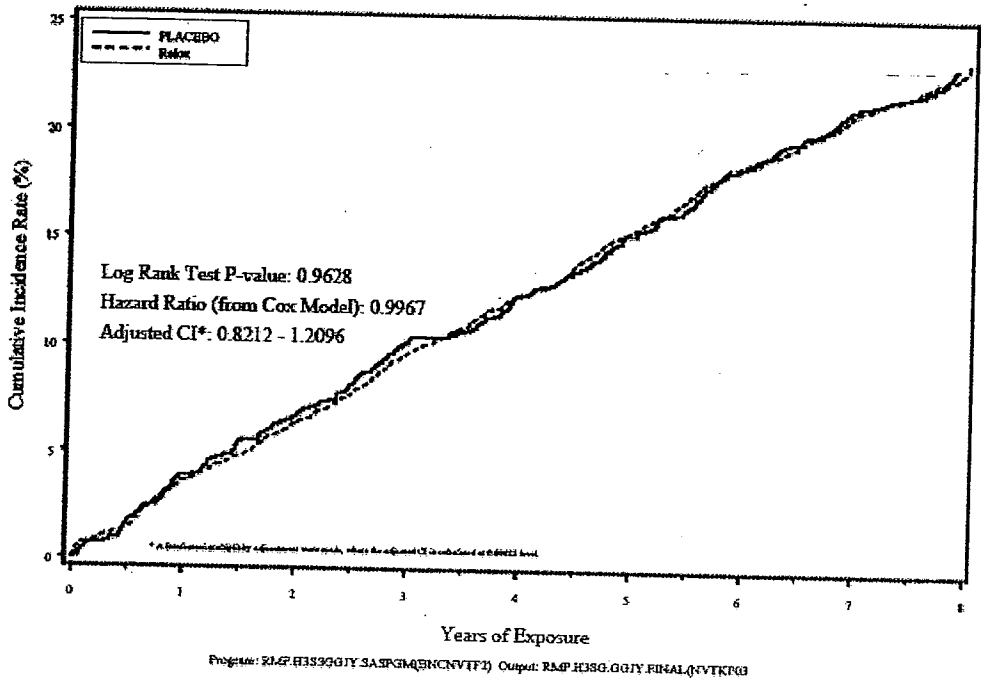

Figure GGJY.11.7. Incidence of nonvertebral fractures, MORE baseline through CORE termination (All patients enrolled in CORE)

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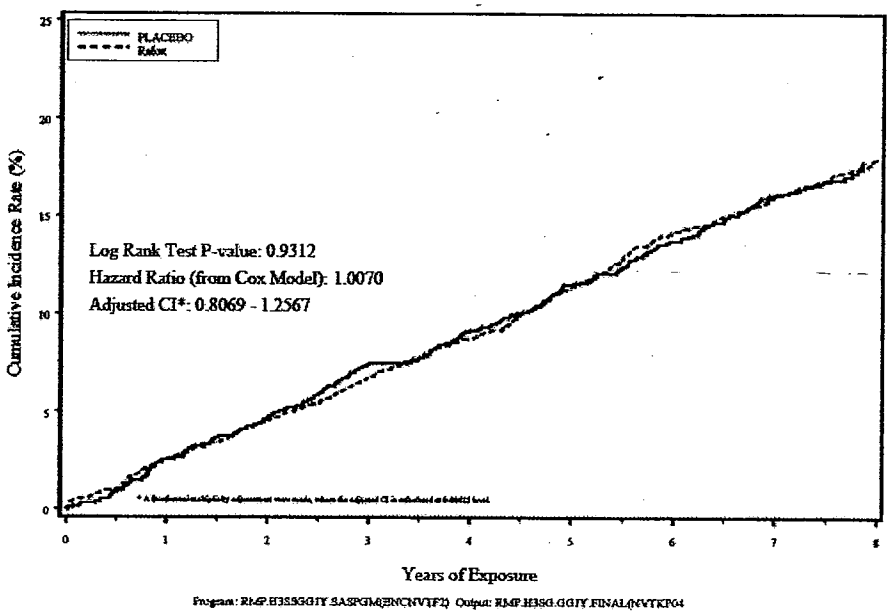

Figure GGJY.11.8. Incidence of nonvertebral-six fractures, MORE baseline through CORE termination (All patients enrolled in CORE)

Subgroup Analyses Based On Baseline Characteristics and Treatment Compliance (11.4.4.2.3)

Subgroup analyses evaluating the incidence of nonvertebral fractures and nonvertebral six fractures were conducted for all patients enrolled in CORE from baseline of MORE through termination of CORE. The subgroups, which were based on MORE baseline demographics, were age, lumbar spine BMD, femoral neck BMD, SQ score (semi-quantitative visual assessment by a radiologist for presence of fractures in the T4-L4 vertebral bodies, of which scoring includes 0 [no fracture], 1 [mild], 2 [moderate], or 3 [severe]), prevalent vertebral fracture, and prevalent nonvertebral fracture, as well as treatment compliance for the patients enrolled in CORE.
There was no effect of raloxifene on incidence of any nonvertebral fracture or nonvertebral-six fracture for any of the subgroups evaluated or for treatment compliance greater than 80%.
The interaction of treatment group and prevalent vertebral fractures was significant at the 0.10 level for both any nonvertebral fractures and for nonvertebral-six fractures ($p = 0.058$ and $p = 0.009$, respectively).
For any nonvertebral fractures and for nonvertebral-six fractures, the treatment effect should be evaluated separately by whether prevalent vertebral fractures were present at MORE baseline. For most of the subgroups analyzed, there was little difference between the proportion of patients in each treatment group, with the exception of those subgroups indicative of more severe osteoporosis, which predisposes a patient to future fractures: SQ = 3 and prevalent vertebral fractures. In those subgroups, there were proportionately fewer raloxifene-treated patients who experienced any nonvertebral fracture or nonvertebral-six fracture compared with placebo patients, although the difference was not statistically significant except for the prevalent

vertebral fractures subgroup on nonvertebral-six fractures in the analysis unadjusted by multiplicity.

Table GGJY.11.14. Subgroup Analyses of Any Nonvertebral Fracture Results (MORE Baseline through CORE Termination, All Patients Enrolled in CORE)

Subgroup Variables	Treatment by Subgroup Interaction p-value	Patients with>=1 Any Nonvertebral Fractures: Placebo N (%)	RLX N (%)	Hazard Ratio (95% CI)	(Adjusted CI *)
Age* (Years)	0.5075				
lower 33%, <=63.0		78 (18.5%)	100 (20.8%)	1.143 (0.878, 1.489)	(0.801, 1.631)
middle 33%, >63.0 AND <=69.2		93 (22.3%)	196 (21.6%)	0.968 (0.755, 1.240)	(0.693, 1.350)
upper 33%, >69.2		124 (27.7%)	238 (26.0%)	0.941 (0.757, 1.169)	(0.703, 1.260)
Lumbar Spine BMD*	0.2642				
lower 33%, <=0.75		108 (25.6%)	215 (24.0%)	0.928 (0.736, 1.169)	(0.680, 1.266)
middle 33%, >0.75 AND <=0.85		99 (23.2%)	189 (21.2%)	0.909 (0.713, 1.159)	(0.655, 1.261)
upper 33%, >0.85		86 (20.0%)	212 (22.9%)	1.181 (0.918, 1.519)	(0.842, 1.657)
Femoral Neck BMD*	0.5550				
lower 33%, <=0.59		122 (28.5%)	251 (27.8%)	0.932 (0.751, 1.157)	(0.696, 1.247)
middle 33%, >0.59 AND <=0.66		92 (21.6%)	186 (20.8%)	0.954 (0.743, 1.225)	(0.682, 1.335)
upper 33%, >0.66		81 (18.3%)	181 (19.8%)	1.116 (0.858, 1.452)	(0.783, 1.590)
SQ Level**	0.1610				
SQ=0,1 or 2		265 (22.1%)	566 (22.5%)	1.024 (0.885, 1.185)	(0.850, 1.234)
SQ=3		29 (36.3%)	55 (27.9%)	0.730 (0.466, 1.145)	(0.412, 1.296)
Prevalent Vertebral Fracture**	0.0578				
No		166 (19.3%)	358 (20.9%)	1.099 (0.914, 1.321)	(0.869, 1.389)
Yes		128 (30.5%)	263 (26.2%)	0.837 (0.677, 1.035)	(0.639, 1.097)
Prevalent Nonvertebral Fracture**	0.2654				
No		111 (17.3%)	274 (19.0%)	1.117 (0.895, 1.393)	(0.842, 1.480)
Yes		184 (28.5%)	348 (27.2%)	0.950 (0.795, 1.136)	(0.757, 1.193)
Treatment Compliance Over 80% During CORE and MORE**	0.7571				
No		143 (24.8%)	316 (25.1%)	1.020 (0.837, 1.243)	(0.793, 1.312)
Yes		152 (21.4%)	306 (20.9%)	0.976 (0.804, 1.187)	(0.762, 1.252)

* Adjusted CI is based on a Bonferroni multiplicity adjustment, where the analysis is tested at the 0.0083 level to control the overall type I error at 0.05.
** Adjusted CI is based on a Bonferroni multiplicity adjustment, where the analysis is tested at the 0.0125 level to control the overall type I error at 0.05.

Program: RMP.H3SSGGJY.SASPGM(BNC1111D) Output: RMP.H3SO.GGJY.FINAL(BNC1111E)

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Table GGJY.11.15. Subgroup Analyses of Nonvertebral-Six Fracture Results (MORE Baseline through CORE Termination, All Patients Enrolled in CORE)

Subgroup Variables	Treatment by Subgroup Interaction p-value	Patients with>=1 Nonvertebral-Six Fractures: Placebo N (%)	RLX N (%)	Hazard Ratio (95% CI)	(Adjusted CI *)
Age* (Years)	0.4401				
lower 33%, <=63.0		56 (13.3%)	141 (15.6%)	1.196 (0.877, 1.630)	(0.788, 1.814)
middle 33%, >63.0 AND <=69.2		71 (17.0%)	149 (16.4%)	0.970 (0.730, 1.289)	(0.662, 1.422)
upper 33%, >69.2		98 (21.9%)	187 (20.4%)	0.931 (0.729, 1.189)	(0.670, 1.294)
Lumbar Spine BMD*	0.4572				
lower 33%, <=0.75		84 (19.9%)	165 (18.4%)	0.920 (0.708, 1.197)	(0.646, 1.311)
middle 33%, >0.75 AND <=0.85		73 (17.1%)	147 (16.5%)	0.961 (0.726, 1.272)	(0.659, 1.402)
upper 33%, >0.85		66 (15.3%)	161 (17.4%)	1.167 (0.875, 1.557)	(0.792, 1.720)
Femoral Neck BMD*	0.7980				
lower 33%, <=0.59		90 (21.8%)	206 (22.8%)	1.061 (0.829, 1.359)	(0.760, 1.481)
middle 33%, >0.59 AND <=0.66		68 (16.0%)	135 (15.1%)	0.934 (0.698, 1.250)	(0.631, 1.383)
upper 33%, >0.66		67 (15.2%)	133 (14.6%)	0.977 (0.728, 1.313)	(0.657, 1.454)
SQ Level**	0.1504				
SQ=0,1 or 2		200 (16.7%)	429 (17.0%)	1.031 (0.872, 1.220)	(0.832, 1.278)
SQ=3		25 (31.3%)	47 (23.9%)	0.708 (0.436, 1.149)	(0.381, 1.313)
Prevalent Vertebral Fracture**	0.0050				
No		119 (13.9%)	274 (16.0%)	1.179 (0.951, 1.462)	(0.896, 1.551)
Yes		106 (25.2%)	202 (20.1%)	0.770 (0.608, 0.975)	(0.570, 1.040)
Prevalent Nonvertebral Fracture**	0.2541				
No		84 (13.1%)	212 (14.7%)	1.142 (0.886, 1.472)	(0.827, 1.578)
Yes		141 (21.5%)	265 (20.7%)	0.945 (0.770, 1.159)	(0.728, 1.226)
Treatment Compliance Over 80% During CORE and MORE**	0.2549				
No		103 (17.9%)	245 (19.4%)	1.106 (0.878, 1.392)	(0.825, 1.483)
Yes		122 (17.2%)	232 (15.8%)	0.919 (0.738, 1.145)	(0.695, 1.216)

* Adjusted CI is based on a Bonferroni multiplicity adjustment, where the analysis is tested at the 0.0083 level to control the overall type I error at 0.05.
** Adjusted CI is based on a Bonferroni multiplicity adjustment, where the analysis is tested at the 0.0125 level to control the overall type I error at 0.05.

Program: RMP.H3SSGGJY.SASPGM(BNC1111D) Output: RMP.H3SO.GGJY.FINAL(BNC1111D)

Time-to-Event Analyses of Nonvertebral Fracture by Subgroup (11.4.4.2.3.1)

The following figures show a time-to-event analysis of any nonvertebral fracture and nonvertebral-six fracture for patients enrolled in CORE with a baseline SQ = 3. Although there was no significant difference between the two treatment groups, proportionately fewer raloxifene-treated patients sustained a fracture over the 8 years of treatment compared with placebo-treated patients.

The figures show a time-to-event analysis of any nonvertebral fracture and nonvertebral-six fracture for patients enrolled in CORE with baseline-prevalent vertebral fracture. Similar to the previous results, although there was no significant difference between the two treatment groups for any nonvertebral fracture, proportionately fewer raloxifene-treated patients sustained a fracture over the 8 years of treatment compared with placebo-treated patients. There were significantly fewer nonvertebral-six fractures for the raloxifene group compared with the placebo group (p=0.0304, hazard ratio 0.77, 95%CI 0.61, 0.98). For both figures the hazard ratio and 95% CI were calculated on the subset populations of either MORE baseline SQ=3 or prevalent vertebral fracture, whereas the calculations in Table GGJY.11.14 and Table GGJY.11.15 utilized all the patients, incorporating the therapy and variable interaction. Thus, the hazard ratio and 95% CI differ in both figures from those in Table GGJY.11.14 and Table GGJY.11.15, although they are similar.

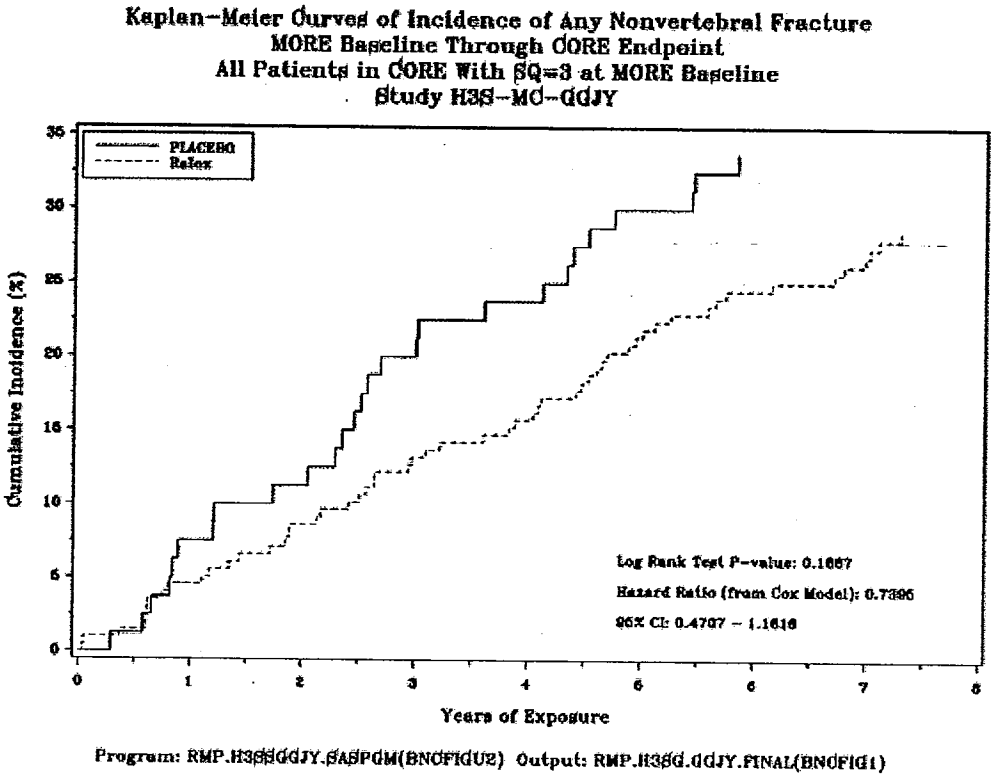

Figure GGJY.11.9. Incidence of any nonvertebral fracture, MORE baseline through CORE termination (All patients in CORE with SQ=3 at MORE baseline)

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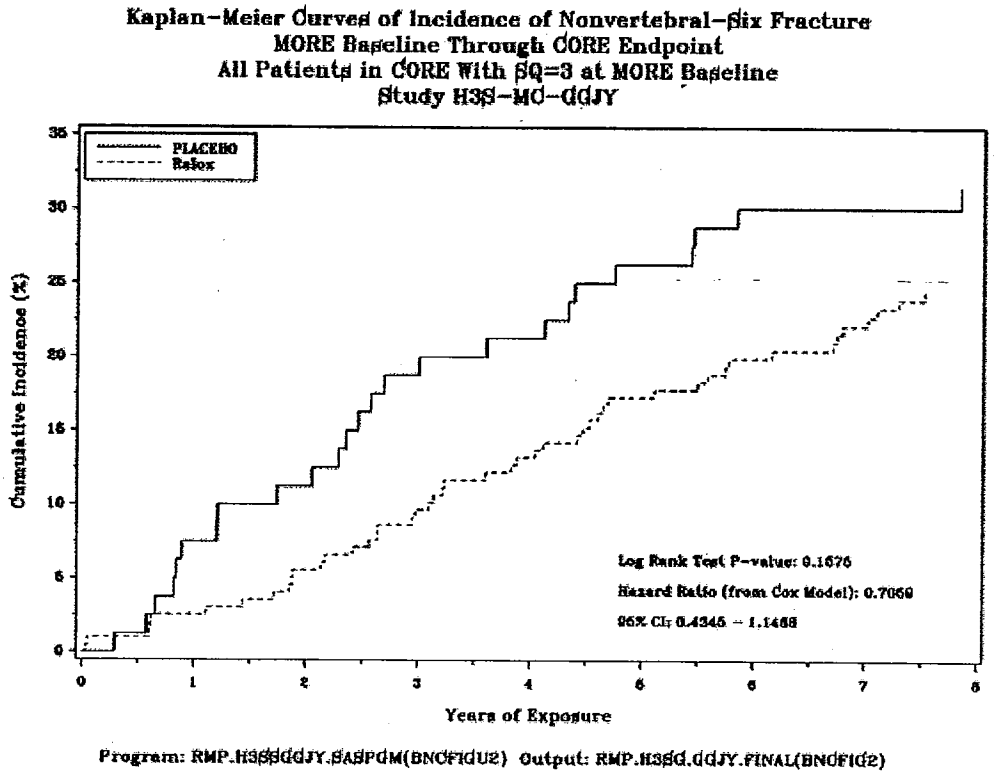

Figure GGJY.11.10. Incidence of nonvertebral-six fracture, MORE baseline through CORE termination (All patients in CORE with SQ=3 at MORE baseline)

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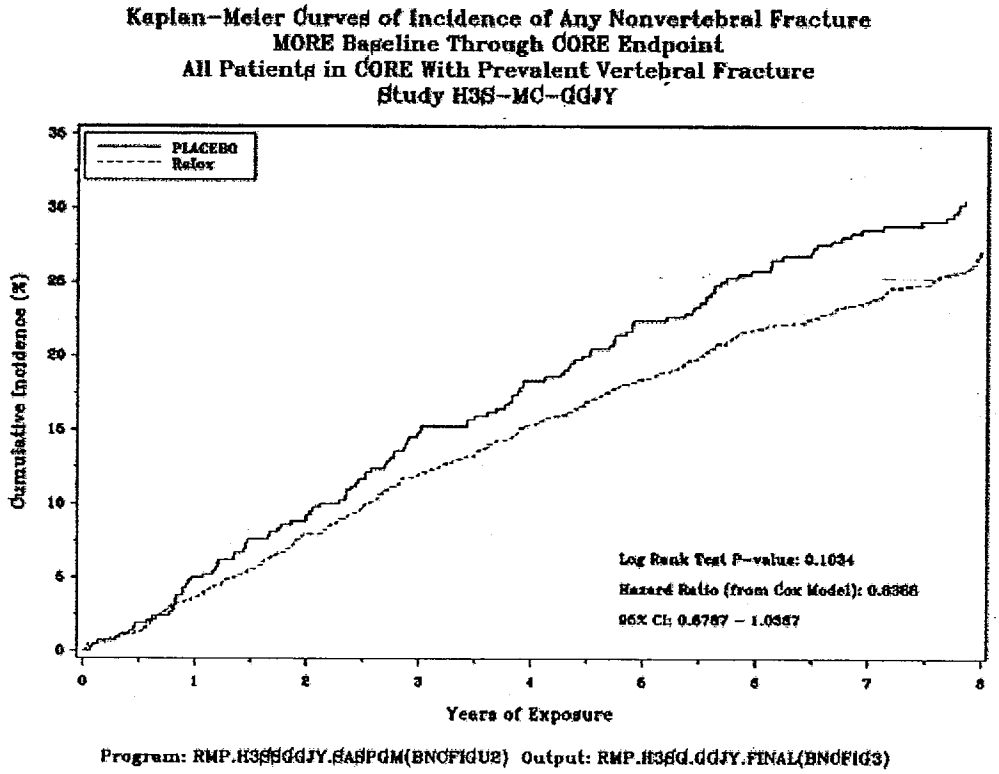

Figure GGJY.11.11. Incidence of any nonvertebral fracture, MORE baseline through CORE termination (All patients in CORE with prevalent vertebral fracture at MORE baseline)

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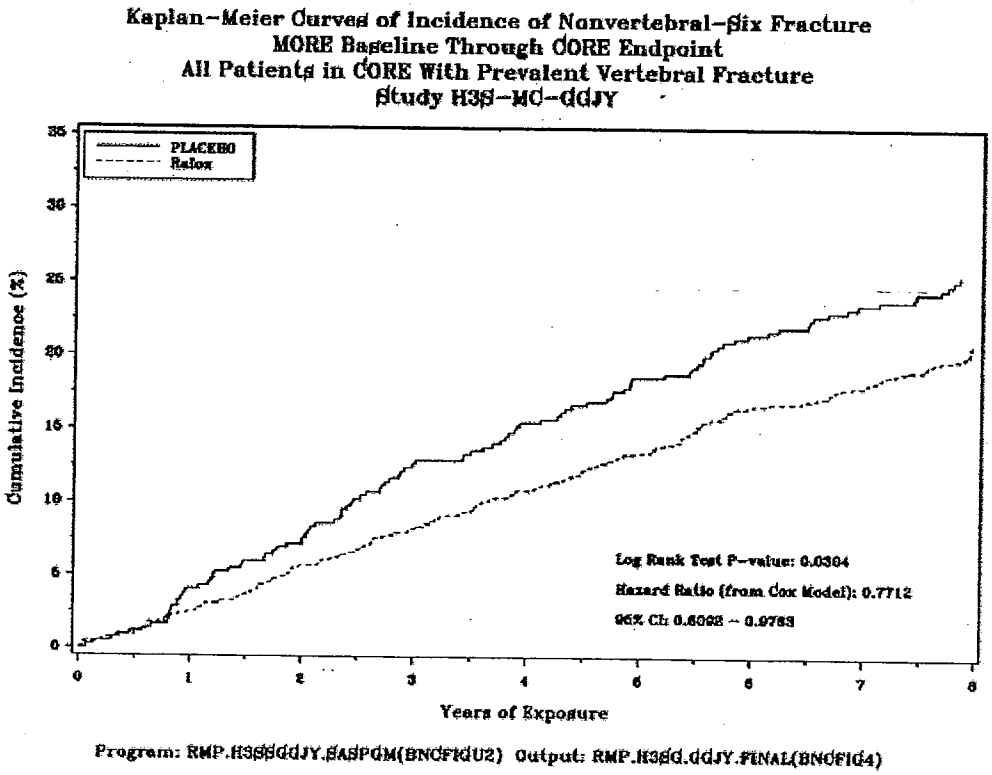

Figure GGJY.11.12. Incidence of any nonvertebral-six fracture, MORE baseline through CORE termination (All patients in CORE with prevalent vertebral fracture at MORE baseline)

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Subset Analyses Based on Concomitant Bone-Active Agents (11.4.4.2.4)

The impact of bone-active agent use on incidence of nonvertebral fractures and nonvertebral-six fractures was further evaluated by looking at the subgroups of patients who did not use any other bone-active agent and/or who took at least one dose of study drug during CORE. The following table shows the incidence of nonvertebral fractures for:

- Patients who did not use any other bone-active agent after the 3rd year of MORE
- Patients who took at least one dose of study drug in CORE
- Patients who did not use any other bone-active agent after the 3rd year of MORE and who took at least one dose of study drug during CORE

Nearly half of the patients in CORE took some other bone-active agent after the 3rd year of MORE.

There was no difference in incidence of nonvertebral fracture or nonvertebral-six fracture between the treatment groups for patients who did not use any other bone-active agent, for patients who took at least one dose of study drug, or for patients who did not use any other bone-active agent and took at least one dose of study drug.

Table GGJY.11.16. Subset Analyses of Nonvertebral Fracture Results by Use of Bone-Active Agents or Study Drug (From MORE Baseline through CORE Termination, All Patients Enrolled in CORE)

Subset	Fracture Location	Placebo	RLX	Hazard Ratio (95% CI)	(Adjusted CI*)
Patients who did not use other bone-active agents after the third year of MORE	Any nonvertebral fracture	111/ 622 (17.8%)	287/1420 (20.2%)	1.163 (0.933, 1.449)	(0.904, 1.495)
	Nonvertebral-six	83/ 622 (13.3%)	218/1420 (15.4%)	1.185 (0.919, 1.527)	(0.886, 1.584)
Patients who took at least one dose of study drug in CORE	Any nonvertebral fracture	230/1018 (22.6%)	480/2182 (22.0%)	0.980 (0.838, 1.147)	(0.819, 1.174)
	Nonvertebral-six	179/1018 (17.6%)	366/2182 (16.8%)	0.957 (0.800, 1.145)	(0.780, 1.174)
Patients who did not use other bone-active agents after the third year of MORE and who took at least one dose of study drug in CORE	Any nonvertebral fracture	94/ 550 (17.1%)	253/1282 (19.7%)	1.194 (0.941, 1.514)	(0.910, 1.567)
	Nonvertebral-six	73/ 550 (13.3%)	193/1282 (15.1%)	1.169 (0.892, 1.533)	(0.858, 1.594)

* A Bonferroni multiplicity adjustment were made, where each of the above analyses is tested at the 0.025 level to control the overall type I error at 0.05.

Program: RMP.H3SGGJY.SASPGM(BNC1110C) Output: RMP.H3SO.GGJY.FINAL(BNC1110C)

Potential Confounders to Nonvertebral Fracture Results (11.4.4.2.5)

Since the primary endpoint for CORE was incidence of breast cancer, concomitant bone-active agent use was allowed. During MORE, the placebo subjects who enrolled in CORE had a lower risk of nonvertebral fractures than the placebo patients who did not enroll in CORE. This difference can be illustrated by comparing the placebo time-to-event analyses of incidence of any nonvertebral fracture or nonvertebral-six fracture for patients who were enrolled in CORE with the population of MORE that did not enroll in CORE.

The following figures show the time-to-event incidence of any nonvertebral fracture or nonvertebral-six fracture for placebo patients in CORE compared with the placebo population of MORE that did not enroll in CORE over a 4-year treatment period in each study. Fewer placebo patients in CORE had a nonvertebral fracture or nonvertebral-six fracture compared with placebo patients enrolled in MORE who did not enroll into CORE.
The following figures show the time-to-event incidence of any nonvertebral fracture or nonvertebral-six fracture for raloxifene patients in CORE compared with the raloxifene population of MORE that did not enroll in CORE over a 4-year treatment period in each study. Unlike the placebo population who enrolled in CORE compared with placebo patients who did not enroll in CORE, the raloxifene patients who enrolled in CORE did not appear to be different in their fracture risk than raloxifene patients who did not enroll in CORE.
Thus, there may be selection bias favoring placebo.

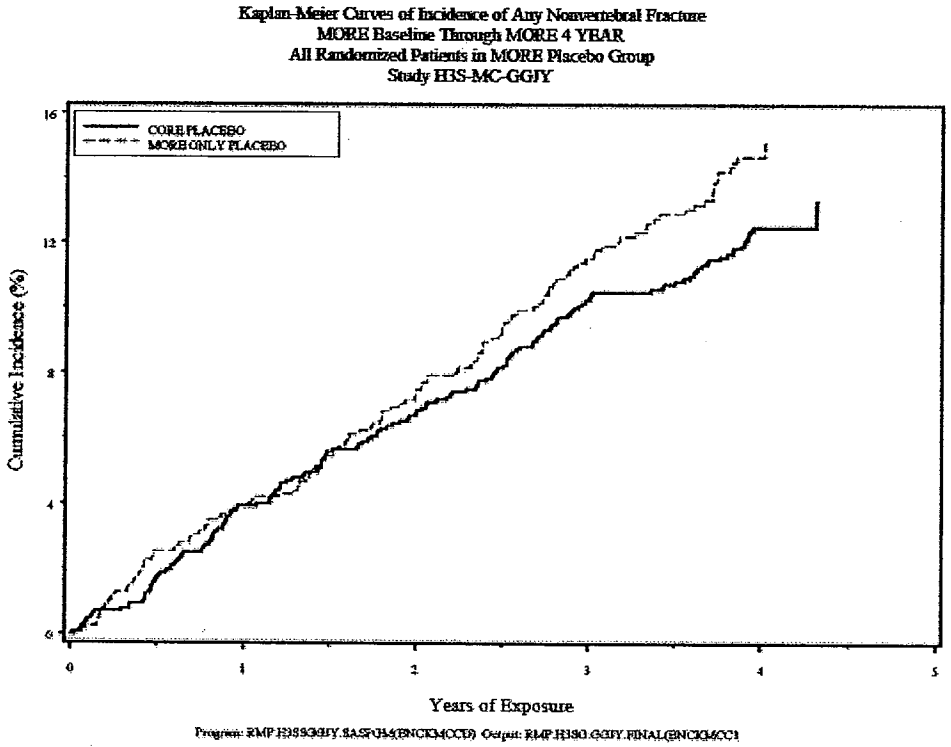

Figure GGJY.11.13. Incidence of nonvertebral fractures in placebo patients (patients enrolled in MORE but *not in CORE* compared with those enrolled *in CORE* from study baseline through 4 years of treatment)

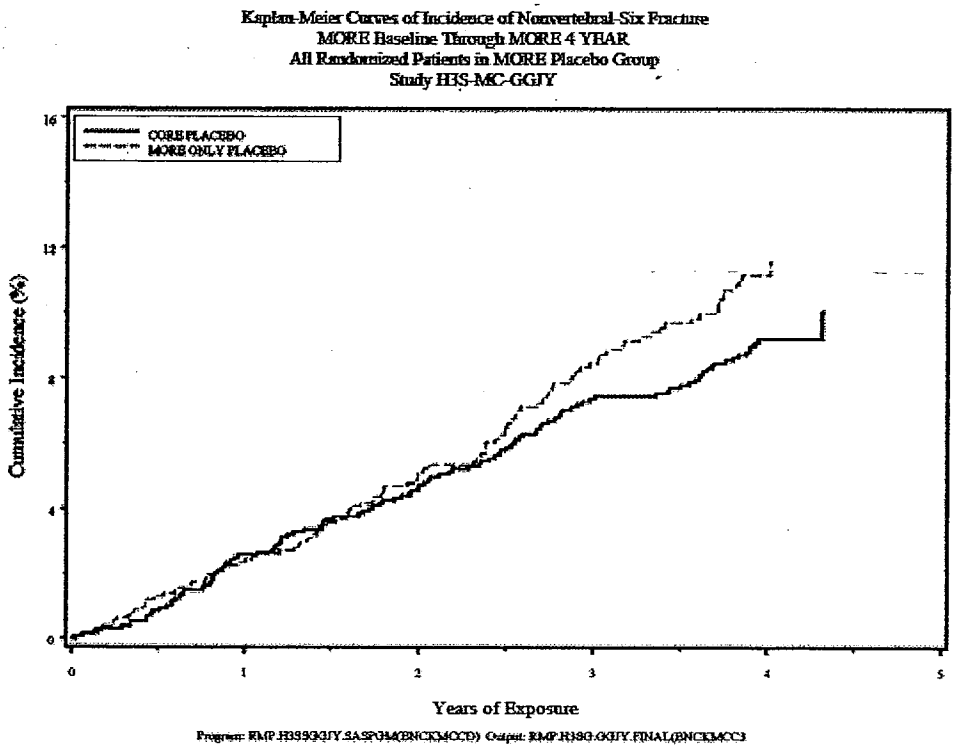

Figure GGJY.11.14. Incidence of nonvertebral-six fractures in placebo patients (Patients enrolled in MORE but not in CORE compared with those enrolled in CORE from MORE baseline through 4 years of treatment)

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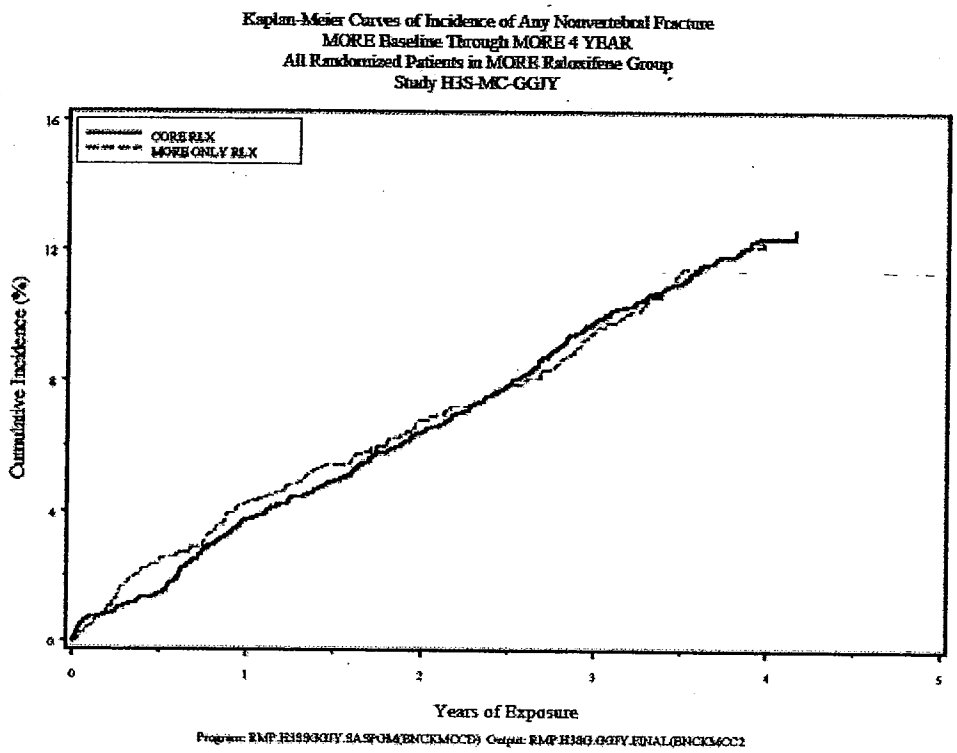

Figure GGJY.11.15. Incidence of nonvertebral fractures in raloxifene patients (Patients enrolled in MORE but not in CORE compared with those enrolled in CORE from study baseline through 4 years of treatment)

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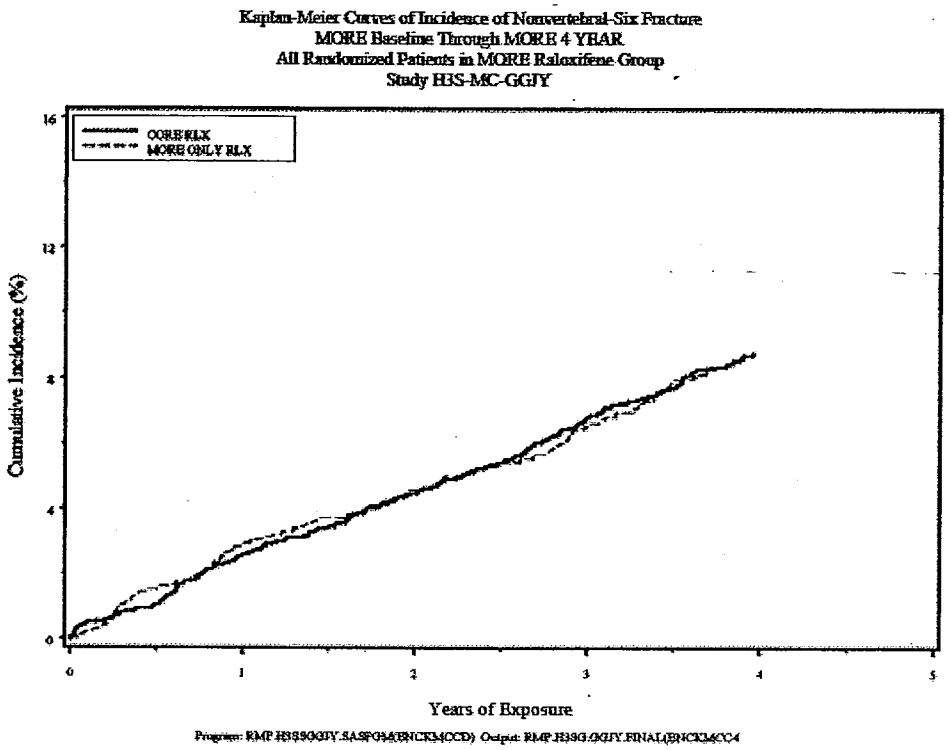

Figure GGJY.11.16. Incidence of nonvertebral-six fractures in raloxifene patients (Patients enrolled in MORE but not in CORE compared with those enrolled in CORE from MORE baseline through 4 years of treatment)

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Specific potential confounders to the nonvertebral fracture efficacy results were identified as SQ score at the end of MORE; incidence of at least one new vertebral fracture during MORE; use of bone-active agents, including bisphosphonates, after the 3rd year of MORE; and resumption of study drug during CORE.

The following table shows the imbalance of the specific potential confounders that could have had an influence on the assessment of nonvertebral fracture efficacy in patients enrolled in CORE. The following confounders had a potential significant effect on the incidence of nonvertebral fractures given their imbalance between patients receiving placebo and those receiving raloxifene: incidence of at least one new vertebral fracture during MORE, bone-active agent use after the 3rd year of MORE, and bisphosphonate use after the 3rd year of MORE.

Table GGJY.11.17. Imbalance Checking of Potential Confounders (Any Nonvertebral Fracture, All Patients Enrolled in CORE)

Variable	Value	Placebo (N=1186)	Ralox (N=2725)	P-value
SQ Score at the End of MORE	0	804 (62.52%)	1651 (60.59%)	0.350
	1	223 (17.34%)	528 (19.38%)	
	2	154 (11.98%)	308 (11.30%)	
	3	98 (7.62%)	231 (8.48%)	
Incidence of at least One New Vertebral Fracture during MORE	NO	1114 (86.63%)	2482 (91.08%)	<0.001
	YES	147 (11.43%)	187 (6.86%)	
Bone-active Agent Use After the 3rd Year of MORE	NO	622 (48.37%)	1420 (52.11%)	0.026
	YES	664 (51.63%)	1305 (47.89%)	
Bisphosphonates Use After the 3rd Year of MORE	NO	782 (60.81%)	1811 (66.46%)	<0.001
	YES	504 (39.19%)	914 (33.54%)	
Use of Other Bone-active Agent After 3rd Year of MORE	NO	1126 (87.56%)	2334 (85.65%)	0.101
	YES	160 (12.44%)	391 (14.35%)	
Resume to Take Study Drug During CORE	NO	268 (20.84%)	543 (19.93%)	0.501
	YES	1018 (79.16%)	2182 (80.07%)	

Program: RMP.H3SGGJY.SASPGM(BNCIMBL) Output: RMP.H3SO.GGJY.FINAL(BNCIMBL2)

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All Patients in PAD from Study GGGK Baseline to Study GGJY Termination (11.4.4.3)

Analyses of nonvertebral fracture incidence were conducted on all patients who were eligible for participation in CORE, also known as the Primary Analysis Dataset (PAD) population.

- The PAD population is the same as the primary breast cancer analyses population.
- In the PAD population, there was no effect of raloxifene on the incidence of nonvertebral fractures or nonvertebral-six fractures.

Table GGJY.11.18. Nonvertebral Fracture Results (MORE Baseline Through CORE Termination, All Patients in PAD)

Fracture Location	Placebo (N=2178)	RLX (N=4333)	Hazard Ratio (95% CI)	(Adjusted CI*)
Any nonvertebral fracture	393 (18.0%)	762 (17.6%)	0.950 (0.841, 1.073)	(0.824, 1.092)
Nonvertebral-six	297 (13.6%)	583 (13.5%)	0.962 (0.837, 1.107)	(0.820, 1.129)

* A Bonferroni multiplicity adjustment were made, where each of the above analyses is tested at the 0.025 level to control the overall type I error at 0.05.

Program: RMP.H3SSGGJY.SASPGM(BNCT117C) Output: RMP.H3SO.GGJY.FINAL(BNCT116C)

All 7705 Patients Enrolled in MORE from MORE Baseline to CORE Termination (11.4.4.4)

Analyses of nonvertebral fracture incidence were also conducted in all 7,705 patients who enrolled in MORE through CORE termination. This population includes patients not eligible for participation in CORE. There was no effect of raloxifene on the incidence of nonvertebral or nonvertebral-six fractures.

Table GGJY.11.19. Nonvertebral Fracture Results (MORE Baseline through CORE Termination, All Patients Enrolled in MORE)

Fracture Location	Placebo (N=2576)	RLX (N=5129)	Hazard Ratio (95% CI)	(Adjusted CI*)
Any nonvertebral fracture	435 (16.9%)	840 (16.4%)	0.947 (0.843, 1.063)	(0.829, 1.081)
Nonvertebral-six	329 (12.8%)	631 (12.3%)	0.941 (0.823, 1.075)	(0.807, 1.096)

* A Bonferroni multiplicity adjustment were made, where each of the above analyses is tested at the 0.025 level to control the overall type I error at 0.05.

Program: RMP.H3SSGGJY.SASPGM(BNCT117C) Output: RMP.H3SO.GGJY.FINAL(BNCT118D)

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Poisson Analyses for Any Nonvertebral Fracture and Nonvertebral-Six Fracture (11.4.4.5)

Most placebo-controlled osteoporosis studies with fracture endpoints have been limited to 3 years of treatment duration, in which multiple nonvertebral fractures in a given subject are uncommon. However, in the current evaluation of approximately 8 years of treatment duration, multiple nonvertebral fractures in a given subject may be a relevant outcome to consider. In order to compare the incident rate (number of fractures/time on therapy) of multiple nonvertebral fractures between the two treatment groups, Poisson regression analyses were used.
The table shows the number of patients with multiple nonvertebral fractures and nonvertebral-six fractures:

- Of the patients enrolled in CORE, fewer raloxifene treated patients (4.4%) than placebo-treated patients (6.0%) sustained more than one nonvertebral fracture sometime between enrollment in MORE and study termination of CORE. Similarly, 2.4% of the raloxifene-treated patients sustained more than one nonvertebral-six fracture compared with 3.6% of the placebo-treated patients.
- Although there were *proportionally fewer* multiple nonvertebral fractures and nonvertebral-six fractures in raloxifene-treated women compared with placebo treated women, there was *no significant difference* between the groups in any of the populations tested (all women enrolled in MORE, the PAD population, and women who enrolled in CORE).

Table GGJY.11.20. Frequency of Nonvertebral Fractures since Randomization Into MORE (All Patients Enrolled in CORE)

Fracture Location	No. of Fracture	PLACEBO (N=1286) n (%)	RALOX (N=2725) n (%)	P-value*
Any Nonvertebral Fractures				0.299
	0	991 (77.06)	2103 (77.17)	
	1	218 (16.95)	503 (18.46)	
	2	60 (4.67)	89 (3.27)	
	3	9 (0.70)	15 (0.55)	
	4	7 (0.54)	12 (0.44)	
	5	1 (0.08)	1 (0.04)	
	6	0 (0.00)	1 (0.04)	
	7	0 (0.00)	1 (0.04)	
Nonvertebral-Six Fractures				0.012
	0	1061 (82.50)	2248 (82.50)	
	1	178 (13.84)	411 (15.08)	
	2	43 (3.34)	48 (1.76)	
	3	4 (0.31)	14 (0.51)	
	4	0 (0.00)	4 (0.15)	

* P-value is obtained using Fisher's Exact test.

Program: RMP.H3SSGGJY.SASPGM(BNCTPOI) OUTPUT: RMP.H3SO.GGJY.FINAL(BNCTPOI1)

Table GGJY.11.21. Poisson Analyses for Nonvertebral Fractures and Nonvertebral-Six Fractures (All Patients Enrolled in CORE, in MORE, and in the PAD Population)

Population	Fracture Location	Incidence Rate Ratio (95% CI)
ALL	Any Nonvertebral Fractures	0.91 (0.82, 1.01)
	Nonvertebral-Six Fractures	0.91 (0.80, 1.03)
CCD	Any Nonvertebral Fractures	0.94 (0.84, 1.06)
	Nonvertebral-Six Fractures	0.97 (0.84, 1.12)
PAD	Any Nonvertebral Fractures	0.91 (0.82, 1.01)
	Nonvertebral-Six Fractures	0.93 (0.82, 1.06)

* ALL-- All Randomized Patients in GGGK(N=7705)

Program: RMP.H3SSGGJY.SASPGM(BNCTPOI) OUTPUT: RMP.H3SO.GGJY.FINAL(BNCTPOI2)

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Subgroup Analyses for Any Nonvertebral Fracture and Nonvertebral-Six Fracture (11.4.4.5.1)

Subgroup analyses for any nonvertebral fractures and for nonvertebral-six fractures using the Poisson method for the baseline characteristics for SQ=3 and for prevalent vertebral fractures were conducted for patients enrolled in CORE (CCD population) as well as for all 7,705 patients enrolled in MORE (designated as "ALL" in the table) and for the PAD population (patients whose investigators enrolled patients in CORE).

Baseline SQ Score

The table below shows the incidence rate of any nonvertebral fractures or nonvertebral six fractures for patients by MORE baseline SQ score. The interaction of treatment group and SQ score was significant at the 0.10 level for nonvertebral-six fractures in all three populations studied (patients enrolled in CORE, all patients in MORE, and the PAD population).
For patients in the SQ = 3 group, there was no significant difference between the treatment groups in incidence of nonvertebral fracture or nonvertebral-six fracture for the CCD population, although the incidence of each was lower in the raloxifene-treated patients.
There were significantly fewer nonvertebral-six fractures in the raloxifene-treated patients in the PAD population (incidence rate ratio 0.65, 95%CI 0.44, 0.95) and in the entire population of MORE (referred to in the table as "ALL") (incidence rate ratio 0.64, 95%CI 0.44, 0.92). There was no significant difference between the treatment groups for any nonvertebral fracture in these two populations.

Table GGJY.11.22. Poisson Analyses for Nonvertebral Fractures by MORE Baseline SQ Score (All Patients Enrolled in CORE, in MORE, and in PAD Population)

Population	Fracture Location	SQ Score	Incidence Rate Ratio (95% CI)	Interaction P-Value
ALL	Any Nonvertebral Fractures	0,1,2	0.92 (0.83, 1.03)	0.315
		3	0.78 (0.56, 1.07)	
	Nonvertebral-Six Fractures	0,1,2	0.94 (0.83, 1.07)	0.051
		3	0.64 (0.44, 0.92)	
CCD	Any Nonvertebral Fractures	0,1,2	0.96 (0.84, 1.09)	0.246
		3	0.75 (0.51, 1.11)	
	Nonvertebral-Six Fractures	0,1,2	1.00 (0.86, 1.17)	0.082
		3	0.66 (0.43, 1.02)	
PAD	Any Nonvertebral Fractures	0,1,2	0.92 (0.83, 1.04)	0.324
		3	0.77 (0.55, 1.08)	
	Nonvertebral-Six Fractures	0,1,2	0.96 (0.84, 1.11)	0.060
		3	0.65 (0.44, 0.95)	

* ALL--All Randomized Patients in MORE(N=7705)

Program: RMP.H3SSGGJY.SASPGM(BNCTPOI) OUTPUT: RMP.H3SO.GGJY.FINAL(BNCTPOI3)

Baseline Prevalent Vertebral Fracture

The table shows the incidence of any nonvertebral fracture or nonvertebral-six fracture for patients in the subgroup in MORE who had at least one baseline prevalent vertebral fracture. The interaction of treatment group and prevalent vertebral fracture was significant at the 0.10 level for nonvertebral-six fractures in patients enrolled in CORE (CCD population).
For patients with a baseline prevalent vertebral fracture, raloxifene-treated patients had significantly fewer nonvertebral-six fractures compared with placebo treatment in the CCD population with prevalent baseline-vertebral fractures (incidence rate ratio 0.78, 95%CI 0.63, 0.96). For patients with a baseline prevalent vertebral fracture, raloxifene-treated patients had significantly fewer nonvertebral-six fractures compared with the placebo group in the entire MORE population (incidence rate ratio 0.82, 95%CI 0.69, 0.99).

Table GGJY.11.23. Poisson Analyses of Nonvertebral Fractures by MORE Baseline Prevalent Vertebral Fracture (All Patients Enrolled in CORE, in MORE, and in PAD Population)

Population	Fracture Location	Prev. of Vert.	Incidence Rate Ratio (95% CI)	Interaction P-Value
ALL	Any Nonvertebral Fractures	0	0.92 (0.80, 1.06)	0.666
		1	0.88 (0.75, 1.02)	
	Nonvertebral-Six Fractures	0	0.96 (0.81, 1.14)	0.222
		1	0.82 (0.69, 0.99)	
CCD	Any Nonvertebral Fractures	0	1.00 (0.85, 1.18)	0.132
		1	0.83 (0.70, 1.00)	
	Nonvertebral-Six Fractures	0	1.11 (0.91, 1.36)	0.017
		1	0.78 (0.63, 0.96)	
PAD	Any Nonvertebral Fractures	0	0.93 (0.81, 1.08)	0.437
		1	0.86 (0.73, 1.01)	
	Nonvertebral-Six Fractures	0	0.99 (0.83, 1.18)	0.168
		1	0.83 (0.69, 1.00)	

*ALL-- All Randomized Patients in GGGK(N=7705)

Program: RMP.H3SSGGJY.SASPGM(BNCTPOI) OUTPUT: RMP.H3SO.GGJY.FINAL(BNCTPOI4)

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Efficacy Conclusions (11.4.5)

CORE was designed to provide additional data on the observation of reduction in risk of invasive breast cancer as seen by the end of 4 years of raloxifene treatment in MORE by continued follow up of a cohort from the MORE population. The patients in CORE were originally enrolled in MORE because they had osteoporosis. Generally, patients with osteoporosis are considered to have a lower risk of breast cancer (Cauley et al. 1996; Zhang et al. 1997). However, the placebo rates of breast cancer observed through 4 years of treatment in MORE were similar to rates expected among average 65 year-old white women (Greenlee et al. 2000; Cummings et al. 1999). In MORE both doses of raloxifene (raloxifene HCl 60 mg and 120 mg) significantly reduced the incidence of invasive breast cancer and invasive ER + breast cancer with no dose differentiation.

Although a secondary endpoint of CORE was to determine the effect of raloxifene on nonvertebral fractures, the safety provision that patients were allowed to use other bone-active agents after the 3rd year of MORE and continuing throughout CORE diminished the likelihood of determining an effect of raloxifene on nonvertebral fractures.

Furthermore, patients were asked to enter into CORE and, in consult with the physician, were given the choice to restart or not to restart study drug.

The secondary endpoint was a priori determined when the protocol was written because a trend toward reduction in incidence of nonvertebral fractures could be observed with increasing time of patients exposed to raloxifene treatment versus placebo during MORE

Patient Populations (11.4.5.1)

Three patient populations were evaluated for the efficacy endpoints:

- Patients of investigators who enrolled patients in CORE, regardless of whether the patients participated in CORE (PAD population; N=6,511)
- Patients who enrolled in CORE (CCD population; N=4,011);
- All 7,705 patients who enrolled in MORE

The durations of treatment evaluated:

- From 1 January 1999 through CORE termination (approximately 5 years of treatment)
- From enrollment into CORE through study termination (approximately 3 years)
- From enrollment into MORE through CORE termination (approximately 8 years)

Demographics (11.4.5.2)

The two treatment groups in CORE (CCD population) were well balanced with regard to breast cancer risk; however, there were differences in osteoporosis severity and in cardiovascular risk. The mean baseline 5-year predicted risk of breast cancer for patients was 1.94 in both CORE

treatment groups, which is considered an elevated risk for breast cancer according to the Gail model (a 5-year predicted risk of breast cancer $\geq$ 1.67 was considered at elevated risk).

Comparison of MORE baseline characteristics of patients who subsequently enrolled in CORE (4,011 patients) with those of patients who did not enroll in CORE (3,694 patients) showed several differences:

- Patients who enrolled in CORE tended to be younger, fewer years postmenopausal, had less severe osteoporosis, and fewer cardiovascular disease-related therapies were utilized than patients who did not enroll in CORE.
- There was a similar family history of breast cancer (defined as breast cancer occurring in a first-degree relative of the patient) in the two patient populations.

Treatment Compliance (11.4.5.3)

Patients in CORE were allowed to continue their *study participation* even if they experienced an adverse event and/or were no longer taking study drug.

- Approximately 20% of the patients enrolled in CORE never took study drug during the study.
- The median time between the end of MORE and enrollment into CORE was 10 months for both treatment groups.
- Compliance in CORE, defined as taking at least 80% of study drug, was 55%.
- If patients who never took study drug are excluded from compliance calculations, 69% of patients were considered compliant.
- There was no difference between the placebo and raloxifene treatment groups, including the 20% of patients who never took study drug.

Concomitant Medications (11.4.5.4)

- Concomitant use of other osteoporosis medications was allowed during the 4th year of MORE and throughout CORE. Nearly half of all patients enrolled in CORE utilized some other bone-active agent at some time point after the 3rd year of MORE.
- There were significantly more patients in the placebo group who took bone-active agents at CORE baseline. Furthermore, proportionally more patients in the placebo group than the raloxifene group took bone active agents throughout CORE.

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Breast Cancer Efficacy (11.4.5.5)

Raloxifene treatment resulted in a significant reduction of adjudicated invasive breast cancer and invasive ER + breast cancer in every population at every treatment duration that was studied.

The PAD population from 1 January 1999 through the end of CORE

- Raloxifene treatment resulted in a 59% reduction in invasive breast cancer, the primary endpoint of the study, and a 66% reduction in invasive ER + breast cancer, a secondary endpoint, in **the PAD population from 1 January 1999 through the end of CORE.**
- There was no difference between the treatment groups in the risk of ER - breast cancer or in the risk of noninvasive breast cancer.
- Time-to-event analyses demonstrated a continuous separation between placebo- and raloxifene- treated patients for invasive and invasive ER + breast cancer cases.
- Every sensitivity analysis conducted confirmed that the primary analysis on adjudicated invasive breast cancer results was robust.
- Subgroup analyses (5-year predicted breast cancer risk according to the Gail model, baseline estradiol, baseline age, baseline BMD, previous use of hormone replacement therapy, and family history of breast cancer defined as breast cancer occurring in a first-degree relative of the patient) demonstrated that patients at increased risk of invasive breast cancer had an overall decrease in the risk of developing breast cancer with raloxifene treatment.
- Furthermore, raloxifene-treated patients with lower risk factors for developing invasive breast cancer generally had a lower risk of developing invasive breast cancer than placebo-treated patients, although the difference may not have been significant.
- These results demonstrate that the primary objective of this study, to determine the effect of raloxifene on invasive breast cancer after 1 January 1999 through the end of CORE was met and that raloxifene continued to reduce the risk of invasive breast cancer as was observed through 4 years of treatment in MORE.

The PAD population from enrollment in MORE through study termination of CORE

- Evaluation of the incidence of invasive breast cancer in **the PAD population from enrollment in MORE through study termination of CORE** demonstrated that raloxifene-treated patients had a 65% risk reduction in developing invasive breast cancer and a 75% risk reduction in developing invasive ER + breast cancer.
- Time-to-event analyses demonstrated that raloxifene had sustained efficacy to reduce the incidence of invasive breast cancer in postmenopausal women with osteoporosis in CORE from randomization in MORE through study termination of CORE (approximately 8 years).

The entire 7,705 patient population of MORE, from MORE enrollment through CORE termination,

The invasive breast cancer risk for **the entire 7,705 patient population of MORE, from MORE enrollment through CORE termination**, was evaluated.

- In agreement with the previous results, raloxifene treatment resulted in a 66% reduction in invasive breast cancer and a 76% reduction in invasive ER + breast cancer in this group of postmenopausal women with osteoporosis.
- Time-to-event analyses of invasive breast cancer in this population showed that the treatment effect of raloxifene was apparent after the 1st year of treatment and had sustained efficacy throughout the 8 years of analyses.

11.4.5.6. Nonvertebral Fracture Efficacy

Raloxifene treatment had a neutral effect on nonvertebral fractures and on nonvertebral six fractures in **patients enrolled in CORE (CCD population) from enrollment in MORE through termination of CORE** (approximately 8 years of therapy) in the predefined efficacy analyses: the time-to-event analyses showed no separation between the placebo- and raloxifene-treated groups.
The following subgroup analyses based on MORE baseline were conducted:

- Age
- Lumbar spine BMD
- Femoral neck BMD
- SQ score (semi-quantitative visual assessment by a radiologist for presence of fractures in the T4-L4 vertebral bodies: the scoring includes 0 = no fracture, 1 = mild, 2 = moderate, or 3 = severe; *Genant et al. 1993*)
- Prevalent vertebral fracture
- Prevalent nonvertebral fracture
- Treatment compliance

There was no effect of raloxifene on incidence of any nonvertebral fracture or nonvertebral-six fracture for any of the subgroups evaluated. However, proportionally fewer raloxifene-treated patients had nonvertebral fractures and nonvertebral-six fractures in the subgroups, indicating more severe osteoporosis, such as SQ=3 and prevalent vertebral fractures. Subset analyses based on concomitant bone-active agents also showed no raloxifene treatment effect.

The nonvertebral fracture incidence in **the PAD population from MORE baseline to CORE termination** was also evaluated. In this population there was no effect of raloxifene on the incidence of nonvertebral fractures or nonvertebral-six fractures.

Similar results were observed in **all 7,705 patients enrolled in MORE from enrollment in MORE through either termination of MORE** *or* **termination of CORE**.

Post-hoc Poisson analyses were conducted on the incidence of any nonvertebral fracture and on nonvertebral-six fracture. In contrast to the survival method, which accounts for time to the first fracture, the Poisson method accounts for incidence rate of fractures and allows for evaluation of multiple fractures. This may be relevant to an osteoporosis study of this duration, because having any osteoporosis-related fracture predisposes a patient to another fracture. Fewer raloxifene-treated patients than placebo-treated patients sustained two or more nonvertebral fractures sometime between enrollment in MORE and termination of CORE. Although proportionally

fewer raloxifene-treated women sustained multiple nonvertebral fractures and nonvertebral-six fractures compared with placebo-treated women, there was no significant difference between the groups in the populations tested.

Subgroup analyses for any nonvertebral fracture and nonvertebral-six fracture using the Poisson method for the baseline characteristics of severe osteoporosis (SQ=3 and prevalent vertebral fractures) were conducted. Generally, raloxifene-treated patients had significantly fewer nonvertebral-six fractures than placebo-treated patients in both of the subgroups indicative of more severe osteoporosis.

No data are currently available from a controlled, blinded clinical trial after long exposure to an anti-resorptive agent. However, the factors that made it unlikely to determine a treatment effect of raloxifene on any nonvertebral fracture or nonvertebral six fracture were:

1. A significant number of confounders, such as baseline severity of osteoporosis and the use of bone active agents, were introduced into CORE that could not have been predicted during protocol development during the 3rd year of MORE, the time when the treatment arms appeared to diverge. Addition of bone-active agents after the 3rd year of MORE likely introduced some selection bias because the elements involved in this clinical decision-making process were not subjected to the rules of the randomization. Furthermore, 20% of patients did not use any study drug while enrolled in CORE.

2. A selection bias against the patients most susceptible to fractures was probably introduced by the time of CORE enrollment as these patients either knowingly used bone-active agents or likely did not enroll in CORE, particularly those placebo patients who were considered early completers due to worsening osteoporosis during MORE.
Of the women who met the mandatory discontinuation rule for MORE nearly all were in the placebo group. Because these women were at high risk for nonvertebral fractures, their removal may have decreased the ability to detect a statistically significant effect on nonvertebral sites.

3. Subsequent fractures are more likely to occur once a patient has experienced the first fracture; this is not taken into consideration in the survival analyses (the primary analyses).

Overall Efficacy Conclusions (11.4.5.7)

- Raloxifene treatment significantly reduced the risk of invasive breast cancer and invasive ER + breast cancer in every population of postmenopausal women with osteoporosis studied over any treatment duration. Raloxifene treatment also reduced the risk of invasive breast cancer and invasive ER + breast cancer in women with elevated breast cancer risk, including those with estradiol levels above 5 pmol/L, a family history of breast cancer, previous use of hormone replacement therapy, a higher baseline BMD, and those who were older. Raloxifene-treated patients with lower risk factors for developing invasive breast cancer generally had a lower risk of developing invasive breast cancer than placebo-treated patients, although the difference may not have been significant.

- Raloxifene had a neutral effect on any nonvertebral fracture or nonvertebral-six fracture, however there were multiple confounders in this study that diminished the likelihood of determining a treatment effect.

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Safety Evaluation (12)

Primary safety analyses were performed for all patients who participated in CORE. In addition, the CORE cohort was analyzed from its randomization in MORE through CORE termination.

The following safety evaluations are discussed in this section:

- Exposure to study drug and time between Studies GGGK and GGJY (see Section 12.1)
- Analysis of common treatment-emergent adverse events (TEAEs) during Study GGJY (see Section 12.2.2.1)
- Analysis statistically significant TEAEs during Study GGJY (see Section 12.2.2.2)
- Analysis of statistically significant TEAEs in the Study GGJY cohort from Study GGGK baseline through Study GGJY termination (see Section 12.2.2.3).
- Analysis of adverse events from Study GGGK termination through Study GGJY termination (see Section 12.2.2.4).
- Listing of deaths during Study GGJY (see Section 12.3.1)
- Summary of serious adverse events (SAEs) during Study GGJY (see Section 12.3.2)
- Discontinuations due to an adverse event during Study GGJY (see Section 12.3.3.1)
- Discussion of clinically significant adverse events (Section 12.3.3)

Adverse events throughout this report are classified using the Medical Dictionary for Regulatory Activities (MedDRA). In MedDRA, all events are classified under one of 26 available system organ classes, the broadest level of classification. Herein, events are generally summarized by both preferred term and high-level term. MedDRA contains approximately 15,000 preferred terms, which represent the second lowest classification hierarchy within the dictionary. Preferred terms are subsequently grouped into one of approximately 1600 high-level terms.

Extent of Exposure (12.1)

Primary safety analyses were performed for all patients enrolled in Study GGJY. Among the 4011 enrolled patients in Study GGJY, 1286 patients received a daily placebo and 2725 patients received raloxifene HCl 60 mg/day. Days-on-therapy during Study GGJY were computed as the therapy stop date minus the therapy start date plus 1 day. Patient-years of exposure were calculated by dividing days on therapy by 365.25.

Table GGJY.12.1 summarizes exposure to study drug during Study GGJY for all patients enrolled in the study who received study drug (3200 patients). Total patient exposure was 8532 patient-years, of which 5804 patient-years was exposure to raloxifene HCl 60 mg/day and 2728 patient-years was exposure to placebo.
Mean exposure to study drug was 2.66 patient-years, and exposure was similar between the two groups.

Table GGJY.12.1. Study Drug Exposure during Study GGJY (All Enrolled Patients Who Took Study Drug during Study GGJY)

	Placebo	Raloxifene	Total	P-Value
	1286	2725	4011	
TOOK STUDY DRUG IN GGJY(N=)	1018	2182	3200	
Missing exposure data	23	48	71	
Non missing exposure data	995	2134	3129	
Study Drug Exposure (Years)				
Minimum	0.00	0.00	0.00	
Mean	2.66	2.66	2.66	0.47*
Maximum	3.61	3.69	3.68	
Std Deviation	0.83	0.88	0.86	

* P-Value is obtained from a two sample t-test.
Program: RMP.H3SGGJY.SASPGM(ECCXP122) Output: RMP.H3SO.GGJY.FINAL(ECCXP122)

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Table GGJY.12.2 summaries time between Study GGGK and Study GGJY for all patients enrolled in Study GGJY. The mean time between studies for all Study GGJY participants was 11.93 months and was similar between treatment groups. When only patients who received study drug in Study GGJY are considered, the mean time between studies was 10.78 months and was similar between treatment groups. The gap between studies was at least 2.6 months for all patients who participated in Study GGJY.

Table GGJY.12.2. Time between Study GGGK and Study GGJY (All Patients Enrolled in Study GGJY)

	Placebo (N=1286)	RLX060 (N=2725)	Total (N=4011)	p-Value[b]
All Patients Enrolled in Study GGJY				
Number of patients	1286	2725	4011	
Mean[a] (months)	12.24	11.78	11.93	0.074
Median (months)	10.58	10.55	10.55	
Standard deviation (months)	7.80	7.58	7.65	
Minimum (months)	3.02	2.60	2.60	
Maximum (months)	59.07	62.03	62.03	
All Study GGJY Patients Who Received Study Drug During Study GGJY				
Number of patients	1018	2182	3200	
Mean[a] (months)	10.84	10.75	10.78	0.634
Median (months)	9.95	10.12	10.09	
Standard deviation (months)	5.24	5.63	5.51	
Minimum (months)	3.02	2.60	2.60	
Maximum (months)	48.66	62.03	62.03	

Abbreviations: N = number, RLX060 = raloxifene HCl 60 mg.

a Time between studies calculated as time from last contact in Study GGGK to enrollment in Study GGJY.

b Means are analyzed using a two-sample t-test.

Source: BCCG123a and BCCG123b

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Adverse Events (12.2)

For purposes of collecting and evaluating all information about Lilly drugs used in clinical trials, a clinical trial adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product that has been reported after informed consent has been obtained without regard to the possibility of a causal relationship. Lack of drug effect is not an adverse event in clinical trials because the purpose of the clinical trial is to establish drug effect.

Prior to study entry, study site personnel questioned each patient and noted the occurrence and nature of any presenting or pre-existing condition(s). During the study, site personnel questioned patients and noted any change in the presenting or pre-existing condition(s) and/or the occurrence and nature of any adverse events. All adverse events occurring after enrollment were reported to Lilly or a designee by case report forms (CRFs). Serious adverse events were reported to Lilly or a designee immediately following the event. In cases where the investigator noticed an unanticipated benefit to the patient, study site personnel recorded the event as an "unanticipated benefit" along with the actual event term.

12.2.1. Brief Summary of Adverse Events

The evaluation of adverse events included assessments of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events causing discontinuation.

Table GGJY.12.3 contains an overview of adverse events reported in all patients enrolled in Study GGJY. All categories of adverse events were reported similarly between the treatment groups.

Table GGJY.12.3. Overview of Adverse Events during Study GGJY (All Patients Enrolled in Study GGJY)

	Number of Patients (%)		
Adverse Event[a]	Placebo (N=1286)	Raloxifene 60 mg/day (N=2725)	Total (N=4011)
Deaths	29 (2.3)	47 (1.7)	76 (1.9)
Serious adverse events	317 (24.7)	622 (22.8)	939 (23.4)
Discontinuations due to an adverse event	31 (2.4)	53 (1.9)	84 (2.1)
Other clinically significant adverse events[b]	10 (0.8)	28 (1.0)	38 (0.9)
Treatment-emergent adverse events	1029 (80.0)	2178 (79.9)	3207 (80.0)

Abbreviations: N = number.

a Patients may be counted in more than one category.

b Adverse events included in this category are endometrial cancer, ovarian cancer, and venous thromboembolism (deep vein thrombophlebitis, pulmonary embolism, and retinal vein thrombosis).

Sources: AP001 000, AET1411, AET1211, and AET129.

12.2.2. Display and Analysis of Adverse Events

The evaluation of adverse events included assessments of TEAEs (events that first occurred or worsened after baseline) and all TEAEs reported from the beginning of Study GGGK through the end of Study GGJY.

Adverse events were classified according to the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA coding dictionary contains the international medical terminology that was developed under the auspices of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

12.2.2.1. Common Treatment-Emergent Adverse Events during Study GGJY

Treatment-emergent adverse events are defined as events that first occurred or worsened after baseline in Study GGJY. These analyses consider the highest severity before entry into Study GGJY as the baseline severity, and compare the proportion of new or worsening events since enrollment in Study GGJY across treatment groups. For each event classification term, the number of patients experiencing a TEAE with that classification term was tabulated. Analyses comparing the incidence of TEAEs were performed using the Fisher's Exact test.

Table GGJY.12.4 summarizes TEAEs by system organ class and preferred term in order of decreasing frequency. This summary only includes TEAEs that occurred in $\geq$ 2% of patients. Table GGJY.14.21 summarizes all TEAEs reported during Study GGJY.

Of the 4011 patients enrolled in Study GGJY, 3207 patients (80.0%) reported at least one TEAE. There was no difference in the proportion of patients who reported at least one TEAE between the placebo (1029 [80.0%]) and raloxifene (2178 [79.9%]) groups (p=0.966).

12.2.2.1.1. System Organ Class Terms

Statistically significant decreases were observed in the raloxifene group compared with the placebo group for three system organ class categories:

- "Investigations"
- "Surgical and medical procedures"
- "Neoplasms benign, malignant and unspecified (including cysts and polyps)"

The terms in the system organ class "Investigations" were reported in 144 patients (11.2%) in the placebo group and 240 patients (8.8%) in the raloxifene group (p=0.018).
In this system organ class, there was a statistically significant decrease in the high-level term "Reproductive organ and breast histopathology procedures" among raloxifene patients compared with placebo patients (p=0.029), which may largely account for the difference in the system organ class overall and can be attributed to the primary endpoint of the trial.
The terms in the system organ class "Surgical and medical procedures" were reported in 243 patients (18.9%) in the placebo group and 416 patients (15.3%) in the raloxifene group.

Two high-level terms under this system organ class, "fracture treatments (excluding skull and spine)" and "skin lesion excisions", were statistically significantly decreased in the raloxifene group compared with the placebo group (p=0.005 and p=0.048 respectively). Additionally, there was a decrease in the preferred term "partial mastectomy" in raloxifene-treated patients compared with placebo-treated patients (p<0.001).

The terms in the third system organ class, "Neoplasms benign, malignant and unspecified (including cysts and polyps)" were reported in 130 patients (10.1) in the placebo group and 201 patients (7.4) in the raloxifene group (p=0.004).
Most of the events under this system organ class were reported under the high-level terms "breast and nipple neoplasms malignant" (47 patients [1.2%]) and "skin neoplasms malignant and unspecified (excluding melanoma)" (46 patients [1.1%]), both of which were statistically significantly reduced among raloxifene-treated patients (p=0.017 and p=0.006, respectively). The decrease in breast and nipple neoplasms as a TEAE is consistent with the breast cancer efficacy data previously presented (see Section 11.4.3). To date, there is no known mechanism of raloxifene to explain the decreased incidence of skin neoplasms; however, an effect of raloxifene on this event cannot be definitively dismissed.

12.2.2.1.2. High-Level and Preferred Terms

The most commonly reported TEAE high-level terms during Study GGJY were, in decreasing order:
"Musculoskeletal and connective tissue signs and symptoms NEC" (not elsewhere classified; 623 patients [15.5%])
"Non-site specific injuries NEC" (538 patients [13.4%])
"Joint related sign and symptoms" (401 patients [10.0%])
"Vascular hypertensive disorders NEC" (372 patients [9.3%])
"Upper respiratory tract infections – pathogen class unspecified" (239 patients [6.0%])
"Elevated cholesterol" (216 patients [5.4%]
"Osteoarthropathies" (208 patients [5.2%])

The most commonly reported TEAE preferred terms during Study GGJY were, in decreasing order, "fall" (470 patients [11.7%]), "hypertension not otherwise specified (NOS)" (371 patients [9.2%]), "back pain" (367 patients [9.1%]), "arthralgia" (365 patients [9.1%]), and "hypercholesterolemia" (215 patients [5.4%]). There were no statistically significant differences between groups for any of these most common high-level or preferred terms.

Among all TEAEs reported in ≥ 2% of patients during Study GGJY, 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 (40 patients [3.1%]) than in raloxifene-treated patients (56 patients [2.1%]) (p=0.046). "Depression" was reported more frequently in patients in the raloxifene group (114 patients [4.2%]) than those in the placebo group (34 patients [2.6%]) (p=0.015). The increase in reporting of depression among raloxifene patients is further discussed (see Section 12.3.3.6).

Table GGJY.12.4. Summary of Common Treatment-Emergent Adverse Events by System Organ Class, High-Level Term, and Preferred Term (Study GGJY Baseline through Termination, All Patients Enrolled in Study GGJY)

System Organ Class: Overall

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	1029 (80.0)	2178 (79.9)	3207 (80.0)	.966
PATIENTS WITH NO TESS	257 (20.0)	547 (20.1)	804 (20.0)	.966

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0022 MEDDRA VERSION: 6.0

System Organ Class: Blood and lymphatic system disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	35 (2.7)	80 (2.9)	115 (2.9)	.762
PATIENTS WITH NO TESS	1251 (97.3)	2645 (97.1)	3896 (97.1)	.762
Anaemias NEC	21 (1.6)	57 (2.1)	78 (1.9)	.391

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0022 MEDDRA VERSION: 6.0

System Organ Class: Cardiac disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	89 (6.9)	235 (8.6)	324 (8.1)	.072
PATIENTS WITH NO TESS	1197 (93.1)	2490 (91.4)	3687 (91.9)	.072
Ischaemic coronary artery disorders	30 (2.3)	81 (3.0)	111 (2.8)	.302
Supraventricular arrhythmias	23 (1.8)	56 (2.1)	79 (2.0)	.627

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0022 MEDDRA VERSION: 6.0

System Organ Class: Congenital, familial and genetic disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	2 (0.2)	9 (0.3)	11 (0.3)	.520
PATIENTS WITH NO TESS	1284 (99.8)	2716 (99.7)	4000 (99.7)	.520

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0022 MEDDRA VERSION: 6.0

System Organ Class: Ear and labyrinth disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	41 (3.2)	98 (3.6)	139 (3.5)	.579
PATIENTS WITH NO TESS	1245 (96.8)	2627 (96.4)	3872 (96.5)	.579
Inner ear signs and symptoms	31 (2.4)	69 (2.5)	100 (2.5)	.914
Vertigo	24 (1.9)	54 (2.0)	78 (1.9)	.903

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0022 MEDDRA VERSION: 6.0

System Organ Class: Endocrine disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	27 (2.1)	48 (1.8)	75 (1.9)	.456
PATIENTS WITH NO TESS	1259 (97.9)	2677 (98.2)	3936 (98.1)	.456

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0022 MEDDRA VERSION: 6.0

System Organ Class: Eye disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	97 (7.5)	207 (7.6)	304 (7.6)	1.00
PATIENTS WITH NO TESS	1189 (92.5)	2518 (92.4)	3707 (92.4)	1.00
Cataracts (excl congenital)	42 (3.3)	84 (3.1)	126 (3.1)	.771

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0022 MEDDRA VERSION: 6.0

System Organ Class: Gastrointestinal disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	243 (18.9)	552 (20.3)	795 (19.8)	.329
PATIENTS WITH NO TESS	1043 (81.1)	2173 (79.7)	3216 (80.2)	.329
Gastrointestinal atonic and hypomotility disorders NEC	39 (3.0)	106 (3.9)	145 (3.6)	.204
Constipation	18 (1.4)	56 (2.1)	74 (1.8)	.168
Nausea and vomiting symptoms	48 (3.7)	95 (3.5)	143 (3.6)	.715
Nausea	36 (2.8)	69 (2.5)	105 (2.6)	.672
Gastrointestinal and abdominal pains (excl oral and throat)	48 (3.7)	82 (3.0)	130 (3.2)	.251
Dyspeptic signs and symptoms	33 (2.6)	78 (2.9)	111 (2.8)	.680
Dyspepsia	28 (2.2)	63 (2.3)	91 (2.3)	.821
Diarrhoea (excl infective)	26 (2.0)	69 (2.5)	95 (2.4)	.374
Diarrhoea NOS	26 (2.0)	66 (2.4)	92 (2.3)	.496

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0022 MEDDRA VERSION: 6.0

System Organ Class: General disorders and administration site conditions

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	139 (10.8)	306 (11.2)	445 (11.1)	.707
PATIENTS WITH NO TESS	1147 (89.2)	2419 (88.8)	3566 (88.9)	.707
Pain and discomfort NEC	43 (3.3)	103 (3.8)	146 (3.6)	.528
Chest pain	36 (2.8)	75 (2.8)	111 (2.8)	.918
Asthenic conditions	41 (3.2)	76 (2.8)	117 (2.9)	.483
Oedema NEC	31 (2.4)	73 (2.7)	104 (2.6)	.671
Oedema peripheral	31 (2.4)	68 (2.5)	99 (2.5)	.914

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0022 MEDDRA VERSION: 6.0

System Organ Class: Hepatobiliary disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	28 (2.2)	60 (2.2)	88 (2.2)	1.00
PATIENTS WITH NO TESS	1258 (97.8)	2665 (97.8)	3923 (97.8)	1.00

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0022 MEDDRA VERSION: 6.0

System Organ Class: Immune system disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	12 (0.9)	39 (1.4)	51 (1.3)	.227
PATIENTS WITH NO TESS	1274 (99.1)	2686 (98.6)	3960 (98.7)	.227

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0022 MEDDRA VERSION: 6.0

System Organ Class: Infections and infestations

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	266 (20.7)	554 (20.3)	820 (20.4)	.801
PATIENTS WITH NO TESS	1020 (79.3)	2171 (79.7)	3191 (79.6)	.801
Upper respiratory tract infections - pathogen class unspecified	80 (6.2)	159 (5.8)	239 (6.0)	.618
Nasopharyngitis	34 (2.6)	54 (2.0)	88 (2.2)	.204
Urinary tract infections	50 (3.9)	116 (4.3)	166 (4.1)	.611
Urinary tract infection NOS	40 (3.1)	92 (3.4)	132 (3.3)	.705
Lower respiratory tract and lung infections	57 (4.4)	93 (3.4)	150 (3.7)	.129
Pneumonia NOS	40 (3.1)	56 (2.1)	96 (2.4)	.046
Influenza viral infections	34 (2.6)	81 (3.0)	115 (2.9)	.613
Influenza	34 (2.6)	81 (3.0)	115 (2.9)	.613

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0022 MEDDRA VERSION: 6.0

System Organ Class: Injury, poisoning and procedural complications

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	270 (21.0)	561 (20.6)	831 (20.7)	.770
PATIENTS WITH NO TESS	1016 (79.0)	2164 (79.4)	3180 (79.3)	.770
Non-site specific injuries NEC	185 (14.4)	353 (13.0)	538 (13.4)	.215
Fall	157 (12.2)	313 (11.5)	470 (11.7)	.528
Lower limb fractures and dislocations	43 (3.3)	74 (2.7)	117 (2.9)	.270
Upper limb fractures and dislocations	38 (3.0)	68 (2.5)	106 (2.6)	.400
Spinal fractures and dislocations	32 (2.5)	65 (2.4)	97 (2.4)	.827
Limb injuries NEC (incl traumatic amputation)	26 (2.0)	55 (2.0)	81 (2.0)	1.00

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0022 MEDDRA VERSION: 6.0

System Organ Class: Investigations

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	144 (11.2)	240 (8.8)	384 (9.6)	.018
PATIENTS WITH NO TESS	1142 (88.8)	2485 (91.2)	3627 (90.4)	.018

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0022 MEDDRA VERSION: 6.0

System Organ Class: Metabolism and nutrition disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	132 (10.3)	270 (9.9)	402 (10.0)	.735
PATIENTS WITH NO TESS	1154 (89.7)	2455 (90.1)	3609 (90.0)	.735
Elevated cholesterol	70 (5.4)	146 (5.4)	216 (5.4)	.940
Hypercholesterolaemia	70 (5.4)	145 (5.3)	215 (5.4)	.881

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0022 MEDDRA VERSION: 6.0

System Organ Class: Musculoskeletal and connective tissue disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	400 (31.1)	923 (33.9)	1323 (33.0)	.084
PATIENTS WITH NO TESS	886 (68.9)	1802 (66.1)	2688 (67.0)	.084
Musculoskeletal and connective tissue signs and symptoms NEC	205 (15.9)	418 (15.3)	623 (15.5)	.641
Back pain	129 (10.0)	238 (8.7)	367 (9.1)	.197
Pain in extremity	67 (5.2)	145 (5.3)	212 (5.3)	.940
Joint related signs and symptoms	128 (10.0)	273 (10.0)	401 (10.0)	1.00
Arthralgia	113 (8.8)	252 (9.2)	365 (9.1)	.681
Osteoarthropathies	55 (4.3)	153 (5.6)	208 (5.2)	.079
Localised osteoarthritis	23 (1.8)	77 (2.8)	100 (2.5)	.051
Osteoarthritis NOS	28 (2.2)	67 (2.5)	95 (2.4)	.657
Muscle related signs and symptoms NEC	42 (3.3)	105 (3.9)	147 (3.7)	.370
Muscle cramp	40 (3.1)	97 (3.6)	137 (3.4)	.515
Arthropathies NEC	25 (1.9)	71 (2.6)	96 (2.4)	.224

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
KARS0022 MEDDRA VERSION: 6.0

System Organ Class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	130 (10.1)	201 (7.4)	331 (8.3)	.004
PATIENTS WITH NO TESS	1156 (89.9)	2524 (92.6)	3680 (91.7)	.004

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
KARS0022 MEDDRA VERSION: 6.0

System Organ Class: Nervous system disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	187 (14.5)	425 (15.6)	612 (15.3)	.397
PATIENTS WITH NO TESS	1099 (85.5)	2300 (84.4)	3399 (84.7)	.397
Neurological signs and symptoms NEC	33 (2.6)	79 (2.9)	112 (2.8)	.608
Dizziness	33 (2.6)	73 (2.7)	106 (2.6)	.916
Headaches NEC	25 (1.9)	58 (2.1)	83 (2.1)	.812
Headache	23 (1.8)	55 (2.0)	78 (1.9)	.714

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
KARS0022 MEDDRA VERSION: 6.0

System Organ Class: Psychiatric disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	87 (6.8)	214 (7.9)	301 (7.5)	.248
PATIENTS WITH NO TESS	1199 (93.2)	2511 (92.1)	3710 (92.5)	.248
Depressive disorders	38 (3.0)	116 (4.3)	154 (3.8)	.052
Depression	34 (2.6)	114 (4.2)	148 (3.7)	.015

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
KARS0022 MEDDRA VERSION: 6.0

System Organ Class: Renal and urinary disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	67 (5.2)	162 (5.9)	229 (5.7)	.382
PATIENTS WITH NO TESS	1219 (94.8)	2563 (94.1)	3782 (94.3)	.382
Bladder and urethral symptoms	27 (2.1)	73 (2.7)	100 (2.5)	.329

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
KARS0022 MEDDRA VERSION: 6.0

System Organ Class: Reproductive system and breast disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	161 (12.5)	300 (11.0)	461 (11.5)	.168
PATIENTS WITH NO TESS	1125 (87.5)	2425 (89.0)	3550 (88.5)	.168
Breast disorders NEC	66 (5.1)	131 (4.8)	197 (4.9)	.696
Breast mass NOS	32 (2.5)	60 (2.2)	92 (2.3)	.573

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
KARS0022 MEDDRA VERSION: 6.0

System Organ Class: Respiratory, thoracic and mediastinal disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	168 (13.1)	335 (12.3)	503 (12.5)	.507
PATIENTS WITH NO TESS	1118 (86.9)	2390 (87.7)	3508 (87.5)	.507
Bronchial conditions NEC	37 (2.9)	85 (3.1)	122 (3.0)	.768
Bronchitis NOS	37 (2.9)	85 (3.1)	122 (3.0)	.768
Coughing and associated symptoms	35 (2.7)	82 (3.0)	117 (2.9)	.688
Cough	33 (2.6)	72 (2.6)	105 (2.6)	1.00
Breathing abnormalities	27 (2.1)	75 (2.8)	102 (2.5)	.236
Dyspnoea	24 (1.9)	61 (2.2)	85 (2.1)	.483

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
KARS0022 MEDDRA VERSION: 6.0

System Organ Class: Skin and subcutaneous tissue disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	109 (8.5)	215 (7.9)	324 (8.1)	.535
PATIENTS WITH NO TESS	1177 (91.5)	2510 (92.1)	3687 (91.9)	.535
Skin injuries and mechanical dermatoses	36 (2.8)	69 (2.5)	105 (2.6)	.672
Contusion	33 (2.6)	67 (2.5)	100 (2.5)	.829

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
KARS0022 MEDDRA VERSION: 6.0

System Organ Class: Social circumstances

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	3 (0.2)	3 (0.1)	6 (0.1)	.393
PATIENTS WITH NO TESS	1283 (99.8)	2722 (99.9)	4005 (99.9)	.393

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
KARS0022 MEDDRA VERSION: 6.0

System Organ Class: Surgical and medical procedures

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	243 (18.9)	416 (15.3)	659 (16.4)	.004
PATIENTS WITH NO TESS	1043 (81.1)	2309 (84.7)	3352 (83.6)	.004
Lens therapeutic procedures	45 (3.5)	84 (3.1)	129 (3.2)	.502
Cataract extraction	42 (3.3)	79 (2.9)	121 (3.0)	.553
Joint therapeutic procedures	37 (2.9)	86 (3.2)	123 (3.1)	.695
Therapeutic procedures NEC	32 (2.5)	55 (2.0)	87 (2.2)	.354

Program: RMP.H3SSGGJY.SASPGM(SPCT125) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
KARS0022 MEDDRA VERSION: 6.0