7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Data sources:

- Placebo-controlled raloxifene trials: RUTH, MORE, and CORE
- Post-marketing information provided by the sponsor
- Active-control raloxifene trial: STAR (Please see Dr. Cortazar's Review)

Safety assessment:

- Incidence rates of AEs were compared between the study arms in the placebo-controlled trials.
  - AEs occurring at a high frequency (≥ 2%) were noted and compared between the placebo and treatment arms
  - SAEs, especially those with a known association to SERMs (tamoxifen and raloxifene) were looked for and compared—irrespective of the % incidence

Reviewer Comments: *The primary endpoints for all of the controlled clinical trials in this sNDA were efficacy endpoints—accordingly, the sample size in each trial was determined based on the expected rates of efficacy events in the experimental and the control arms. Therefore, statistical significance testing of safety events is not highly reliable and conclusive: risk of both type 1 and type 2 errors is high. Safety conclusions have to be made considering these limitations of analyses of the submitted trials data, and the data from other sources (eg, known class effects, post-marketing data, etc.).*

Major findings:

Safety Observations Consistently Observed

Venous thromboembolic event (VTE): A *statistically significant* increase in serious but uncommon VTEs (deep vein thrombosis [DVT], pulmonary embolism [PE], and other VTEs) was observed in the raloxifene arms (compared with the placebo arms) in RUTH (44% increase) and MORE (89% increase) trials.

Numerical increases in the incidence of DVT and the incidence of PE (DVT and PE events counted separately rather than under single VTE events category) were observed in raloxifene (compared with placebo) assigned patients in RUTH, MORE, and CORE (statistically significant for DVT in MORE).

- VTEs are reflected in the current United States (US) label under the Contraindications and Warnings sections.

Cancer: There were no statistically significant differences in the incidence of endometrial cancer, uterine sarcoma, ovarian cancer, or other cancers in raloxifene (compared with placebo) assigned patients.

All-Cause Mortality: There were no statistically significant differences in the incidence of all-cause mortality in raloxifene (compared with placebo) assigned patients.

Hot flushes, leg cramps, and peripheral edema: There were statistically significant increases in the incidences of *hot flushes*, *leg cramps* (*muscle spasms*), and *peripheral edema* in raloxifene assigned patients in RUTH and MORE. There was a higher incidence of hot flashes and leg cramps in CORE.

- Hot flushes, leg cramps, and peripheral edema are reflected in the current US label.

Safety Observations in RUTH only

Death due to stroke:

- In RUTH a statistically significant (p=0.0499) 49% increase in the incidence of the *death due to stroke* was observed in raloxifene (compared with placebo) assigned patients.
- No such increase was observed in MORE.
- An increase was observed in CORE but was not statistically significant.

Note that MORE and CORE enrolled patients with osteoporosis who were at a much lower risk for cardiovascular (CV) events than the RUTH patients—based on the baseline cardiovascular risk factors).

In RUTH, raloxifene treatment did **not** increase the incidence of coronary events, *all-cause mortality*, *death due to a CV event*, or cerebrovascular events, including all *strokes*. Additionally, raloxifene did **not** increase the incidence of early CHD events.

No single risk factor could statistically identify which patients treated with raloxifene would experience a *death due to stroke*. Based on clinical judgment, the risk factors of previous *atrial fibrillation*, *stroke*, or *transient ischemic attack* (*TIA*) might have contributed to the increased incidence of *death due to stroke* in RUTH raloxifene-assigned patients.

- Lilly has proposed that a warning statement be added to the US label reflecting that an increase in *death due to stroke* was observed in women with documented CHD or at increased risk for coronary events. It was also proposed that the warning include a statement that the benefit/risk balance of raloxifene should be considered in postmenopausal women with a history of *stroke* or other significant *stroke* risk factors, such as *atrial fibrillation* and *TIA*.

Cholelithiasis: In RUTH, there was a *statistically significantly* greater incidence of *cholelithiasis* in raloxifene- compared with placebo-assigned patients (3.3% versus 2.6%).

- This increase was not statistically significant in MORE or CORE.
- There were no statistically significant differences in the incidence of *cholecystitis* or *cholecystectomy* in raloxifene- compared with placebo-assigned patients in RUTH, MORE, or CORE.

- It is proposed that *cholelithiasis* be added to the US label AE section.

7.1.1 Deaths

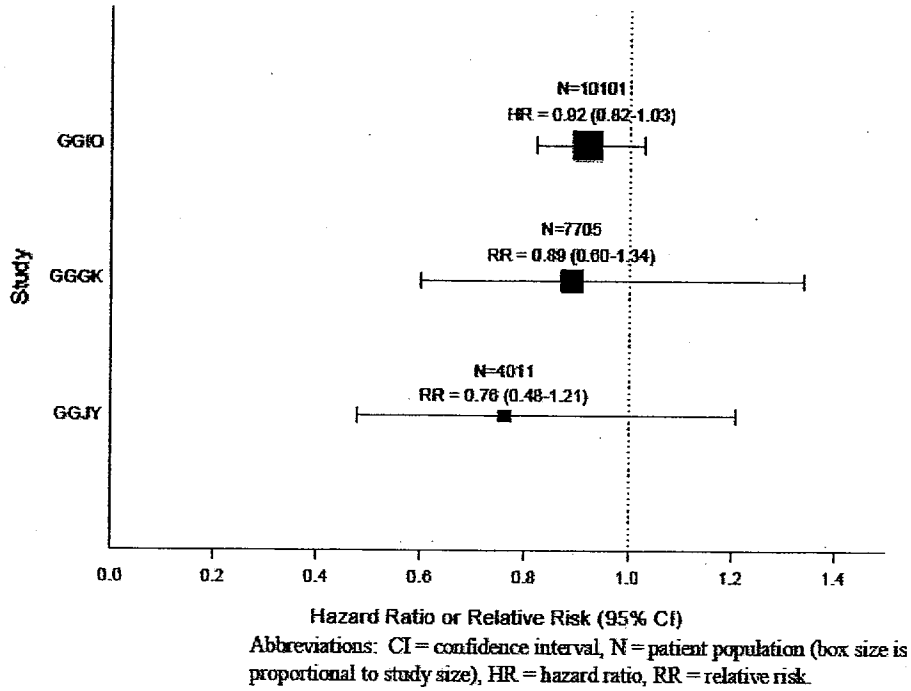
Mortality in the placebo-controlled trials

The incidence of *all-cause mortality* was lower in MORE and CORE than in RUTH. Given the population of patients studied in RUTH (women at high-risk for CV disease), this result is not surprising.

RUTH

One of the secondary objectives of RUTH was to assess whether raloxifene changed the incidence of *all-cause mortality*. *Death* was an adjudicated study endpoint. Results of the *all-cause mortality* analysis and the analyses of *death* due to specific causes for RUTH are shown in the following figures and tables.

- The ***all-cause mortality*** incidence was lower in the raloxifene- than placebo-assigned patients, but this difference was not statistically significant.
- ***Deaths*** were classified into **CV and non-CV causes**.
  - Compared to the placebo group, there was no statistically significant increase or decrease in the incidence of ***deaths due to CV causes*** in the raloxifene group; however, there was a statistically significant decrease in the incidence of ***deaths due to non-CV causes*** in the raloxifene group.
- **Cardiovascular *deaths*** were classified into **coronary and non-coronary causes**.
  - There was no statistically significant difference between treatment groups for ***coronary deaths*** **or** ***non-coronary deaths***.



Abbreviations: CI = confidence interval, N = patient population (box size is proportional to study size), HR = hazard ratio, RR = relative risk.

Figure 8 All-Cause mortality hazard ratio or relative risk for all randomized RUTH/GGIO and MORE/GGGK and all CORE/GGJY patients.

Table 18 Mortality (All Randomized RUTH/GGIO Patients).

Mortality endpoint classification	Placebo 5,057 n (%)	Raloxifene 5,044 n (%)	Hazard Ratio (95% CI)	P Value
All deaths	**595 (11.77)**	**554 (10.98)**	**0.92 (0.82,1.03)**	**.1603**
Cardiovascular death	**355 (7.02)**	**362 (7.18)**	**1.01 (0.87,1.17)**	**.9129**
Coronary death	**274 (5.42)**	**255 (5.06)**	**0.92 (0.78,1.09)**	**.3401**
Acute MI	45 (0.89)	33 (0.65)	0.73 (0.46,1.14)	.1614
Sudden death	137 (2.71)	128 (2.54)	0.92 (0.73,1.18)	.5198
Unwitnessed death	4 (0.08)	3 (0.06)	0.74 (0.17,3.32)	.6968
Heart failure with history of CAD	59 (1.17)	57 (1.13)	0.96 (0.66,1.37)	.8045
Related to undergoing a CAP	11 (0.22)	9 (0.18)	0.81 (0.34,1.96)	.6395
Specific cause of coronary death unavailable	18 (0.36)	25 (0.50)	1.37 (0.75,2.51)	.3069
Non-coronary death	**81 (1.60)**	**107 (2.12)**	**1.31 (0.98,1.74)**	**.0697**
Cerebrovascular disease (stroke or other cause)	**39 (0.77)**	**59 (1.17)**	**1.49 (1.00,2.24)**	**.0499**
Aortic, mesenteric, renal, or lower limb PVD	11 (0.22)	15 (0.30)	1.35 (0.62,2.93)	.4517
Related to undergoing an NCAP	1 (0.02)	2 (0.04)	NA	NA
Venous thromboembolic event	5 (0.10)	10 (0.20)	1.98 (0.68,5.79)	.2032
Endocarditis/myocarditis	1 (0.02)	0 (0.00)	NA	NA
Valvular disease	6 (0.12)	7 (0.14)	1.15 (0.39,3.42)	.8000
Other non-coronary death	**8 (0.16)**	**5 (0.10)**	**0.62 (0.20,1.88)**	**.3903**
Specific cause of non-coronary death unavailable	10 (0.20)	9 (0.18)	0.89 (0.36,2.19)	.7973
Non-cardiovascular death	**231**	**188**	**0.80**	**.0264**

	(4.57)	**(3.73)**	**(0.66,0.98)**	
Cancer	103 (2.04)	97 (1.92)	0.93 (0.70,1.23)	.6050
Breast cancer	0 (0.00)	2 (0.04)	NA	NA
Other cancer	103 (2.04)	95 (1.88)	0.91 (0.69,1.20)	.5099
Accidental/Suicide/Homicide	6 (0.12)	8 (0.16)	1.32 (0.46,3.79)	.6099
Other non-cardiovascular death	**97 (1.92)**	**61 (1.21)**	**0.62 (0.45,0.86)**	**.0033**
Specific cause of non-cardiovascular death unavailable	25 (0.49)	22 (0.44)	0.88 (0.49,1.55)	.6493
Cause of death unavailable	9 (0.18)	4 (0.08)	0.44 (0.14,1.43)	.1595

Abbreviations: CAD = coronary artery disease, CAP = coronary arterial procedure, CI = confidence interval, MI = myocardial infarction, NA = not applicable, NCAP = non-coronary arterial procedure, PBO = placebo, PVD = peripheral vascular disease, RLX = raloxifene.

p-Value is obtained from a log-rank test. Statistical test is not performed when the total number of patients in a category is less than 5.

Source: Program: RMP.H3SSGGIO.SASPGM(CVCMMORT), Data: MP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN, Output: RMP.H3SO.GGIO.FINAL(CVTHRMOR).

- In RUTH, 98 *deaths* were due to a cerebrovascular etiology—all due to *stroke*.
  - No statistically significant differences in the incidence of *stroke* was observed between the two treatment groups, but a statistically significant increase in the incidence of *death due to cerebrovascular disease*(*stroke*) was observed in women assigned to raloxifene (59/5044, 1.2%, p=0.0499) compared with those assigned to placebo (39/5057, 0.8%).
  - The incidence of *death due to stroke* was 2.2 per 1000 patient-years for raloxifene versus 1.5 per 1000 patient-years for placebo, corresponding to an ARD of +0.7 *deaths due stroke* per 1000 patient-years.
  - The increase in the incidence of *death due to stroke* in the raloxifene group was observed after Year 3 of the trial and remained consistently increased thereafter, becoming statistically significant in Year 7.
  - The majority of adjudicated *strokes* were ischemic in origin. Although not statistically significantly different, there was a clinically relevant greater incidence of patients who *died due to ischemic stroke* in the raloxifene group compared with the placebo group: HR 1.79, 95% CI 0.97-3.30, p=0.06. In contrast, the incidence of patients who *died due to a hemorrhagic stroke* was similar between treatment groups (HR 0.82, 95% CI 0.36-1.90, p=0.65).

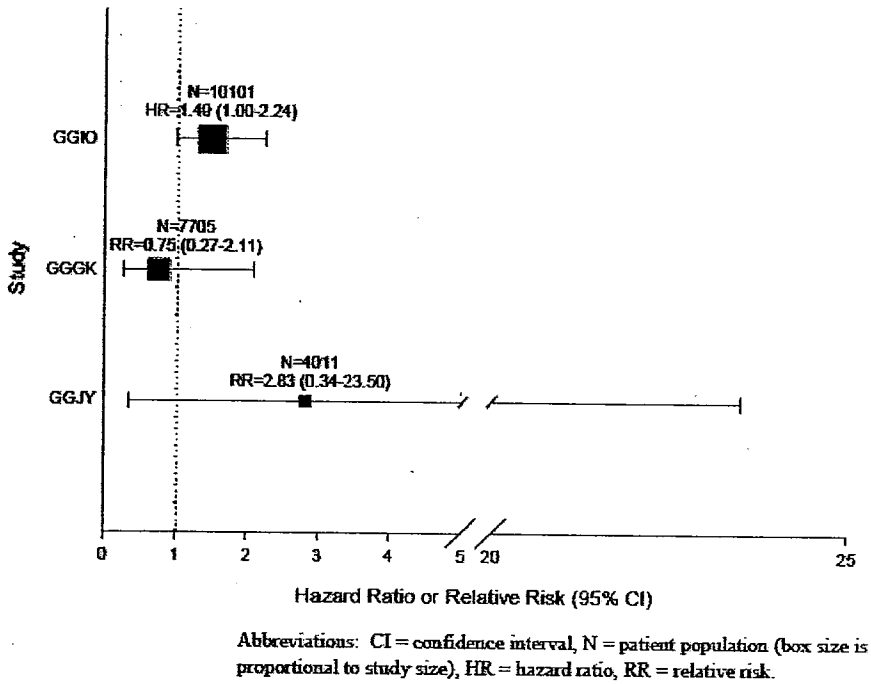


Figure 9 Death due to stroke: hazard ratio for all randomized RUTH/GGIO patients and relative risk MORE/GGGK and CORE/GGJY patients.

The increased *death due to stroke* for raloxifene-assigned patients in RUTH/GGIO is perplexing, given that there was no statistically significant increase in the incidence of all *strokes* in the raloxifene group and that no statistically significant increase in the incidence of *death due to stroke* has been observed in previous raloxifene clinical studies.

Mortality in placebo-controlled trials

MORE

In MORE, *death* was not adjudicated and *all-cause mortality* incidence was lower in the raloxifene- than placebo-assigned patients, but this was not statistically significant.

- There was no statistically significant increase for any cause of *death* for raloxifene- compared with placebo-assigned patients.
- The figure above presents the MORE *death due to stroke* data. The figure shows HRs for adjudicated endpoint data and RRs for the investigator-reported events to be consistent with individual study a priori analyses. There was no statistically significant treatment group difference for the incidence *death due to stroke*.

Mortality in placebo-controlled trials

CORE

All-cause mortality incidence was lower in the raloxifene- than placebo assigned patients in CORE, but this was not statistically significant.

- No statistically significant differences were found between treatment groups in terms of cause of *death*
- The figure above showed the CORE adjudicated *death due to stroke* data. There was no statistically significant treatment group difference for the incidence of *death due to stroke*.

The incidence of *all-cause mortality* was lower in MORE and CORE than in RUTH. Given the population of patients studied in RUTH/GGIO (high-risk for CV disease), this result is not surprising.

Table 19 Mortality (All Randomized MORE/GGGK and All CORE/GGJY Patients)

	GGGK			GGJY		
Event	PBO N=2576 n (%)	RLX N=5129 n (%)	RR (CI) [a]	PBO N=1286 n (%)	RLX N=2725 n (%)	RR (CI) [a]
Death	36(1.4)	64(1.3)	0.89 (0.60,1.34)	29(2.3)	47(1.7)	0.76 (0.48,1.21)

Abbreviations: CI = confidence interval, n = patients with event, N = patient population, PBO = placebo, RLX = raloxifene, RR = relative risk

[a] The 95% confidence interval is based on the Mantel-Haenszel method.

Note: There were no statistically significant treatment group differences within a study (Fisher's exact test, $p<0.05$).

Source: RMP.H3SO.CTD1(SFRDT1MO), RMP.H3SO.CTD1(SFRDT1CO).

Table 20 Death due to Stroke (All Randomized MORE/GGGK and All CORE/GGJY Patients)

	GGGK		GGJY	
Adjudicated Cause of Death	PBO N=2576 n (%)	RLX N=5129 n (%)	PBO N=1286 n (%)	RLX N=2725 n (%)
Death due to Stroke	6(0.23)	9(0.18)	1(0.08)	6(0.22)

Abbreviations: n = patients with event, N = patient population, PBO = placebo, RLX = raloxifene.

Note: There were no statistically significant treatment group differences within a study (Fisher's exact test, $p<0.05$).

Source: RMP.H3SO.CTD1(SFRFSTGK), RMP.H3SO.CTD1(SFRFSTJY).

For the 4,011-patient 8-year MORE/CORE data, *deaths* were reviewed by an adjudicator to identify those due to CV causes (*fatal MI, sudden death, death related to a coronary procedure, death from heart failure*, or *fatal acute stroke)*. There was no statistically significant difference between treatment groups in the incidence of these causes of *death*.

The applicant discussed *death due to stroke* **spontaneous reporting data:** As of 01 August 2006, there have been 24 spontaneous *death due to stroke* cases reported to Lilly out of an estimated 11.6 million patient-years of exposure. The National Center for Health Statistics estimates age-adjusted *death due to stroke* for US women at 0.6 per 1000 patient-years.

The spontaneous reporting data include the recent time period after the issue of a potential increase in *death due to stroke* was made public on 12 April 2006, with targeted information provided to physicians and pharmacists, which often increases spontaneous reporting. Increased reporting has not been observed.

Reviewer Comments: *Above information is not reliable—the data are gathered by spontaneous reporting. Similarly, the data on exposure are based on sales figures and is an estimate—these numbers are not based on an actually measured patient compliance. It is quite likely that the real incidence of death due to stroke will be underestimated.*

Mortality Safety Summary

In the three placebo-controlled trials: RUTH, MORE, and CORE, and the comparator-controlled P-2, there was a small, but consistent numerically lower incidence of *all-cause mortality* in patients assigned to raloxifene versus comparator.

An increase in the incidence of *deaths due to stroke* was observed in patients assigned to raloxifene. This is a new finding not previously seen in prior clinical studies with raloxifene and the clinical relevance is not understood. The incidences of *all stroke*, *hemorrhagic stroke*, and *ischemic stroke* were not statistically significantly different between placebo- and raloxifene-assigned patients. ***Reviewer Comments****: The other studies might not have detected the difference due to smaller sample size and shorter duration of treatment. It would seem that although the incidence of strokes was not increased by raloxifene, if a patient developed a stroke, it was more likely to be fatal.*

In the cohort of patients followed for up to 8 years from randomization in MORE to the end of participation in MORE or CORE, there were no statistically significant treatment group differences in incidences of *deaths due to all CV causes* or *deaths due to coronary causes* or *deaths due to cerebrovascular causes*. ***Reviewer Comments:*** *however this could be because this is a smaller cohort and might not have adequate power to detect a difference between the two study arms for an event of low frequency.*

In summary, based on the totality of the available data, raloxifene does not seem to affect the overall mortality, including CV mortality.

7.1.2 Other Serious Adverse Events

The *other SAEs* for RUTH, MORE, and CORE are defined as the events meeting any one of the following criteria:

- Initial or prolonged inpatient hospitalization
- Life-threatening
- Severe or permanent disability
- Cancer
- Congenital anomaly, or
- Significant for other reason

For RUTH, there were specifically-defined primary and secondary endpoints related to AEs. **If one of the AEs associated with a study endpoint was serious in nature, it was not designated an SAE unless it met certain additional criteria as described in the RUTH protocol.**

There were no statistically significant differences between treatment groups in overall SAE incidences for RUTH, MORE, and CORE. In RUTH, all-cause hospitalizations were statistically significantly decreased for the raloxifene treatment group compared with the placebo treatment group (51.5% versus 54.2% of patients, p=0.006).

Serious AEs, coded by Preferred Terms (PTs) and High Level Terms (HLTs), that were reported *statistically significantly* **more often in the raloxifene** treatment group than the placebo treatment group included:

RUTH (placebo %, raloxifene %):

- HLT *pulmonary thrombotic and embolic conditions* (0.6, 1.0)
- PT *PE* (0.6, 1.0)
- PT *bladder cancer* (0.0, 0.1)

- No SAEs in the raloxifene treatment group that were ≥2-fold the incidence of the placebo treatment group were reported with an incidence of ≥1%; for most events the incidence was less than 0.1%;
- Adverse events associated with predefined primary and secondary endpoints were not considered SAEs unless they met certain additional criteria. Accordingly, d*eath, MI, invasive breast cancer, stroke*, and *VTE* are not included here; these events are discussed in other subsections.
- Although the PT *bladder cancer* was reported statistically significantly more often in the raloxifene group compared with the placebo group as an SAE, there was no statistically significant difference between treatment groups for the HLT *bladder neoplasms malignant* to which *bladder cancer* is mapped.
- In review of TEAEs, 14 events mapped to the HLT *bladder neoplasms malignant*; there were no statistically significant between-treatment group differences. No apparent relationship between bladder cancer and raloxifene treatment has been established. The incidence of bladder cancer, based upon RSSC, was not statistically significantly

different between the placebo (4/5057 [0.08%]) and raloxifene (10/5044 [0.20%], p=0.109) treatment groups;

MORE (placebo %, raloxifene %):
- HLT *oedema NEC* (0.0, 0.3)
- PT *oedema peripheral* (0.0, 0.2)
- HLT *musculoskeletal and connective tissue signs and symptoms NEC* (0.9, 1.7)
- PT *neck pain* (0.0, 0.2)
- HLT *biliary tract and gallbladder therapeutic procedures* (0.6, 1.1)
- PT *bunion operation* (0.0, 0.2)
- HLT *peripheral embolism and thrombosis* (0.4, 0.9)
- PT *DVT* (0.3, 0.8)

- There were no SAEs in the raloxifene treatment group that were reported with an incidence of ≥1% that were ≥2-fold the incidence of the placebo treatment group
- *Gallbladder* disease is discussed in further detail elsewhere;

CORE (placebo %, raloxifene %):
- HLT *spinal fractures and dislocations* (0.2, 0.8)
- HLT *osteoarthropathies* (0.4, 1.1)
- HLT *breathing abnormalities* (0.1%, 0.5)

- HLT *osteoarthropathies* was the only SAE in the raloxifene group that was reported with an incidence of ≥1%. Also it was a > 2-fold increase in the incidence over the placebo.
- The low incidence of spinal fractures may be due to the provision that allowed patients to use other bone-active agents in CORE (approximately 50% used agents other than raloxifene).
  - Statistically significantly fewer patients in the raloxifene than the placebo group used an additional bone active agent.
  - The incidence of treatment-emergent *spinal fractures and dislocations*, irrespective of seriousness, was similar for the raloxifene 65/2725 (2.4%) and placebo 32/1286 (2.5%, p=0.827) treatment groups.
- Differences in the incidence of SAEs between the treatment groups are likely due to multiple statistical comparisons and may not reflect any true treatment effects.

Serious AEs (coded by PTs and HLTs) that were reported *statistically significantly* **more often in the placebo** treatment group than the raloxifene treatment group included:

RUTH (placebo %, raloxifene %):
- No statistically significant treatment group differences

MORE (placebo %, raloxifene %):
- HLT *gastrointestinal atonic and hypomotility disorders NEC* (0.5, 0.2),
- PT *lower respiratory tract infection NOS* (0.2, 0.0),
- HLT *upper respiratory tract infections - pathogen class unspecified* (0.2, 0.0),

- PT *hip fracture* (0.2, 0.0),
- HLT histopathology procedures NEC (0.7, 0.1),
- PT *biopsy NOS* (0.7, 0.1),
- HLT *appetite disorders* (0.2, 0.0),
- HLT *breast and nipple neoplasms malignant* (1.7, 0.6),
- PT *breast cancer female* (0.8, 0.3), *breast cancer NOS* (0.5, 0.2),
- HLT *breast neoplasms unspecified malignancy* (0.2, 0.0),
- PT *breast neoplasms NOS* (0.2, 0.0),
- PT *cerebral ischaemia* (0.3, 0.1),
- PT *coma* (0.2, 0.0),
- HLT *bladder disorders NEC* (0.5, 0.2),
- HLT *bone therapeutic procedures NEC* (0.3, 0.0),
- PT *joint arthroplasty* (0.5, 0.2),
- PT *colectomy NOS* (0.4, 0.2),
- HLT *soft tissue therapeutic procedures NEC* (0.2, 0.0),
- HLT *therapeutic procedures NEC* (3.0, 2.2),
- PT *lump excision* (0.2, 0.0) ,
- HLT *non-site specific necrosis and vascular insufficiency NEC* (0.2, 0.0);

CORE (placebo %, raloxifene %):

- HLT *abdominal and gastrointestinal infections* (0.5, 0.1),
- PT *femoral neck fracture* (0.4, 0.1),
- HLT *breast neoplasms unspecified malignancy* (1.8, 0.9),
- PT *breast cancer NOS* (0.5, 0.1),
- HLT *skin neoplasms malignant and unspecified - excluding melanoma* (1.6, 0.7),
- PT *basal cell carcinoma* (1.4, 0.6),
- HLT *fracture treatments - excluding skull and spine* (1.0, 0.4).

SAEs for the 4,011-patient 8-year MORE/CORE (GGGK/GGJY) data

Serious AEs (PTs and HLTs) that were reported statistically significantly more often in the raloxifene compared with the placebo treatment group:

- HLT *spinal fractures and dislocations* (0.3, 1.0)
- PT *knee arthroplasty* (0.5, 1.2)

SAEs for the 7,705-patient MORE/CORE (GGGK/GGJY) data

SAEs in the raloxifene treatment group that were reported with an IR greater than one per 1000 patient-years that were ≥2-fold the incidence of the placebo treatment group were

- HLT *spinal fractures and dislocations*
  - placebo [IR = 0.51]; raloxifene [IR = 1.03]
- HLT *pulmonary thrombotic and embolic conditions*
  - placebo [IR = 0.36]; raloxifene [IR = 1.14]
- PT *PE*
  - placebo [IR = 0.36]; raloxifene [IR = 1.14]

- The SAE most consistently observed at a greater incidence in raloxifene than in the placebo assigned patients was *thrombotic and embolic conditions (VTE). VTE* is a known SAE associated with use of raloxifene and therefore this is not an unexpected finding.

7.1.3 Dropouts and Other Significant Adverse Events

Adverse Events Leading to Discontinuation

- In RUTH, the number of patients who reported at least one AE that led to discontinuation of study drug was not statistically significantly different between the two treatment groups (24% versus 25%, p=0.067).
- In MORE, the overall incidence of discontinuation due to AE was similar between treatment groups (11% versus 12%, p=0.15).
- In CORE, the incidence of discontinuation for any reason and the incidence of discontinuation due to AE were similar between treatment groups.

Adverse events leading to discontinuation that were reported statistically significantly more often in the raloxifene group than the placebo group included:

RUTH/GGIO (placebo %, raloxifene %):

- PT *vomiting* (0.0, 0.3),
- HLT *nausea and vomiting symptoms* (0.3, 0.6),
- PT *oedema peripheral* (0.2, 0.6),
- HLT *oedema NEC* (0.2, 0.7),
- PT *muscle spasms* (1.0, 1.6),
- HLT *muscle related signs and symptoms NEC* (1.0, 1.6),
- PT *renal cell carcinoma stage unspecified* (0.0, 0.1),
- PT *headache* (0.1, 0.3),
- HLT *headaches NEC* (0.1, 0.3),
- HLT *paralysis and paresis excluding congenital and cranial nerve* (0.0, 0.1),
- **PT *hot flush* (0.7, 1.4)**
- **HLT *peripheral vascular disorders NEC* (0.8, 1.6)**

- *Muscle spasms* led to statistically more discontinuations
- Study drug discontinuation was reported in statistically significantly more raloxifene-assigned patients than placebo-assigned patients at the HLT *paralysis and paresis (excluding congenital and cranial nerve.* In a retrospective assessment of these 128 patients, approximately 76% of them had at least one corresponding investigator reported *stroke* during the trial. Although there was no statistically significant difference between treatment groups in the incidence of all *strokes*, stroke severity was not collected.

Reviewer Comments:

- *An excess of strokes and death due to stroke is observed in RUTH (See the table below). Excess was not statistically significant for incidence of stroke, but was statistically significant for death due to stroke. There are 25 more strokes and 20 more deaths due to stroke in the raloxifene arm.*

- *Raloxifene may have no effect on the incidence of nonfatal strokes but it be increasing the incidence of fatal strokes.*
- *Raloxifene increases the risk of VTE, does not increase the risk of coronary (arterial thromboembolism), and hence it can not be expected to increase the risk of arterial ischemic strokes. But it would increase the risk of venous thrombi which can be more fatal but can not be reliably diagnosed.*

Table 21 RUTH: Death, death due to stroke, stroke, deep venous thrombosis, and pulmonary embolism events; incidence rates, absolute risk difference, and relative risk.

	Raloxifene 5,044	Placebo 5,057	Raloxifene IR	Placebo IR	Absolute Risk Difference	Relative Risk (95% CI)
Death	554	595	20.68	22.45	-1.77	0.92 (0.82, 1.04)
Death due to Stroke	59	39	2.20	1.47	+0.73 (N = +20)	1.50 (0.98, 2.30)
Stroke	249	224	9.46	8.60	+0.86 (N = +27)	1.10 (0.91, 1.32)
Deep vein thrombosis	65	47	2.44	1.78	+0.66	1.37 (0.94, 1.99)
Pulmonary embolism	36	24	1.35	0.91	+0.44	1.49 (0.89, 2.49)

Abbreviations: IR = Incidence Rate per 1000 Patient-years.

MORE/GGGK (placebo %, raloxifene %):

- PT *diarrhoea NOS* (0.0, 0.2),
- HLT *diarrhoea excluding infective* (0.0, 0.2),
- HLT *physical examination procedures* (0.0, 0.2),
- HLT *joint related signs and symptoms* (0.0, 0.2%),
- PT *arthralgia* (0.0, 0.2),
- **HLT *peripheral vascular disorders NEC* (0.1, 0.7),**
- **PT *flushing* (0.1, 0.7);**

Incidence of the PT *DVT* was greater in the raloxifene treatment group (placebo, 0.2%; raloxifene 0.5%, p=0.051), although the difference was not statistically significant; Multiplicity may have contributed to some of the noted treatment group differences in incidence of discontinuation due to AE.

CORE/GGJY: There were no statistically significant treatment group differences in CORE, the continuation study from MORE.

Reviewer Comments: *note that while CORE was a continuation of MORE, the patient population was essentially a self-selected voluntary population and these results are impossible to interpret for a conclusion.*

Adverse events leading to discontinuation that were reported statistically significantly more often in the placebo treatment group than the raloxifene treatment group included:

RUTH/GGIO (placebo %, raloxifene %):

- HLT *muscle pains* (0.1, 0.0),
- PT *myalgia* (0.1, 0.0),
- HLT *breast and nipple neoplasms malignant* (1.1, 0.7),
- PT *breast cancer* (1.0, 0.6),
- HLT *hepatic neoplasms malignant* (0.1, 0.0),
- PT *hepatic neoplasm malignant* (0.1, 0.0),
- HLT *respiratory tract and pleural neoplasms malignant cell type unspecified NEC* (0.3, 0.1),
- HLT *bronchospasm and obstruction* (0.2, 0.0),
- HLT *alopecias* (0.1, 0.0),
- PT *alopecia* (0.1, 0.0);

MORE/GGGK (placebo %, raloxifene %):

- HLT *breast and nipple neoplasms malignant* (1.2, 0.4),
- PT *breast cancer female* (0.6, 0.2),
- PT *breast cancer in situ* (0.2, 0.0),
- PT *breast cancer NOS* (0.4, 0.1),
- PT *dizziness* (0.2, 0.0);

CORE/GGJY (placebo %, raloxifene %):

- No statistically significant treatment group differences.

7.1.3.1 Overall profile of dropouts

The three placebo controlled trials enrolled different patient populations:

- Patients in RUTH were at high risk for cardiovascular events
- Patients in MORE had osteoporosis
- Patients in CORE were those willing to continue from MORE

- Nearly twice the number of patients in the RUTH trial discontinued treatment when compared to MORE (24% and 25% in RUTH; 11% versus 12% in MORE).

Reviewer Comments: *Patients with multiple cardiovascular risk factors are more likely to discontinue treatment, whether they are in the placebo or raloxifene arms.*

7.1.3.2 Adverse events associated with dropouts

The following events led to treatment discontinuation:

- Hot flushes
- VTE (DVT and PE)
- Strokes
- Death due to stroke
- Peripheral vascular disorders NEC

- Hot flushes and VTE (DVT and PE) have a well known association with raloxifene and other SERMs /ER agonist-antagonists
- Higher number of both the strokes and death due to stroke were seen in the RUTH trial, though only the incidence of the later was statistically significant different between the two arms.

7.1.3.3 Other significant adverse events

Hematological or other lab abnormalities

- Marked hematological or other lab abnormalities meeting the definition of AE or SAE were not seen with raloxifene in the placebo-controlled trials

AEs requiring dose reductions

- No adverse event led to dose reduction—dose reduction was not a treatment option for continuation after an SAE

Other Adverse Events of Interest

- Adverse events of special interest (eg, AEs known to be associated with SERMs or estrogens) were investigated in further detail using Raloxifene Special Search Categories (RSSCs).

Cancer

All Cancers

RUTH

For overall *cancer* (all *cancer* types) in RUTH/GGIO, based upon RSSC, there were no statistically significant treatment group differences overall or for any specific type of cancer. For adjudicated all *breast cancer*, compared with placebo, there was a statistically significant decrease in incidence for raloxifene-assigned patients (HR 0.67, 95% CI 0.47-0.96, p=0.027)

MORE and CORE

For MORE/GGGK and CORE/GGJY, based upon RSSC, overall *cancer* and *breast cancer* were statistically significantly reduced for raloxifene- compared with placebo-assigned patients. Other than *breast cancer*, no other specific type of cancer was associated with a statistically significant treatment group difference, except for *skin cancer* where there was a statistically significantly greater incidence in the placebo treatment group in CORE.

For the 4011-patient 8-year MORE/CORE analyses, there was a statistically significant treatment group difference in the incidence of *cancer*, excluding *breast cancer* and *non-melanoma skin cancer*: placebo, 6.3%, raloxifene, 4.6% (p=0.027).
No individual cancer type other than *breast cancer* showed a statistically significant treatment group difference.

For the 7705-patient MORE/CORE data, the IR of overall *cancer* was lower for raloxifene-assigned patients: placebo, IR=19.1; raloxifene, IR=14.3 per 1000 patient years—this is essentially driven by reduced breast cancer incidence.

Breast Cancer

Breast cancer is discussed in detail in the Integrated Summary of Efficacy because *breast cancer* is being evaluated as an efficacy endpoint.

Uterine Cancer

The incidence of *endometrial cancer* and *uterine cancer* for RUTH, MORE, and CORE trials is shown in the table below. Only the patients with an intact uterus were considered for uterine-related cancer analyses. There were no statistically significant or clinically relevant treatment group differences in the incidence of *endometrial cancer* or *uterine cancer* in RUTH, MORE, or CORE.

For the 4011-patient 8-year MORE/CORE data, the incidence of *uterine cancer* was similar between raloxifene- and placebo-assigned patients.
Similar observations were made for the 7705-patient MORE/CORE data.
Kaplan-Meier curves for *endometrial cancer* plus *uterine cancer* and for *endometrial cancer* are presented for RUTH below.

Table 22 Endometrial and Uterine Cancer (All Randomized RUTH/GGIO, MORE/GGGK, and All CORE/GGJY Patients)

	GGIO		GGGK		GGJY	
	PBO N=5057	RLX N=5044	PBO N=2576	RLX N=5129	PBO N=1286	RLX N=2715
RSSC [a]	n (%)	n (%)	n (%)	N (%)	n (%)	n (%)
Endometrial and uterine cancer	17(0.4)	21(0.5)	5(0.3)	8(0.2)	3(0.3)	4(0.2)
Endometrial cancer	16(0.4)	17(0.4)	5(0.3)	5(0.1)	2(0.2)	4(0.2)
Uterine cancer	1(0.0)	4(0.1)	0(0.0)	3(0.1)	1(0.1)	0(0.0)

Abbreviations: n = patients with event, N = patient population, PBO = placebo, RLX = raloxifene, RSSC = raloxifene special search category.

[a] Only patients with an intact uterus were considered for the denominator: GGIO (PBO = 3882, RLX = 3900); GGGK (PBO = 1999, RLX = 3960); GGJY (PBO = 1008, RLX = 2138).

Note: There were no statistically significant treatment group differences within a study ($p<0.05$). Significance was based upon Cochran-Mantel-Haenszel test, stratified by country (not performed for $n<5$).

Source: RMP.H3SO.CTD1(SFRSCRC1), RMP.H3SO.CTD1(SFRRCMO), RMP.H3SO.CTD1 (SFRRCCO).

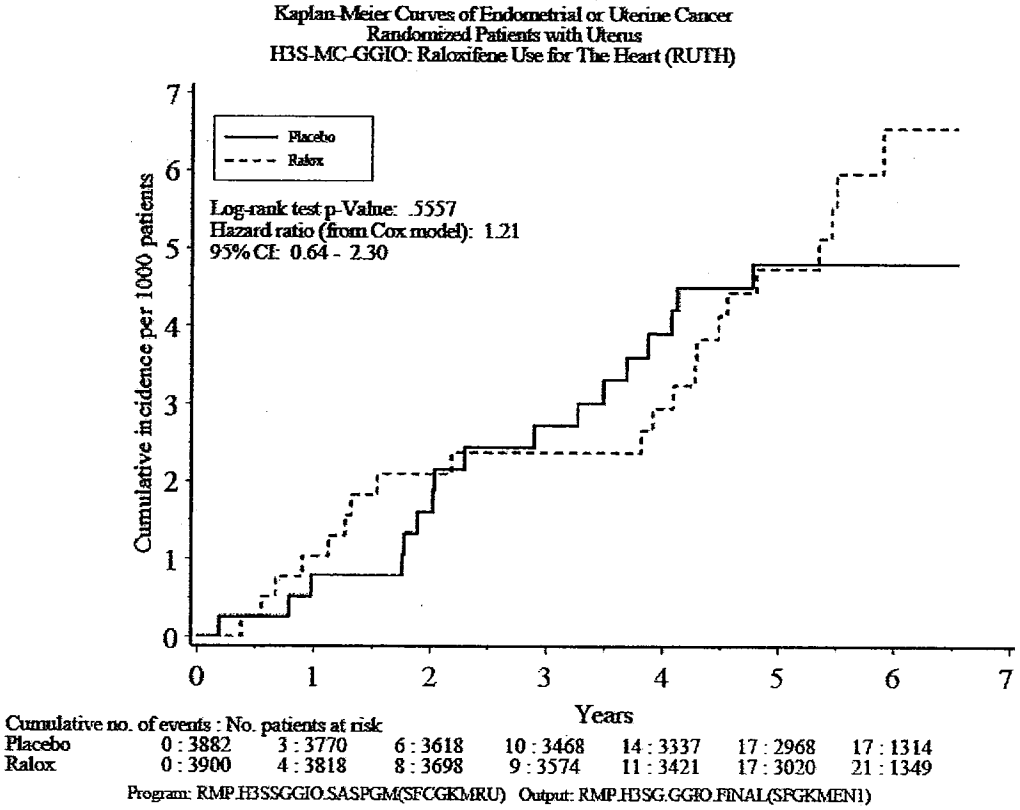


Figure 10 RUTH/GGIO Kaplan-Meier curves for endometrial plus uterine cancers.

Uterine Sarcoma

- In RUTH/GGIO, 1 of 5054 patients assigned to raloxifene and no patients assigned to placebo reported a *uterine sarcoma.*
- In MORE/GGGK, 1 of 5129 patients assigned to raloxifene and 1 of 2576 patients assigned to placebo reported a *uterine sarcoma.*
- In CORE/GGJY, *uterine sarcoma* was not reported.

These data suggest that there is no treatment group difference in regard to the incidence of *uterine sarcoma.*

Ovarian Cancer

RUTH

The figure below show displays the K-M curves for the 27 cases of *ovarian cancer* in RUTH.

- RUTH analyses for *ovarian cancer* only included patients who had at least one ovary at baseline.
- The IR of *ovarian cancer* was 0.7 and 0.4 per 1000 patient-years for the raloxifene and placebo treatment groups, respectively.
- The incidence of *ovarian cancer* was increased in raloxifene-assigned patients (HR 1.69, 95% CI 0.78-3.70), but this finding was not statistically significant.

MORE

The figure below shows the K-M curves for the 12 cases of *ovarian cancer* in MORE. All patients were included for MORE ovarian analyses, because baseline oophorectomy status was not ascertained.

- The incidence of *ovarian cancer* was decreased in raloxifene assigned patients (HR 0.49, 95% CI 0.16-1.50), but this finding was not statistically significant.

CORE

All patients were included for CORE ovarian analyses. Two cases each were observed in the placebo and treatment arms.

- There were no statistically significant treatment group differences in the incidence of *ovarian cancer*.

MORE/CORE

Similar findings were observed for the 7705-patient GGGK/GGJY data, with the IR of *ovarian cancer* lower for raloxifene-assigned patients: placebo, IR = 0.51; raloxifene, IR = 0.25 per 1000 patient-years.

Other analyses of ovarian cancers in raloxifene trials

Safety data from 7 randomized, double-blind, placebo-controlled raloxifene trials that included a total of 9,837 postmenopausal women (3,218 placebo- and 6,619 pooled raloxifene-assigned patients), with total exposure to therapy of 10,081 patient-years for placebo- and 21,406 patient-years for raloxifene-assigned patients, has been examined (Neven et al. 2002). The studies (RUTH was not included in this reveiw) and doses:

- H3S-MC-GGGF (30, 60, 150-mg/day) (Delmas et al. 1997)
- H3S-MC-GGGG (30, 60, 150-mg/day) (Johnston et al. 2000)
- H3S-MC-GGGH (60, 150-mg/day) (Freedman et al. 2001)
- H3S-MC-GGGK (60, 120-mg/day) (Ettinger et al. 1999)
- H3S-MC-GGHV (60-mg/day) (Johnell et al. 1999)

- H3S-MC-GGGP (60, 150- mg/day) (Meunier et al. 1999)
- H3S-MC-GGHD (60, 150-mg/day)

Following a median follow-up of 47 months, 8 cases of *ovarian cancer* in the placebo treatment group (0.25%) and 8 cases in the raloxifene treatment group (0.12%, p=0.140) were confirmed by a blinded adjudication review board. The RR of *ovarian cancer* associated with raloxifene therapy was 0.50, 95% CI 0.19-1.35. The IR of *ovarian cancer* was 0.8 for placebo and 0.4 per 1000 patient-years for raloxifene.

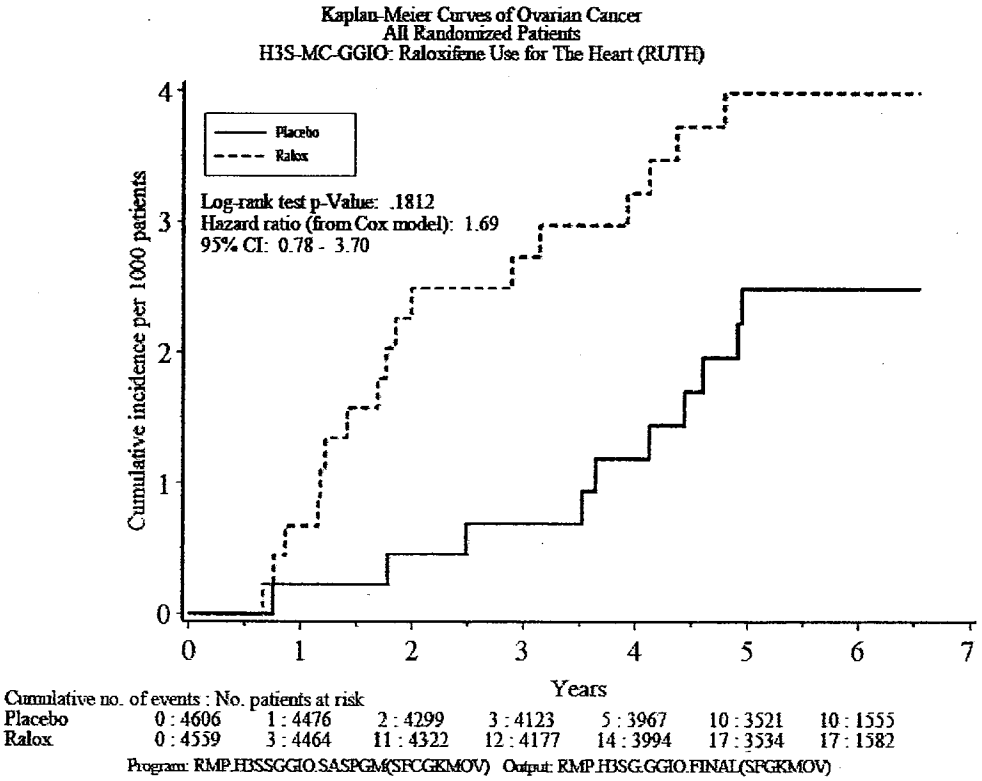


Figure 11 RUTH/GGIO Kaplan-Meier curves for ovarian cancer.

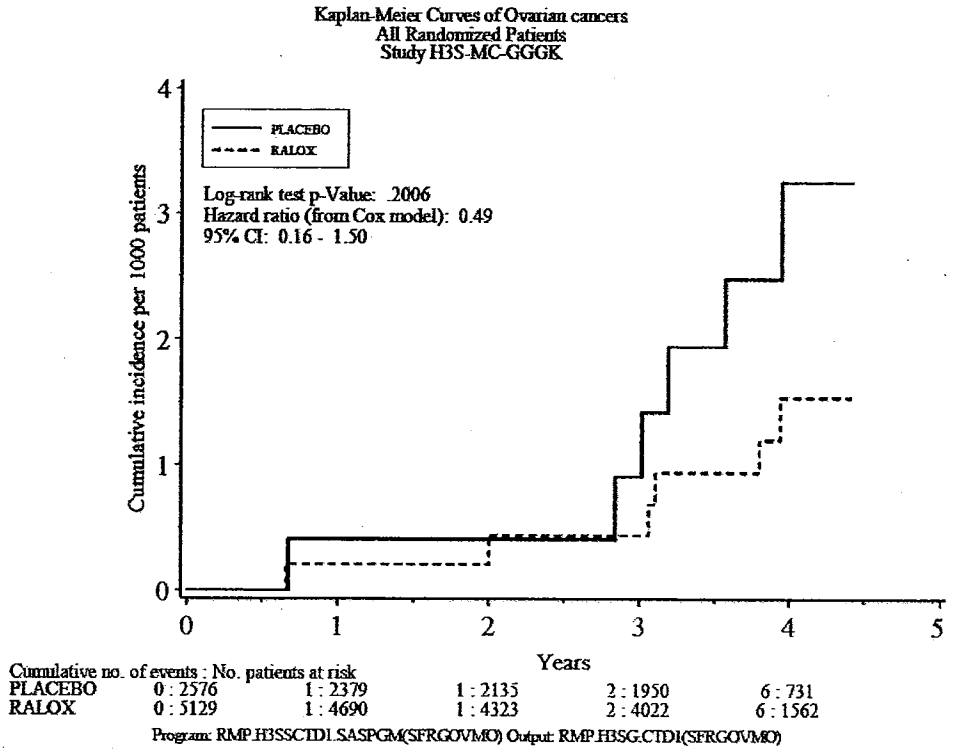


Figure 12 MORE/ Kaplan-Meier curves for ovarian cancer.

Table 23 Ovarian Cancer (All Randomized RUTH/GGIO, MORE/GGGK, and All CORE/GGJY Patients)

	GGIO [a]		GGGK		GGJY	
	PBO N=4606	RLX N=4559	PBO N=2576	RLX N=5129	PBO N=1286	RLX N=2725
RSSC	n (%)	n (%)	n (%)	N (%)	n (%)	n (%)
Ovarian cancer	10(0.2)	17(0.4)	6(0.2)	6(0.1)	2(0.2) [b]	2(0.1)

Abbreviations: n = patients with event, N = patient population, PBO = placebo, RLX = raloxifene, RSSC = raloxifene special search category.

[a] For this analysis, in GGIO, only patients with at least one ovary were included: PBO = 4606 of 5057 and RLX = 4559 of 5044.

[b] One patient received placebo for 4 years in GGGK and subsequently was enrolled in GGJY, but did not take study drug. While participating in GGJY, she took marketed raloxifene for approximately 15 months before developing ascites; 2 months later she was documented to have ovarian cancer.

Note: There were no statistically significant treatment group differences within a study ($p<0.05$). Significance was based upon Cochran-Mantel-Haenszel test, stratified by country (not performed for $n<5$).

Source: RMP.H3SO.CTD1(SFRSCRC), RMP.H3SO.CTD1(SFRRCMO), RMP.H3SO.CTD1 (SFRRCCO).

Cancer Safety Summary

In summary, no statistically significant increase in the incidence of *endometrial cancer*, *uterine sarcoma*, *ovarian cancer*, or other cancers have been observed in placebo controlled raloxifene studies.

7.1.4 Other Search Strategies

- Fairly extensive literature (clinical trials and review articles in the peer-reviewed journals) is available on SERMs/ER agonist-antagonists such as raloxifene and tamoxifen. No safety signals (other than what has been described in this review) were identified.
- No safety signals were identified that would support use of special algorithms (combination of clinical findings that could be drug related AEs).

7.1.5 Common Adverse Events

AEs related to estrogen agonist and antagonist effects of raloxifene can be expected to be common, similar to the common AEs seen with tamoxifen.

7.1.5.1 Eliciting adverse events data in the development program

- The safety of raloxifene was examined in over 35,000 patients in 4 large studies (3 placebo- and 1 comparator-controlled) in 3 different study populations.
- Patients in each of these studies were exposed to study drug for multiple years (with more than 8000 patients with ≥5 years of exposure). Thus, the data from these studies allow for a robust assessment of the safety of raloxifene treatment for the reduction in incidence of *invasive breast cancer*.
- Although all patients in these 4 studies (RUTH/GGIO, MORE/GGGK, CORE/GGJY, P-2) were postmenopausal women, due to important differences among these studies in patient populations and study design, the safety data from each study are reported separately rather than pooled.

Reviewer Comments: *The US label had already been updated based upon the MORE data, and no changes were deemed necessary based upon the CORE AE data. At the time of review proposed changes to safety sections of the label were under negotiation based upon the RUTH data.*

RUTH/GGIO

RUTH was a multinational, multicenter, randomized, double-bind, placebo-controlled study that enrolled 10,101 postmenopausal women ≥55 years old with CHD (5,034 patients) or multiple risk factors for CHD (5,067 patients). RUTH assessed the effects of raloxifene (60 mg/day) compared with placebo on the incidence of major coronary events and *invasive breast cancer*.

- The active treatment phase ended after the last randomized patient had been followed for ≥5 years.
- All randomized patients are included in the safety analyses for RUTH.
    - When patients stopped study drug, they were encouraged to continue in the study.

In RUTH, there were two co-primary endpoints.

- The **primary coronary study endpoint** was the combined endpoint of *coronary death, nonfatal myocardial infarction (MI)*, and *hospitalized acute coronary syndrome (ACS) other than MI.*
- The **breast cancer primary study endpoint** was *invasive breast cancer.*

- The **secondary study endpoints** were *all breast cancer, fractures, all-cause mortality, coronary death, nonfatal* (including silent) *MI, hospitalized ACS other than MI, myocardial revascularization, stroke, all-cause hospitalization, non-coronary arterial revascularization or non-traumatic lower extremity amputation*, and *VTE (DVT, PE, intracranial thrombosis*, and other *VTEs*).
- *Breast cancer, coronary events, stroke, VTE*, electrocardiograms (ECGs), and *death* were adjudicated by committees comprised of experts blinded to treatment assignment who were not employees of Eli Lilly and Company (Lilly). Lilly employees, blinded to treatment assignment, adjudicated the secondary outcomes of *fracture, myocardial revascularization, non-coronary arterial revascularization, lower extremity amputation*, and *all-cause hospitalization.*

MORE/GGGK

MORE was a multinational, multicenter, randomized, double-blind, placebo-controlled study that enrolled 7,705 postmenopausal women ≤80 years old with osteoporosis and assessed the effects of raloxifene on bone density and fracture incidence. MORE had a 3-year core treatment phase that was used as the basis for the osteoporosis treatment indication and a 1 year extension phase used to assess secondary endpoints such as CV events, *breast cancer*, and uterine safety. There were 2 raloxifene treatment groups: 60 mg/day and 120 mg/day. The 60 mg/day and 120 mg/day safety data are pooled for comparison with placebo.

- All randomized patients are included in the safety analyses for MORE.
- For MORE, the Coding Symbol and Thesaurus for Adverse Reaction Terminology (COSTART) dictionary was used to code AEs. In the currently presented analyses, these AEs were recoded using MedDRA.
- MORE AEs presented were generally **non-solicited**.
- **Solicited AEs in MORE:** *MI, coronary artery bypass graft surgery, percutaneous coronary intervention, stroke, endometrial cancer*, and *breast cancer* were solicited.
  - *Breast cancer, vertebral fractures*, and *dementia* were **adjudicated** in MORE.
- In MORE, gynecological examination was a specific safety assessment. Patients with *vaginal bleeding* were referred to a gynecologist for an endometrial evaluation to ascertain whether there was associated *endometrial cancer* or *endometrial hyperplasia.*

CORE/GGJY

CORE was a double-blind, follow-up to MORE that assessed the long-term effects of raloxifene (60 mg/day) versus placebo on the reduction in incidence of *invasive breast cancer* in postmenopausal women with osteoporosis who had participated in MORE. Of 180 investigative sites (7,705 patients) that participated in MORE, 130 sites agreed to participate in CORE; from

these sites, 4,011 of 6,511 eligible patients chose to enroll in CORE. Patients enrolled in CORE were not re-randomized; instead, the randomization assignment from MORE was carried forward into CORE. Patients who had been assigned to receive raloxifene (either 60 or 120 mg/day) in MORE were assigned to receive raloxifene (60 mg/day) in CORE (n = 2,725), and patients who had been assigned to receive placebo in MORE continued on placebo in CORE (n = 1,286). Resumption of study drug was not a prerequisite for enrolling in CORE, and when patients stopped study drug, they were allowed to continue in the study. Of the CORE enrollees, 811 women (20%) did not take study medication, either because they met one of the criteria excluding them from taking drug or because they chose not to. Patients were treated for up to 4 years.

- All 4,011 patients were included in safety analyses.
- All *breast cancer* cases reported by investigators were adjudicated by an independent review board comprised of physicians, none of whom were employed by Lilly.
- In CORE AEs were generally non-solicited
- **Solicited AEs in CORE:** *Breast cancer*, *nonvertebral fracture*, *uterine cancer*, *endometrial hyperplasia*, *postmenopausal vaginal bleeding*, and *VTE* (*DVT*, *PE*, and other *VTE* of which only *retinal vein thrombosis* was observed).

GGGK/GGJY Data (MORE plus CORE follow-up data)

There were 7,705 patients randomized in MORE, of which a subset of 4,011 chose to continue participation in CORE. In the CORE CSR, 8-year analyses using the 4,011 patients are presented (from the MORE baseline through CORE termination).
One must be careful in interpretation of the 4,011-patient 8-year GGGK/GGJY data analyses for the following reasons:

- AEs reported during MORE by a large proportion of patients who did not continue into CORE are not considered in the analyses;
- For the 3,694 patients who did not continue into CORE, no AE reporting is available for them after MORE.
- In regard to risk for some AEs, patients continuing into CORE were characteristically different from those who did not continue, which may have been due to selection bias (patients who chose to continue may have been healthier than those patients who did not choose to continue); and
- The beginning of CORE did not coincide exactly with the end of MORE. The median time between the end of participation in MORE and the subsequent enrollment in CORE was 10.6 months (range = 2.6 to 62 months) for both treatment groups.

Other Studies

The indication being sought for raloxifene, and reviewed in this document, is for the **reduction in incidence of *invasive breast cancer* in postmenopausal women with osteoporosis** with currently approved raloxifene dosing.

Several other clinical studies have evaluated raloxifene. B5U-MCJEAA (JEAA), H3S-MC-JOAA (JOAA), and H3S-MC-GGHW (GGHW) were the studies that examined the effect of

raloxifene in patients **with *breast cancer***; these studies randomized patients to doses of raloxifene greater than 60 mg/day. Thus, JEAA, JOAA, and GGHW were studies not intended to examine reduction in *breast cancer* incidence, which is the focus for this submission. Also, in JEAA, a different formulation of raloxifene (LY156758) was utilized rather than the current formulation (LY139481), and JOAA enrollment was stopped early due to insufficient response. However, to be inclusive, since these patients were treated with raloxifene and were examined for effect on *breast cancer*, the JEAA Summary and manuscript (Buzdar et al. 1988), JOAA Synopsis and manuscript (Gradishar et al. 2000), and GGHW Synopsis and manuscript (Dowsett et al. 2001) are included.

Because patients in JEAA, JOAA, and GGHW already had breast cancer entering the study and because the patient populations were small (203 total patients in JEAA, JOAA, and GGHW compared with over 35,000 patients in RUTH, MORE, CORE, and P-2), these studies are not summarized further in the current document.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

- MORE and CORE AEs are coded in MedDRA version 6.0 while RUTH AEs were coded using version 8.0.
- Potential mapping differences had no effect on the current RSSC (Raloxifene Special Search Categories) analyses because RSSC analyses utilize all the LLTs observed in RUTH, MORE, and CORE, regardless of MedDRA version. Where this coding dictionary difference does have an effect is when preferred terms (PTs) are being compared directly among studies.

Data Presentation

- Data are grouped together by AE subject matter rather than study, and where possible, presented together in a single table for RUTH, MORE, and CORE studies.
- Because P-2 was an active comparator study, and because AEs were coded to MedDRA for RUTH, MORE, and CORE but to CTC for P-2, the P-2 toxicity (AE) data are presented separately.
- Because certain RUTH data were captured as study endpoints (eg, *VTE*, *MI*, *stroke*), these analyses are also presented separately.

- Observations about TEAEs (based upon analyses of MedDRA terms), mortality, serious adverse events (SAEs), and discontinuations due to AE are presented.
    - Additionally, RSSCs were developed to examine more closely TEAEs of interest, including TEAEs of potential relevance to selective estrogen receptor modulators (SERMs) or hormone therapy.
    - Each RSSC was generated by grouping multiple MedDRA lower level terms (LLTs) observed in the raloxifene safety data (RUTH, MORE, and CORE) into a clinically relevant event category; the RSSCs apply to both the placebo and raloxifene treatment groups.

- When describing incidence data, "incidence rate" (IR) refers to the number of patients with a recorded event per number of patient years; eg, "the IR was 1.7 per 1000 patient years." For TEAE analyses, "incidence" refers to whether a patient had an event recorded at least once during the study period being examined. However, incidence also takes on a second definition when describing hazard ratios (HRs) and their confidence intervals (CIs). In text, when interpreting HRs, an "increase or decrease" in "incidence" is used to describe differences in risk in raloxifene- versus placebo-assigned patients; eg, "there was a 44% increase in incidence for raloxifene-assigned patients (HR 1.44, 95% CI 1.06-1.95)."

- P-values are not presented in the tables that present GGIO, GGGK, and GGJY data, but statistically significant differences ($p<0.05$) are noted with asterisks.

- Data were examined and subsequently presented in this document in the following order:
  (1) Classification of AEs by MedDRA hierarchy: system organ class (SOC), high level term (HLT), then PT;
  (2) Percent reporting of events in raloxifene treatment group: ≥2% incidence, <2% incidence;
  (3) AEs of interest (*MI*, *stroke*, *arrhythmia*, *VTE*, *cancer*, *uterine/endometrial cancer*, *ovarian cancer*, *benign gynecological conditions*, *hot flush*, *leg cramp*, *influenza-like syndrome*, *peripheral edema*, *cataracts*, and *gallbladder disease*).

7.1.5.3 Incidence of common adverse events

Adverse Events ≥2% Incidence (raloxifene > placebo and placebo > raloxifene)

The following table lists the TEAEs reported in ≥2% of *raloxifene-assigned* patients with a statistically significantly greater incidence in the raloxifene group in RUTH, MORE, and CORE.

- For comparison, TEAEs reported in ≥2% of *placebo-assigned* patients with a statistically significantly greater incidence in the placebo compared with the raloxifene treatment group are also presented.

Table 24 Statistically Significant Treatment-Emergent Adverse Events for Events Reported in ≥2% of Patients Listed by Preferred Term (All Randomized RUTH/GGIO, MORE/GGGK, and All CORE/GGJY Patients)

GGIO PTs with RLX > PBO [a]	GGGK PTs with RLX > PBO [a]	GGJY PTs with RLX > PBO [a]
arthritis cholelithiasis dyspepsia hot flush intermittent claudication muscle spasms oedema peripheral	biopsy endometrium endometrial disorder NOS flushing influenza-like illness muscle cramp oedema peripheral uterine dilation and curettage	depression
GGIO PTs with PBO > RLX [b]	**GGGK PTs with PBO > RLX**	**GGJY PTs with PBO > RLX**
acute coronary syndrome anxiety constipation osteoporosis rash	biopsy breast biopsy NOS hypercholesterolaemia hypertension NOS pruritus	Pneumonia NOS

Abbreviations: NOS = not otherwise specified, PT = preferred term, PBO = placebo, RLX = raloxifene.
Note: GGIO data are presented in MedDRA 8.0; GGGK and GGJY data are presented in MedDRA 6.0.

[a] Treatment-emergent adverse events reported in ≥2% of raloxifene-assigned patients with the incidence greater in the raloxifene than placebo treatment group.

[b] Treatment-emergent adverse events reported in ≥2% of placebo-assigned patients with the incidence greater in the placebo than raloxifene treatment group.

Note: Significance ($p<0.05$) for GGIO was based upon Cochran-Mantel-Haenszel test, stratified by country (not performed for n <5). Significance for GGGK was based upon Pearson's Chi-square test it total ≥10, Fisher's exact if 5≤total<10, and not applicable otherwise. Significance for GGJY was based upon Fisher's exact test if ≥5, otherwise not applicable.

Source: RMP.H3SO.GGIO.FINAL(SFTTEAEA), RMP.H3SO.GGJY.FINAL(AET1411), RMP.H3SO.CTD1(SFRTAEM1).

Incidence for the 7 TEAEs in RUTH which were associated with a *statistically significant* treatment group difference (and comparisons of results to those observed for MORE and CORE

The following table summarizes the incidences for the 7 TEAEs in RUTH/GGIO (*arthritis*, *cholelithiasis*, *dyspepsia*, *hot flush*, *intermittent claudication*, *muscle spasms*, and *oedema peripheral*) that were associated with a statistically significant treatment group difference, comparing results to those observed for MORE/GGGK and CORE/GGJY.

Four of the 7 TEAEs noted for RUTH are already reported in the US label (*arthritis*, *dyspepsia*, *hot flush*, and *oedema peripheral*). A fifth RUTH TEAE, *muscle spasm*, is also already reported in the US label, but indirectly as *leg cramp*. *Muscle cramp* in MedDRA 6.0 is equal to *muscle spasms* in MedDRA 8.0. *Muscle cramp* (*muscle spasms*) is described as *leg cramp* in the current US label. In RUTH, MORE, and CORE, a majority of the LLTs mapping to *muscle cramp* and *muscle spasms* were associated with *leg cramps*.

Of the 7 TEAEs noted for RUTH, *intermittent claudication* and *cholelithiasis* are the 2 TEAEs not reported in the current US label, and these TEAEs are discussed in greater detail later in this section.

Table 25 Treatment-Emergent Adverse Events Reported in ≥2% of Raloxifene-Assigned Patients with the Incidence *Statistically Significantly Greater* in the Raloxifene than Placebo Group (All Randomized RUTH/GGIO Patients and Corresponding Data from Randomized MORE/GGGK and All CORE/GGJY Patients; SOC Preferred Term)

System Organ Class Preferred Term	GGIO		GGGK		GGJY	
	PBO N=5057	RLX N=5044	PBO N=2576	RLX N=5119	PBO N=1286	RLX N=2726
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal disorders						
Dyspepsia	183(3.6)	*226(4.5)	213(8.3)	381(7.4)	28(2.2)	63(2.3)
General disorders and administration site conditions						
Oedema peripheral	591(11.7)	*713(14.1)	167(6.5)	*413(8.1)	31(2.4)	68(2.5)
Hepatobiliary disorders						
Cholelithiasis	131(2.6)	*168(3.3)	45(1.8)	93(1.8)	12(0.9)	35(1.3)
Musculoskeletal and connective tissue disorders						
Muscle cramp (muscle spasms)[a]	422(8.3)	*611(12.1)	169(6.6)	*503(9.8)	40(3.1)	97(3.6)
Arthritis [b]	117(2.3)	*148(2.9)	167(6.5)	291(5.7)	24(1.9)	53(1.9)
Vascular disorders						
Flushing (flushing or hot flush)[c]	238(4.7)	*391(7.8)	163(6.3)	*541(10.6)	11(0.9)	30(1.1)
Intermittent claudication	97(1.9)	*128(2.5)	10(0.4)	18(0.4)	4(0.3)	3(0.1)

Abbreviations: n = patients with event, N = patient population, NOS = not otherwise specified, PBO = placebo, RLX = raloxifene.

[a] Muscle cramp in MedDRA 6.0 is equal to muscle spasms in MedDRA 8.0.

[b] Term that was classified as not otherwise specified in MedDRA 6.0 but not in MedDRA 8.0 (eg, hypertension NOS [6.0] = hypertension [8.0]).

[c] Terms that map to flushing in MedDRA 6.0 map to either flushing or hot flush in MedDRA 8.0. Because hot flush was not a MedDRA 6.0 term, and because combining terms would lead to duplicative counts, hot flush was utilized in the table for GGIO and flushing for GGGK and GGJY. The incidence of flushing for GGIO was 39(0.8)% and 52(1.0)% for PBO and RLX, respectively.

* Denotes statistically significantly greater incidence than other treatment group within study ($p<0.05$). Significance for GGIO was based upon Cochran-Mantel-Haenszel test, stratified by country (not performed for n <5). Significance for GGGK was based upon Pearson's Chi-square test if total ≥10, Fisher's exact if 5≤total<10, and not applicable otherwise. Significance for GGJY was based upon Fisher's exact test if ≥5, otherwise not applicable.

Note: When criteria were met for an event to be included in the table for one study, the incidence of that event is included for each study to enable comparison of terms among the studies.

Note: GGIO was analyzed with MedDRA 8.0; GGGK and GGJY were analyzed with MedDRA 6.0.

Source: RMP.H3SO.GGIO.FINAL(SFTTEAEA), RMP.H3SO.CTD1(SFRTAEM1), RMP.H3SO.GGGY.FINAL(AET1411).

Incidence of TEAEs reported in ≥2% of raloxifene assigned patients and the incidence was *greater* in the raloxifene group *in at least one of the three* placebo controlled studies

The following table summarizes the incidence of TEAEs reported in ≥2% of raloxifene assigned patients and the incidence was greater in the raloxifene group in at least one of the three placebo controlled studies.

- When criteria were met for an event in one study, the incidence of that event is included for each study to enable comparison of terms among the studies.

Almost all of the events that met the criteria of ≥2% incidence in the raloxifene treatment group with incidence greater in raloxifene-assigned patients in one study did not meet these criteria in all the studies examined.

- *Vertigo*, *diarrhoea*, *oedema peripheral*, *pain in extremity*, and *muscle cramp* (*muscle spasms*) were the only terms to meet the criteria in all three placebo controlled studies. For *vertigo*, *diarrhoea*, and *pain in extremity*, treatment group differences were small in all cases.

For events that were reported in ≥2% of raloxifene-assigned patients, there were no TEAEs (PTs) that were reported *statistically significantly* in more raloxifene- than placebo-assigned patients consistently in RUTH/GGIO, MORE/GGGK, and CORE/GGJY (all three).

However, the incidences of *oedema peripheral*, *muscle cramp* (*muscle spasms*), and *hot flush* (*hot flush* or *flushing*) were *statistically significantly* greater in raloxifene- than placebo-assigned patients for both RUTH/GGIO and MORE/GGGK (two).

For the 4,011-patient 8-year MORE/CORE data, *biopsy endometrium*, *flushing*, *influenza like illness*, *muscle cramp*, *pollakiuria*, and *uterine polyp not otherwise specified* (*NOS*) were reported in ≥2% of raloxifene-assigned patients with the incidence statistically significantly greater in the raloxifene than the placebo treatment group.

Table 26 Treatment-Emergent Adverse Events Reported in ≥2% of Raloxifene-Assigned Patients with the Incidence *Greater* in the Raloxifene than Placebo Group (All Randomized GGIO, GGGK, and All GGJY Patients; SOC Preferred Term)

	GGIO		GGGK		GGJY	
	PBO	RLX	PBO	RLX	PBO	RLX
System Organ Class	N=5057	N=5044	N=2576	N=5129	N=1206	N=2725
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorders						
Anaemia [a]	291(5.8)	314(6.2)	69(2.7)	138(2.7)	19(1.5)	52(1.9)
Cardiac disorders						
Angina pectoris	519(10.3)	540(10.7)	68(2.6)	125(2.4)	20(1.6)	46(1.7)
Cardiac failure congestive	131(2.6)	146(2.9)	7(0.3)	31(0.6)	6(0.5)	11(0.4)
Mitral valve incompetence	90(1.8)	104(2.1)	19(0.7)	38(0.7)	3(0.2)	9(0.3)
Ear and labyrinth disorders						
Vertigo	220(4.4)	256(5.1)	113(4.4)	237(4.6)	24(1.9)	54(2.0)
Endocrine disorders						
Hypothyroidism	165(3.3)	184(3.7)	43(1.7)	94(1.8)	14(1.1)	33(1.2)
Gastrointestinal disorders						
Nausea	284(5.6)	295(5.9)	232(9.0)	494(9.6)	36(2.8)	69(2.5)
Diarrhoea [a]	326(6.5)	341(6.8)	204(7.9)	416(8.1)	26(2.0)	66(2.4)
Vomiting [a]	184(3.6)	212(4.2)	142(5.5)	301(5.9)	22(1.7)	43(1.6)
Dyspepsia	183(3.6)	*226(4.5)	213(8.3)	381(7.4)	28(2.2)	63(2.3)
Haemorrhoids	82(1.6)	85(1.7)	65(2.5)	132(2.6)	8(0.6)	23(0.8)
Hiatus hernia	83(1.6)	91(1.6)	55(2.1)	112(2.2)	19(1.5)	38(1.4)
Constipation	376(7.4)	295(5.9)	187(7.3)	371(7.2)	18(1.4)	56(2.1)
General disorders and administration site conditions						
Oedema peripheral	591(11.7)	*713(14.1)	167(6.5)	*413(8.1)	31(2.4)	68(2.5)
Influenza like illness	31(0.6)	21(0.4)	296(11.5)	*692(13.5)	9(0.7)	17(0.6)
Fatigue	341(6.7)	341(6.8)	177(6.9)	369(7.1)	20(1.6)	32(1.2)
Asthenia	238(4.7)	265(5.3)	101(3.9)	190(3.7)	22(1.7)	34(1.2)
Pyrexia	159(3.1)	159(3.2)	126(4.9)	226(4.4)	12(0.9)	14(0.5)
Pain [a]	69(1.3)	70(1.4)	55(2.1)	113(2.2)	7(0.5)	16(0.6)
Hepatobiliary disorders						
Cholelithiasis	131(2.6)	*168(3.3)	45(1.8)	93(1.8)	12(0.9)	35(1.3)

System Organ Class Preferred Term	GGIO		GGGK		GGJY	
	PBO N=5057	RLX N=5044	PBO N=2576	RLX N=5119	PBO N=1286	RLX N=2725
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Infections and infestations						
Urinary tract infection	625(12.4)	659(13.1)	262(10.2)	512(10.0)	40(3.1)	92(3.4)
Upper respiratory tract infection [a]	248(4.9)	244(4.8)	230(8.9)	513(10.0)	17(1.3)	44(1.6)
Bronchitis [a]	350(6.9)	387(7.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Influenza	453(9.0)	440(8.7)	65(2.5)	167(3.3)	34(2.6)	81(3.0)
Cystitis (bladder infection NOS) [b]	145(2.9)	165(3.3)	55(2.1)	88(1.7)	8(0.6)	13(0.5)
Pharyngitis	93(1.8)	100(2.0)	58(2.3)	155(3.0)	9(0.7)	11(0.4)
Bronchitis acute [a]	99(2.0)	124(2.5)	5(0.2)	9(0.2)	4(0.3)	11(0.4)
Respiratory tract infection [a]	103(2.0)	110(2.2)	4(0.2)	12(0.2)	8(0.6)	11(0.4)
Injury, poisoning and procedural complications						
Fall	169(3.3)	194(3.7)	1006(39.1)	1933(37.7)	157(12.2)	313(11.5)
Joint sprain	39(0.8)	53(1.1)	66(2.6)	139(2.7)	11(0.9)	22(0.8)
Investigations						
Arteriogram coronary	223(4.4)	228(4.5)	10(0.4)	22(0.4)	3(0.2)	6(0.2)
Biopsy endometrium	3(0.1)	1(0.0)	86(3.3)	*226(4.4)	3(0.2)	3(0.1)
Weight increased	98(1.9)	102(2.0)	87(3.4)	184(3.6)	6(0.5)	11(0.4)
Cardiac murmur [a]	108(2.1)	110(2.2)	23(0.9)	58(1.1)	2(0.2)	7(0.3)
Metabolism and nutrition disorders						
Diabetes mellitus [a]	382(7.6)	388(7.7)	12(0.5)	39(0.8)	6(0.5)	18(0.7)
Gout	85(1.7)	106(2.1)	7(0.3)	15(0.3)	3(0.2)	7(0.3)
Musculoskeletal and connective tissue disorders						
Arthralgia	559(11.1)	512(10.2)	558(21.7)	1207(23.5)	113(8.8)	252(9.3)
Pain in extremity	554(11.0)	583(11.6)	348(13.5)	750(14.6)	67(5.2)	145(5.3)
Back pain	602(11.9)	652(12.9)	617(24.0)	1211(23.6)	129(10.0)	238(8.7)
Osteoarthritis [a]	565(11.2)	579(11.5)	111(4.3)	199(3.7)	28(2.2)	67(2.5)
Muscle cramp (muscle spasms) [c]	422(8.3)	*611(12.1)	169(6.6)	*503(9.8)	40(3.1)	97(3.6)
Neck pain	86(1.7)	108(2.1)	153(5.9)	326(6.4)	12(0.9)	39(1.4)
Tendonitis	61(1.2)	59(1.2)	78(3.0)	165(3.2)	12(0.9)	21(0.8)
Joint swelling	78(1.5)	72(1.4)	75(2.9)	159(3.1)	15(1.2)	22(0.8)
Shoulder pain	135(2.7)	153(3.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Osteopenia	140(2.8)	150(3.0)	0(0.0)	3(0.1)	0(0.0)	0(0.0)
Arthritis [a]	117(2.3)	*148(2.9)	167(6.5)	291(5.7)	24(1.9)	53(1.9)

System Organ Class Preferred Term	[illegible]		[illegible]		[illegible]	
	PBO N=1057	RLX N=5044	PBO N=2576	RLX N=5129	PBO N=1286	RLX N=2725
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Chest wall pain	39(0.8)	43(0.9)	41(1.6)	114(2.2)	9(0.7)	20(0.7)
Localised osteoarthritis	0(0.0)	0(0.0)	46(1.8)	108(2.1)	23(1.8)	77(2.8)
Nervous system disorders						
Dizziness	545(10.8)	555(11.0)	252(9.8)	439(8.6)	33(2.6)	73(2.7)
Headache	398(7.9)	392(7.8)	238(9.2)	502(9.8)	23(1.8)	55(2.0)
Cerebrovascular accident	216(4.3)	238(4.7)	24(0.9)	37(0.7)	5(0.4)	26(1.0)
Hypoaesthesia	130(2.6)	139(2.8)	65(2.5)	139(2.7)	8(0.6)	28(1.0)
Diabetic neuropathy	106(2.1)	126(2.5)	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Sciatica	115(2.3)	121(2.4)	67(2.6)	108(2.1)	18(1.4)	36(1.3)
Memory impairment	43(0.9)	54(1.1)	49(1.9)	121(2.4)	13(1.0)	34(1.2)
Paraesthesia	100(2.0)	112(2.2)	74(2.9)	124(2.4)	10(0.8)	17(0.6)
Psychiatric disorders						
Insomnia	384(7.6)	386(7.7)	155(6.0)	284(5.5)	21(1.6)	48(1.8)
Depression	364(7.2)	374(7.4)	193(7.5)	379(7.4)	34(2.6)	*114(4.2)
Renal and urinary disorders						
Cystitis NOS (cystitis or cystitis glandularis) [d]	0(0.0)	0(0.0)	89(3.5)	206(4.0)	15(1.2)	39(1.4)
Urinary incontinence	103(2.0)	113(2.2)	72(2.8)	108(2.1)	10(0.8)	35(1.3)
Reproductive system and breast disorders						
Endometrial disorder [a]	0(0.0)	0(0.0)	79(3.1)	*216(4.2)	4(0.3)	6(0.2)
Respiratory, thoracic and mediastinal disorders						
Cough	531(10.5)	552(10.9)	273(10.6)	555(10.8)	33(2.6)	72(2.6)
Bronchitis [a]	0(0.0)	0(0.0)	255(9.9)	552(10.8)	37(2.9)	85(3.1)
Rhinitis NOS (rhinitis or nasal congestion) [a]	34(0.7)	36(0.7)	91(3.5)	192(3.7)	3(0.2)	10(0.4)
Dyspnoea exertional	136(2.7)	147(2.9)	13(0.5)	37(0.7)	1(0.1)	9(0.3)
Dyspnoea	539(10.7)	529(10.5)	157(6.1)	276(5.4)	24(1.9)	61(2.2)
Asthma [a]	102(2.0)	108(2.1)	51(2.0)	99(1.9)	19(1.5)	29(1.1)
Skin and subcutaneous tissue disorders						
Rash [a]	108(2.1)	77(1.5)	89(3.5)	202(3.9)	6(0.5)	21(0.8)
Sweating increased (hyperhidrosis) [c]	104(2.1)	132(2.6)	46(1.8)	111(2.2)	6(0.5)	9(0.3)
Social circumstances						
Family stress [a]	1(0.0)	0(0.0)	65(2.5)	146(2.9)	3(0.2)	2(0.1)

System Organ Class Preferred Term	GGIO		GGGK		GGJY	
	PBO N=5057	RLX N=5044	PBO N=2976	RLX N=5119	PBO N=1286	RLX N=2726
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Surgical and Medical Procedures						
Cataract operation (cataract extraction) [g]	305(6.0)	316(6.3)	132(5.1)	228(4.5)	42(3.3)	79(2.9)
Coronary angioplasty	218(4.3)	225(4.5)	0(0.0)	0(0.0)	3(0.2)	2(0.1)
Cholecystectomy	100(2.0)	118(2.3)	22(0.9)	65(1.3)	13(1.0)	14(0.5)
Uterine dilation and curettage	17(0.3)	22(0.4)	32(1.2)	*101(2.0)	2(0.2)	7(0.3)
Vascular disorders						
Flushing (flushing or hot flush)[b]	238(4.7)	*391(7.8)	163(6.3)	*541(10.6)	11(0.9)	30(1.1)
Hypertension [a]	672(13.3)	633(12.6)	269(10.4)	464(9.1)	113(8.8)	259(9.5)
Intermittent claudication	97(1.9)	*128(2.5)	10(0.4)	18(0.4)	4(0.3)	3(0.1)
Varicose veins [a]	147(2.9)	140(2.8)	46(1.8)	120(2.3)	11(0.9)	16(0.6)

Abbreviations: HLT = high level term, n = patients with event, N = patient population, NEC = not elsewhere classified, NOS = not otherwise specified, PBO = placebo, PT = preferred term, RLX = raloxifene, SOC = system organ class.

* Denotes statistically significantly greater incidence than other treatment group within study ($p<0.05$). Significance for GGIO was based upon Cochran-Mantel-Haenszel test, stratified by country (not performed for n <5). Significance for GGGK was based upon Pearson's Chi-square test if total ≥10, Fisher's exact if 5≤total<10, and not applicable otherwise. Significance for GGJY was based upon Fisher's exact test if ≥5, otherwise not applicable.

Note: GGIO was analyzed with MedDRA 8.0; GGGK and GGJY were analyzed with MedDRA 6.0.

Note: The incidences and terms are bolded for those events that met the criteria of ≥2% of patients with incidence of reported events greater in the RLX treatment group in each of the 3 studies presented.

Note: If a term was not present in a study under the appropriate HLT to compare to another study, than the incidence given was zero, even if that term was present under another dissimilar HLT. This is noted in the footnotes where potentially clinically relevant.

Lettered-footnotes appear on next page.

[a] Term that was classified as not otherwise specified in MedDRA 6.0 but not in MedDRA 8.0 (eg, hypertension NOS [6.0] = hypertension [8.0]). For the term bronchitis, terms were compared under the HLT bronchial conditions NEC. Note that for GGIO, under the HLT lower respiratory tract and lung infections, the incidence of bronchitis was 16.7% (842/5057) and 17.6% (890/5044) for PBO- and RLX-assigned patients, respectively.

[b] Terms that map to cystitis in MedDRA 8.0 map to cystitis acute NOS, bladder infection NOS, or cystitis NOS in MedDRA 6.0, but only bladder infection NOS is related to the infections and infestations SOC. Thus, cystitis was used for GGIO and bladder infection NOS for GGGK and GGJY.

[c] Muscle cramp in MedDRA 6.0 is equal to muscle spasms in MedDRA 8.0 under the HLT muscle related signs and symptoms. Muscle spasms is a MedDRA 6.0 PT but under the HLT musculoskeletal and connective tissue signs and symptoms NEC; incidence was low (<2%) for each treatment group.

[d] Terms that map to cystitis NOS in MedDRA 6.0 map to cystitis or cystitis glandularis in MedDRA 8.0. Because cystitis NOS was not a MedDRA 8.0 term and there was no incidence of cystitis or cystitis glandularis in GGIO, cystitis was used for GGIO and cystitis NOS for GGGK and GGJY. Note that for GGIO, under the HLT urinary tract infections, the incidence of cystitis was 2.9% (145/5057) and 3.3% (165/5044) for PBO- and RLX-assigned patients, respectively.

[e] Terms that map to rhinitis NOS in MedDRA 6.0 map to either rhinitis or nasal congestion in MedDRA 8.0. Because rhinitis NOS was not a MedDRA 8.0 term and rhinitis did not show up, and because combining terms would lead to duplicative counts, nasal congestion was used for GGIO while rhinitis NOS was used for GGGK and GGJY. The incidence of nasal congestion for GGGK was 2.0% (51/5057) and 2.2% (113/5044) for PBO and RLX, respectively. The incidence of nasal congestion for GGJY was 0.2% (2/5057) and 0.1% (4/5044) for PBO and RLX, respectively.

[f] Sweating increased in MedDRA 6.0 is equal to hyperhidrosis in MedDRA 8.0.

[g] Cataract extraction in MedDRA 6.0 is equal to cataract operation in MedDRA 8.0.

[h] Terms that map to flushing in MedDRA 6.0 map to either flushing or hot flush in MedDRA 8.0. Because hot flush was not a MedDRA 6.0 term, and because combining terms would lead to duplicative counts, hot flush was used for GGIO and flushing for GGGK and GGJY. The incidence of flushing for GGIO was 0.8% (39/5057) and 1.0% (52/5044) for PBO and RLX, respectively.

Source: RMP.H3SO.GGIO.FINAL(SFTTEAEA), RMP.H3SO.CTD1(SFRTAEM1), RMP.H3SO.GGGY.FINAL(AET1411).

Intermittent Claudication

RUTH

Intermittent claudication was reported statistically significantly more often in patients assigned to raloxifene than assigned to placebo; p=0.031.

- Raloxifene 128/5044 2.5%
- Placebo 97/5057 1.9%

- *Intermittent claudication* can be a symptom of lower extremity peripheral arterial disease. In RUTH, approximately 11% of patients had a history of lower extremity arterial disease at baseline. About one-third of these patients reported the TEAE of *intermittent claudication.*
- Of the 225 total *intermittent claudication* reports, one event was reported serious, due to worsening of preexisting *intermittent claudication.* This patient was on raloxifene and had preexisting peripheral vascular disease and had had a iliac-popliteal bypass 2 years prior to randomization.

The increased incidence of *intermittent claudication* for raloxifene-assigned patients in RUTH is inconsistent with results from MORE and CORE, where the incidence within the placebo treatment group was equal to or numerically greater than that of raloxifene treatment group.

Four preferred terms (PTs) were further examined: *peripheral vascular disorder, peripheral ischaemia, peripheral occlusive disease*, and *poor peripheral circulation.* Incidences were not statistically significantly different between treatment groups in RUTH, MORE, or CORE.

Additionally, *leg amputation* data was also looked at. The incidence for *leg amputation* was numerically greater for placebo- than for raloxifene-assigned patients.
In RUTH, *non-traumatic lower extremity amputations* and *non-coronary arterial revascularization* were adjudicated study endpoints. There were no statistically significant treatment group differences in incidence of *non-traumatic lower extremity amputations* (HR 0.92, 95% CI 0.60-1.41, p=0.7004) or *non-coronary arterial revascularization* (HR 1.05, 95% CI 0.85-1.29, p=0.6654).

Table 27 Treatment-Emergent Adverse Events Relevant to Intermittent Claudication by Specified MedDRA Preferred Terms (All Randomized RUTH/GGIO, MORE/GGGK, and All CORE/GGJY Patients)

	GGIO		GGGK		GGJY	
HLT Event Terms PT Event Terms	PBO N=5057 n (%)	RLX N=5044 n (%)	PBO N=2576 n (%)	RLX N=5129 n (%)	PBO N=1186 n (%)	RLX N=2725 n (%)
Peripheral vascular disorders NEC						
Peripheral vascular disorder [a]	82(1.6)	86(1.7)	4(0.2)	19(0.4)	5(0.4)	5(0.2)
Peripheral vasoconstriction, necrosis, and vascular insufficiency						
Peripheral ischaemia	11(0.2)	9(0.2)	3(0.1)	4(0.1)	1(0.1)	1(0.0)
Peripheral occlusive disease	61(1.2)	57(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Poor peripheral circulation	5(0.1)	3(0.1)	2(0.1)	10(0.2)	0(0.0)	1(0.0)
Limb therapeutic procedures						
Leg amputation	33(0.7)	20(0.4)	0(0.0)	2(0.0)	0(0.0)	0(0.0)

Abbreviations: NEC = not elsewhere classified, NOS = not otherwise specified, PBO = placebo, RLX = raloxifene.

[a] Term that was classified as not otherwise specified in MedDRA 6.0 but not in MedDRA 8.0 (eg, peripheral vascular disorder NOS [6.0] = peripheral vascular disorder [8.0]).

Note: There were no statistically significant ($p<0.05$) treatment group differences within a study (GGIO: Cochran-Mantel-Haenszel test, stratified by country [not performed for n <5]; GGGK: Pearson's Chi-square test if total ≥10, Fisher's exact if 5≤total<10, and not applicable otherwise; GGJY: Fisher's exact test if ≥5, otherwise not applicable).

Source: RMP.H3SO.GGIO.FINAL(SFTTEAEA), RMP.H3SO.CTD1(SFRTAEM1), RMP.H3SO.GGGY.FINAL(AET1411).

Cholelithiasis

RUTH

- The incidence of *cholelithiasis* was statistically significantly greater for raloxifene- than for placebo-assigned patients in GGIO (p=0.028)

MORE and CORE

- The incidence of cholelithiasis was not statistically significantly different between treatment groups in MORE and CORE.
- In MORE/GGGK, the incidence of cholelithiasis was 1.8% for both placebo- and raloxifene-assigned patients.
- Overall incidence was lower in MORE/GGGK and CORE/GGJY compared with RUTH/GGIO.

- *Cholecystectomy* rates were similar between treatment groups in RUTH/GGIO, MORE/GGGK, and CORE/GGJY based upon both MedDRA and RSSC data.

Dyspepsia

- The incidence of *dyspepsia* was statistically significantly greater for raloxifene- than placebo-assigned patients in RUTH; p=0.026.
- The incidence of *dyspepsia* was lower for raloxifene-assigned patients in MORE/GGGK, and similar between treatment groups in CORE/GGJY.

Dyspepsia represents one of several possible descriptions of *abdominal discomfort* or *abdominal pain*. Therefore, clinically relevant MedDRA terms (eg, *abdominal pain*) were reviewed for GGIO, GGGK, and GGJY.

- Raloxifene-assigned patients had equal to or numerically less reported incidences of epigastric, abdominal, and stomach discomfort, and abdominal pain than placebo-assigned patients.

Table 28 Abdominal Pain (Dyspepsia) Treatment-Emergent Adverse Events by Specified MedDRA Terms (All Randomized RUTH/GGIO, MORE/GGGK, and All CORE/GGJY Patients)

	GGIO		GGGK		GGJY	
HLT Event Terms PT Event Terms [a]	PBO N=5057 n (%)	RLX N=5044 n (%)	PBO N=2576 n (%)	RLX N=5129 n (%)	PBO N=1286 n (%)	RLX N=2725 n (%)
Abdominal event; patients with ≥1 event [a]	672(13.3)	661(13.1)	467(18.1)	879(17.1)	75(5.8)	149(5.5)
Dyspeptic signs and symptoms						
Dyspepsia	183(3.6)	*226(4.5)	213(8.3)	381(7.4)	28(2.2)	63(2.3)
Epigastric discomfort [b]	13(0.3)	12(0.2)	0(0.0)	3(0.1)	0(0.0)	0(0.0)
Gastrointestinal signs and symptoms NEC						
Abdominal discomfort	30(0.6)	23(0.5)	19(0.7)	37(0.7)	4(0.3)	8(0.3)
Stomach discomfort	12(0.2)	8(0.2)	4(0.2)	6(0.1)	1(0.1)	3(0.1)
Gastrointestinal and abdominal pains (excluding oral and throat)						
Abdominal pain [c]	258(5.1)	237(4.7)	173(6.7)	341(6.6)	20(1.6)	38(1.4)
Abdominal pain lower	26(0.5)	26(0.5)	46(1.8)	71(1.4)	4(0.3)	9(0.3)
Abdominal pain upper	253(5.0)	236(4.7)	93(3.6)	163(3.2)	22(1.7)	32(1.2)

Abbreviations: HLT = high level term, n = patients with event, N = patient population, NEC = not elsewhere classified, NOS = not otherwise specified, PBO = placebo, PT = preferred term, RLX = raloxifene.

[a] Seven PTs were selected for review and overall incidence is a nonduplicative count for these 7 terms. HLTs are included as headers for reference.

[b] Epigastric discomfort maps to gastrointestinal signs and symptoms NEC in MedDRA 6.0 and dyspeptic signs and symptoms in MedDRA 8.0, and is summarized in this table under dyspeptic signs and symptoms.

[c] Term that was classified as not otherwise specified in MedDRA 6.0 but not in MedDRA 8.0 (eg, hypertension NOS [6.0] = hypertension [8.0]).

* Denotes statistically significantly greater incidence than other treatment group within study ($p<0.05$). Significance was based upon Chi-square test.

Source: RMP.H3SO.CTD1(SFRDPPRU), RMP.H3SO.CTD1(SFRDPPMO), RMP.H3SO.CTD1(SFRDPPCO).

Arthritis

- *Arthritis* was reported at a statistically significantly greater incidence in patients assigned to raloxifene (148/5044, 2.9%) than patients assigned to placebo (117/5057, 2.3%, p=0.042) in RUTH.
  - The increased incidence of arthritis for raloxifene-assigned patients in RUTH was inconsistent with results from MORE/GGGK and CORE/GGJY, where the incidence within the placebo treatment group was greater than or equal to that of raloxifene treatment group.

Arthritis is a general term describing many diseases associated with joint inflammation or joint disorders. Given the significant p-value in RUTH/GGIO, a more comprehensive analysis of relevant MedDRA event terms was conducted.

- *Arthritis*, along with 9 other PTs, maps to the HLT *arthropathies NEC*, where the incidence of events mapped to this HLT was similar between treatment groups.
- The HLT *arthropathies NEC* maps to the high level group term (HLGT) *joint disorders*, which includes 3 other relevant HLTs: *joint related signs and symptoms*, *osteoarthropathies*, and *rheumatoid arthropathies*.
- In RUTH/GGIO, as well as in MORE/GGGK and CORE/GGJY, there were no statistically significant treatment group differences for these 4 HLTs.
- Approximately 3000 events were contained within these 4 HLTs for RUTH/GGIO, and *arthritis* was the only PT to have a statistically significantly greater incidence in raloxifene assigned patients.

Table 29 Joint Disorder Treatment-Emergent Adverse Events by Specified MedDRA High Level Terms (All Randomized RUTH/GGIO, MORE/GGGK, and All CORE/GGJY Patients)

	GGIO		GGGK		GGJY	
	PBO N=5057	RLX N=5044	PBO N=2576	RLX N=5129	PBO N=1286	RLX N=2725
HLT [a]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Arthropathies NEC	199(3.9)	218(4.3)	194(7.5)	344(6.7)	25(1.9)	71(2.6)
Joint related signs and symptoms	614(12.1)	576(11.4)	617(24.0)	1314(25.6)	128(10.0)	273(10.0)
Osteoarthropathies	655(13.0)	653(13.0)	169(6.6)	317(6.2)	55(4.3)	153(5.6)
Rheumatoid arthropathies	28(0.6)	25(0.5)	21(0.8)	26(0.5)	3(0.2)	11(0.4)

Abbreviations: HLT = high level term, n = patients with event, N = patient population, NEC = not elsewhere classified, PBO = placebo, RLX = raloxifene.

[a] Four HLTs were selected for review as potentially relevant to arthritis.

Note: There were no statistically significant (p<0.05) treatment group differences within a study (GGIO: Cochran-Mantel-Haenszel test, stratified by country [not performed for n <5]; GGGK: Pearson's Chi-square test if total ≥10, Fisher's exact if 5≤total<10, and not applicable otherwise; GGJY: Fisher's exact test if ≥5, otherwise not applicable).

Source: RMP.H3SO.GGIO.FINAL(SFTTEAEA), RMP.H3SO.CTD1(SFRTAEM1), RMP.H3SO.CTD1(SFRTAEC0).

Depression

The incidence of *depression* (PT) was statistically significantly increased for raloxifene-assigned patients in CORE/GGJY. In CORE/GGJY, there was no statistically significant treatment group difference for the HLT *depressive disorders*.

- This finding is inconsistent with results from GGIO and GGGK, as well as past raloxifene studies in which *depression* was a primary endpoint.

Several terms can be used to describe *depression*.

- *Depressed mood*, was statistically significantly lower among raloxifene-assigned patients in CORE/GGJY.
- Major *depressive disorder*, *dysthymic disorder*, *depressed mood*, and *feeling of despair* all were reported at a greater incidence for placebo-assigned patients in CORE/GGJY.

Biopsy Endometrium

- In **RUTH**/GGIO, there was no statistically significant treatment group difference for incidence of *biopsy endometrium*, with 4 (0.04%) patients in the entire study reporting the event.
- Raloxifene-assigned patients in **MORE**/GGGK reported the term *biopsy endometrium* at a statistically significantly greater incidence than placebo-assigned patients.
  - A detailed analysis of uterine safety was conducted in MORE/GGGK and it included biopsy data:
    - There was no increased reporting of any gynecological malignancies.
- In **CORE**/GGJY, there was no statistically significant treatment group difference for incidence of *biopsy endometrium*.

Diabetes Mellitus

RUTH

The incidence of *diabetes mellitus* was greater than 2% in each treatment group in RUTH/GGIO, with a similar incidence between treatment groups.

- The incidence of the HLT *diabetes mellitus including subtypes* for placebo- versus raloxifene-assigned patients was 9.63% (487/5057) versus 9.40% (474/5044)
- The incidence of the PT *diabetes mellitus* was 7.55% (382/5057) versus 7.69% (388/5044)

In RUTH/GGIO, analyses of **fasting glucose and hemoglobin A1c (HbA1c)** were performed separately on patients with and without *diabetes mellitus* at baseline:

- No statistically significant differences between treatment groups for the **fasting glucose *or* HbA1c** analytes were noted for **patients without *diabetes mellitus***.
- No statistically significant difference between treatment groups was noted among **patients with *diabetes mellitus*** for changes in **fasting glucose**.

- For **patients with *diabetes mellitus*** at baseline, **HbA1c** decreased among diabetics in both treatment groups over time and the magnitude of change was statistically significantly greater in the placebo group.

- **Mean weight** statistically significantly decreased in both treatment groups, but statistically significantly more for placebo patients.

MORE

- The incidence of *diabetes mellitus NOS* was less than 2% in each treatment group in MORE/GGGK with no statistically significant treatment group differences.
- The incidence of *diabetes mellitus non-insulin-dependent* was less than 2% in each treatment group in MORE/GGGK, with a statistically significantly greater incidence observed for the raloxifene compared with the placebo treatment group.
    - This difference was considered to be due, in part, to baseline imbalances between treatment groups, as indicated by statistically significant imbalances in baseline fasting glucose.
- Among patients without *diabetes at baseline*, the incidence of *diabetes* reported post-baseline was not statistically significantly different between treatment groups.

- **Fasting glucose mean change** was similar between treatment groups in MORE/GGGK, but high outlier incidence was statistically significantly greater in the 60-mg raloxifene treatment group compared with the placebo treatment group.
    - However, this finding was in large part due to treatment group differences in baseline fasting glucose, where a statistically significantly greater proportion of raloxifene patients at baseline had a fasting glucose level above 140 mg/dL.
    - After adjusting for this baseline difference, the statistically significant treatment group difference was no longer observed, and there was no statistically significant difference for high delta outliers (placebo 55 of 2576 [2.1%] patients and raloxifene 148 of 5129 [2.9%] patients).

CORE

In CORE/GGJY, the incidence of *diabetes mellitus* was less than 2% in each treatment group and similar between treatment groups.

7.1.5.4 Common adverse event tables

- Please see 7.1.5.3 for the common adverse event tables.

7.1.5.5 Identifying common and drug-related adverse events

A large number of AEs were seen in the 3 placebo-controlled raloxifene trials. These are listed and discussed in 7.1.5.3.

- The following events are of special concern as they cause significant morbidity (eg, need for treatment and hospitalization) and mortality, and a higher incidence is seen in the raloxifene arms (than placebo arms) across the trials. Notably, increased thromboembolic events can be expected as a class effect with estrogen agonist-antagonists or SERMs.
  - Venous thromboembolism (VTE)
    - DVT
    - PE

Reviewer Comments: *Incidence of thromboembolic AEs appears to be lower when compared with tamoxifen.*

7.1.5.6 Additional analyses and explorations

Adverse Events in ≥2% of Raloxifene-Assigned Patients

In RUTH/GGIO, there were 7 TEAEs reported in ≥2% of raloxifene-assigned patients where there was a statistically significantly greater incidence in the raloxifene than placebo treatment group.

- Of these, 5 are already reported in the US label: *arthritis*, *dyspepsia*, *leg cramp*, *peripheral edema*, and *hot flush.*
- *Intermittent claudication* and *cholelithiasis* were the other 2 events.

There was no evidence of underlying peripheral vascular disease or any obvious biologically plausible explanation associated with the reporting of *intermittent claudication* for raloxifene-assigned patients in RUTH/GGIO. An increase in reporting of *intermittent claudication* was not observed in MORE/GGGK or CORE/GGJY for raloxifene-assigned patients.

The incidence of *cholelithiasis* was not statistically significantly different between groups in GGGK or GGJY, and it was not associated with statistically significant treatment group differences in the incidence of *cholecystectomy* in GGIO, GGGK, or GGJY.

Based upon GGIO, GGGK, and GGJY data, raloxifene appears to have a neutral effect on mood.

Raloxifene appears to have a neutral effect in regard to *diabetes mellitus*, including fasting glucose and HbA1c levels, regardless if the patient has or does not have *diabetes mellitus* when starting raloxifene treatment.

In summary, for MedDRA-based TEAE analyses, *leg cramp*, *peripheral edema*, and *hot flush* were the AEs occurring with increased incidence in raloxifene- compared with placebo-assigned patients; these events are known raloxifene-associated AEs and are already reported in the raloxifene US label.

7.1.6 Less Common Adverse Events

Adverse Events <2% Incidence

TEAEs reported in <2% of raloxifene-assigned patients with a statistically significantly greater incidence in the raloxifene group are listed in the table below

- For comparison, TEAEs reported in <2% of patients in the placebo treatment group with a statistically significantly greater incidence in the placebo than the raloxifene treatment group are also presented.

In GGIO, GGGK, and GGJY, there were many observations where the incidence was statistically significantly greater for the placebo than the raloxifene group. These findings suggest that many of the treatment group differences were probably due to chance associations that can be seen with multiple analyses.

- When similar findings are observed among studies, then the finding is less likely to be due to chance.
- There were no consistent findings among any combination of GGIO, GGGK, or GGJY for events reported in <2% of patients and associated with a statistically significant treatment group difference, except for when the incidence was less for raloxifene-compared with the placebo-assigned patients (*breast cancer*, *hemorrhage*, *impaired healing*, *partial mastectomy*, and *sinus bradycardia*).

Table 30 Statistically Significant Treatment-Emergent Adverse Events for Events Reported in <2% of Patients Listed by Preferred Terms (All Randomized RUTH/GGIO, MORE/GGGK, and All CORE/GGJY Patients)

GGIO PTs with RLX > PBO *	GGGK PTs with RLX > PBO *	GGJY PTs with RLX > PBO *
angioneurotic oedema	cardiac failure congestive	drug hypersensitivity
atherosclerosis obliterans	cervical polyp	post procedural pain
azotaemia	deep vein thrombosis	
blood creatinine increased	diabetes mellitus non-insulin-dependent	
blood urea increased	diaphragmatic hernia NOS	
calculus urinary	disturbance in attention	
chronic sinusitis	eructation	
corneal scar	eye haemorrhage NOS	
dyspnoea exacerbated	eye swelling	
erythema	face lift	
extrapyramidal disorder	gastrointestinal pain NOS	
eyelid oedema	hypertriglyceridaemia	
fasciitis	phlebitis superficial	
gastrointestinal infection	pulmonary fibrosis	
head discomfort	rash maculo-papular	
hepatic function abnormal	trigeminal neuralgia	
joint injection	uterine cyst	
maculopathy	uterine polyp NOS	
malnutrition	vaginosis fungal NOS	
mesenteric occlusion		
mitral valve sclerosis		
multiple allergies		
neurosis		
nocturia		
paresis		
peripheral coldness		
pulmonary embolism		
rehabilitation therapy		
retinal disorder		
sensation of heaviness		
sinus tachycardia		
spinal fusion surgery		
subcutaneous abscess		
urinary retention		
urinary tract disorder		
urosepsis		
vaginal mycosis		
varicose vein operation		
venous insufficiency		

GGIO PTs with PBO > RLX [a]	GGGK PTs with PBO > RLX [a]	GGJY PTs with PBO > RLX [a]
abdominal strangulated hernia	anasarca	basal cell carcinoma
acute tonsillitis	aplasia NOS	breast cancer NOS
atrioventricular block	blood cholesterol increased	eye irritation
breast cancer	blood urine	femoral neck fracture
bronchoscopy	breast cancer female	humerus fracture
c-reactive protein increased	breast cancer NOS	hyperthyroidism
diverticulum oesophageal	breast engorgement	nerve compression
eye discharge	breast lump removal NOS	partial mastectomy
fistula	breast mass NOS	patella fracture
fungal skin infection	cautery to nose	vision blurred
haemoptysis	colectomy NOS	weight decreased
haemorrhage	coma	
hand fracture	ecchymosis	
helicobacter infection	electrocardiogram ST segment depression	
hyperchlorhydria	haemorrhage NOS	
hypertrophy breast	head discomfort	
impaired healing	impaired healing	
injury	joint arthroplasty	
irritability	joint dislocation	
lung disorder	left ventricular failure	
oral fungal infection	leukocytosis	
osteoporotic fracture	lump excision	
partial mastectomy	lung infection NOS	
proctoscopy	multiple allergies	
rash pruritic	nasal dryness	
scar	oral neoplasm NOS	
sensation of foreign body	periarthritis	
sinus bradycardia	proteinuria	
spinal compression fracture	rhinitis allergic NOS	
surgery	scotoma	
thyroid cyst	sinus bradycardia	
tibia fracture	synovitis	
	thrombocythaemia	
	umbilical hernia NOS	
	urge incontinence	

Abbreviations: NOS = not otherwise specified, PT = preferred term, PBO = placebo, RLX = raloxifene.

[a] Treatment-emergent adverse events reported in <2% of raloxifene-assigned patients with the incidence greater in the raloxifene than placebo treatment group.

[b] Treatment-emergent adverse events reported in <2% of placebo-assigned patients with the incidence greater in the placebo than raloxifene treatment group.

Note: GGIO data are presented in MedDRA 8.0. GGGK and GGJY data are presented in MedDRA 6.0.

Note: Statistically significant ($p<0.05$) treatment group differences within a study were based upon GGIO: Cochran-Mantel-Haenszel test, stratified by country [not performed for n <5]; GGGK: Pearson's Chi-square test it total ≥10, Fisher's exact if 5≤total<10, and not applicable otherwise; GGJY: Fisher's exact test if ≥5, otherwise not applicable.

Source: RMP.H3SO.GGIO.FINAL(SFTTEAEA), RMP.H3SO.GGJY.FINAL(AET1411), RMP.H3SO.CTD1(SFRTAEM1).

Adverse Events in <2% of Raloxifene-Assigned Patients

Based upon MedDRA data, there were no consistent findings among any combination of RUTH/GGIO, MORE/GGGK, or CORE/GGJY for the events reported in <2% of patients and associated with a statistically significant treatment group difference where the incidence was greater for raloxifene-assigned patients.

- However, some of these events were deemed potentially clinically relevant and are discussed in greater detail in other sections, including *pulmonary embolism*, *cardiac failure congestive*, *DVT*, *diabetes mellitus non- insulin dependent*, *uterine cyst*, *uterine polyp NOS*.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

RUTH

- A limited number of clinical chemistry laboratory tests (fasting lipids, fibrinogen, and Hemoglobin A1c [HbA1c]) were performed in RUTH/GGIO.
  - Hemoglobin A1c findings are discussed in relationship to diabetes above.
- Hematology and urinalysis were not examined.

MORE

- A comprehensive collection and analysis of laboratory analytes was performed in MORE/GGGK. These are listed and described in the Clinical Study Report in the Appendix. A large number of analyses were performed; variability in findings was common. There were no clinically relevant observations that need a label revision.

CORE

- Regular laboratory testing was not part of the study procedures.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

- The three placebo controlled studies that are reviewed have the best chance to provide a signal of an effect of raloxifene on a laboratory test. RUTH and MORE can be expected to be more informative.
- All three studies have fairly long follow ups and can be considered suitable for assessing the late developing abnormalities. CORE is not informative, however.

7.1.7.3 Standard analyses and explorations of laboratory data

Chemistry

RUTH

- In RUTH/GGIO, **total bilirubin** decreased over time in both treatment groups and the magnitude of change was statistically significantly greater in the raloxifene group.
- However, raloxifene use was not associated with any apparent clinically relevant effect on any laboratory analytes recorded, including aspartate transaminase (**AST**), total **bilirubin**, blood urea nitrogen (**BUN**), **creatinine**, or **fasting glucose**.

MORE

Analytes collected in GGGK included serum chemistry and serum liver-related chemistry.

- A statistically significant increase in **uric acid** from baseline to endpoint was observed for raloxifene- compared with placebo-assigned patients, but there were no statistically significant treatment group differences in outliers.
  - The change in uric acid was not correlated with changes in urea nitrogen, increases were small (0.2 mg/dL), and there were no statistically significant treatment group differences in the reporting of *gout* or *hyperuricemia.*
- A statistically significant decrease in **creatine phosphokinase (CPK)** from baseline to endpoint was observed for raloxifene- patients compared with placebo-assigned patients, and there were parallel findings for some of the outlier analyses.
  - The reduction in CPK with raloxifene treatment is of unknown clinical.
- Statistically significant treatment group differences related to decreases in **calcium, phosphorus, alkaline phosphatase, albumin, and total protein** within raloxifene- compared with placebo-assigned patients were observed. These were observed for mean change and outlier types.
  - These findings are consistent with skeletal anti resorptive effects and have been observed with other anti resorptive agents.

Hematology

- Analytes collected in MORE/GGGK as **numeric data** included hematology (both red blood cell [RBC] and WBC related).
- Analytes reported as **categorical (abnormal/normal) data** in MORE/GGGK included both red and white blood cell morphology.

There were some statistically significant treatment group differences in **RBC-related parameters** and **platelets**, generally due to decreases observed in the raloxifene treatment group.

There was a statistically significant decrease from baseline to endpoint observed for **platelets** in the raloxifene compared with placebo treatment group.

- The absolute values of the decreases in these analytes were small, and there were no statistically significant differences between the raloxifene and placebo treatment groups in the incidence of TEAEs potentially related to low RBC indices or platelets.
- The noted decreases in RBC indices are likely due to the selective estrogen receptor modulator (SERM) profile of raloxifene, since similar decreases in RBC indices have been observed for oral contraceptives and tamoxifen, thought to be due to a hemo-dilutional effect.

There were some statistically significant treatment group differences in **WBC-related parameters**, generally due to increases observed in the raloxifene treatment group.

- These findings were not deemed clinically relevant since, with the exception of leukocyte count, there were not a statistically significantly greater number of high outliers for the raloxifene treatment group.
- There were no statistically significant differences between the raloxifene and placebo treatment groups in the incidence of TEAEs potentially related to high WBC indices.

Urinalysis

In MORE/GGGK, analytes reported as categorical (abnormal/normal) data included urinalysis chemistry and urinalysis microscopic.

- A statistically significant increase in yeast and bacteria was observed for raloxifene compared with placebo patients, but this did not align with any TEAE findings.

7.1.7.4 Additional analyses and explorations

Biochemical Markers for Cardiovascular Risk

RUTH/GGIO

- Raloxifene statistically significantly reduced total cholesterol (>2%), low-density lipoprotein-cholesterol (LDL-C; >4%), non-high-density lipoprotein-cholesterol (non-HDL-C; >3%), total cholesterol/HDL-C (>2%), and fibrinogen (>3%) levels compared with placebo from baseline to Year 1.
- There was no statistically significant difference between treatment groups in triglyceride levels. Raloxifene statistically significantly increased HDL-C levels (>2%) compared with placebo. The results of baseline to endpoint analyses were consistent with the results of change from baseline to Year 1 analyses.
- Of note, 73% of RUTH/GGIO patients used lipid lowering agents post-baseline, and thus decreases in lipid parameters observed for raloxifene-assigned patients must be interpreted in the context of the lipid lowering effects of these medications. Due to the small magnitude of treatment group differences, these changes were deemed not likely to be clinically relevant.

MORE/GGGK

- Compared with the placebo, raloxifene assigned patients had statistically significantly greater median percentage decreases of total cholesterol (>5%), LDL-C (>8%), and fibrinogen (>10%). There were also statistically significantly greater decreases in LDL-C/HDL-C ratio and apolipoprotein B in raloxifene- compared with placebo-assigned patients.
- Median percentage change in triglyceride concentration was statistically significantly different between the placebo and raloxifene treatment groups; but this difference was driven by a decrease for the placebo group (approximately 3%) and a non-clinically relevant increase for the raloxifene (approximately 1%) treatment group.

In summary, while the consistent lowering of total cholesterol, LDL-C, LDL-C/HDL-C ratio, and fibrinogen suggests that raloxifene might reduce the incidence of major coronary events, RUTH/GGIO endpoint results did not demonstrate a cardio-protective effect of raloxifene.

7.1.7.5 Special assessments

- Hepatic metabolism of raloxifene occurs through a glucuronide pathway rather than a cytochrome P450 pathway
- Raloxifene does not appear to be associated with any liver-related abnormalities.

Clinical Laboratory Safety Summary

- In summary, for laboratory shifts that were observed, there were no apparent relationships to any corresponding AEs that were clinically relevant.
- For RUTH/GGIO, MORE/GGGK, and CORE/GGJY there were no findings suggestive of a change in the current safety profile in regard to clinical laboratory data.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In breast cancer studies, height, weight, and body mass index are of interest as peripheral conversion of steroid hormones to estrogens occurs in the fatty tissues. However, adequate analyses of data on BMI and breast cancer incidence require large population studies with long follow-up. The results from such studies have generally remained inconclusive or controversial.

- In RUTH/GGIO, height, weight, body mass index (BMI), SBP, diastolic blood pressure (DBP), and heart rate were assessed.
- In MORE/GGGK, height, weight, SBP, DBP, and heart rate were assessed.
- In CORE/GGJY, height, weight, and BMI were assessed.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

- The three placebo-controlled studies and are reviewed in this part of the NDA review.

7.1.8.3 Standard analyses and explorations of vital signs data

- In RUTH, height, weight, body mass index (BMI), SBP, diastolic blood pressure (DBP), and heart rate data were assessed. While statistically significant differences between treatment groups were present for BMI, weight, and heart rate, none of these was of a magnitude considered clinically relevant.
- In MORE, height, weight, SBP, DBP, and heart rate were assessed. While statistically significant differences between treatment groups were present for weight and sitting heart rate, none of these was of a magnitude considered clinically relevant.
- In CORE, height, weight, and BMI were assessed. There were no statistically significant treatment group differences.

In summary, there were no findings suggestive of a safety issue in regard to vital signs and physical findings.

7.1.8.4 Additional analyses and explorations

- As there were no findings suggestive of a safety issue in regard to vital signs and physical findings, and the population sizes and follow-ups were inadequate in these studies for evaluating the effect of change in BMI on breast cancer incidence, no additional analyses or explorations were conducted.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

MORE

- A standard 12-lead electrocardiogram (ECG) was performed at baseline and at the ECG endpoint (48 months or at the patient's early discontinuation). The ECGs were then analyzed using the NOVACODE method.
- Relative risks of having developed ECG abnormalities consistent with MI for each of the raloxifene groups and for the pooled raloxifene group compared with the placebo group along with the 95% confidence intervals.

CORE

- There are several important limitations to the cardiovascular (CV) safety data, including ECG data, collected in CORE. Unlike MORE, CV events were not solicited in CORE and no additional clinical information was collected to properly ascertain that an event had occurred.

RUTH

- Electrocardiograms were scheduled at baseline, Year 2, Year 4, and the final visit, if not performed in the 3 months prior to the final visit.
- Almost all patients had an ECG tracing performed at baseline (99.88%). Compliance with ECGs was consistent between treatment groups at all scheduled times.
- Due to the manner in which the ECG findings were recorded on the ECG forms, ECG changes for an individual patient can be assessed. However, when the data are assessed collectively for all randomized patients, interpretation is limited regarding treatment group differences between the proportions of normal and abnormal ECGs and the changes in abnormal ECG findings between scheduled ECGs. Therefore, conclusions regarding the clinical relevance of these findings cannot be made.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

- The three placebo controlled trials were selected for this review. Data from RUTH and MORE are presented and discussed further.
- Data for cardiovascular safety, including ECG data, were systematically collected in RUTH and MORE, but not in CORE.

7.1.9.3 Standard analyses and explorations of ECG data

RUTH

Note that all patients who enrolled into RUTH were at high risk of for a cardiovascular event. Evaluation of CV events was a primary objective in RUTH, but no difference in the CV events between the treatment and placebo arms was found.

- At baseline, 40.73% of patients had an abnormal ECG but this did not differ significantly between treatment groups.
- At baseline, of those patients with an abnormal ECG, significantly more raloxifene assigned patients had an ECG showing atrial fibrillation or flutter as compared to placebo-assigned patients.
- At Year 4 and the final visit, significantly more placebo-assigned patients had abnormal ECG readings compared to raloxifene-assigned patients.
- For patients with a normal baseline ECG, significantly more placebo-assigned patients developed a subsequent abnormal ECG than raloxifene-assigned patients; the proportion of patients in the placebo group with pathologic ST-T depression was significantly greater than in the raloxifene group.

Myocardial infarctions in MORE

- In MORE, a trend towards a reduction in the number of patients with ECG-diagnosed MI among the raloxifene-treated patients compared to the placebo-treated patients was noted.
- No statistically significant differences between the different treatment groups were seen.
- When the raloxifene data (60 mg/day and 120 mg/day doses) were pooled, there was a near statistically significant reduction in the proportion of patients with new ECG-diagnosed MI, with the magnitude of the reduction approximately 20%.

Cardiac Arrhythmia (RUTH, MORE, and CORE)

- In RUTH/GGIO, MORE/GGGK, and CORE/GGJY, there were no statistically significant differences between the placebo and raloxifene treatment groups in the incidence of *arrhythmia*, including *atrial fibrillation*, except for a statistically significant increase in the placebo treatment group for *supraventricular arrhythmias other than atrial fibrillation* in MORE/GGGK.

- For the 7,705-patient MORE/CORE data, the *arrhythmia* IR was 15.6 per 1000 patient-years for placebo-assigned patients and 15.8 per 1000 patient-years for raloxifene assigned patients.

Table 31 Cardiac Arrhythmia (All Randomized RUTH/GGIO, MORE/GGGK, and All CORE/GGJY Patients)

RSSC Subcategory RSSC	GGIO		GGGK		GGJY	
	PBO N=5057	RLX N=5044	PBO N=2576	RLX N=5129	PBO N=1286	RLX N=2725
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All Arrhythmia	744(14.7)	696(13.8)	178(6.9)	346(6.8)	35(2.7)	94(3.5)
Supraventricular Arrhythmias	441(8.7)	409(8.1)	81(3.1)	158(3.1)	23(1.8)	56(2.0)
Atrial fibrillation	323(6.4)	309(6.1)	32(1.2)	87(1.7)	15(1.2)	44(1.6)
SVAs other than atrial fib	151(3.0)	127(2.5)	*56(2.2)	79(1.5)	9(0.7)	13(0.5)
Ventricular Arrhythmias	47(0.9)	53(1.1)	13(0.5)	18(0.4)	3(0.2)	10(0.4)
Cardiac Conduction Disorder	171(3.4)	162(3.2)	39(1.5)	84(1.6)	1(0.1)	8(0.3)
Other Arrhythmias	186(3.7)	175(3.5)	67(2.6)	127(2.5)	10(0.8)	29(1.1)

Abbreviations: n = patients with event, N = patient population, PBO = placebo, RLX = raloxifene, RSSC = raloxifene special search category.

* Denotes statistically significantly greater incidence than other treatment group within study based upon Cochran-Mantel-Haenszel test, stratified by country ($p<0.05$). For incidence less than 5, statistical tests were not performed.

Source: RMP.H3SO.CTD1(SFRSCCR), RMP.H3SO.CTD1(SFRCRMO), RMP.H3SO.CTD1(SFRCRCO).

7.1.9.4 Additional analyses and explorations

- No additional analyses or explorations were conducted.
  - Raloxifene has been marketed and has been in widespread use for several years. No report that would indicate that there is an increased risk of cardiac arrhythmias has emerged.
- CV data was not systematically collected (solicited) in CORE, the continuation of MORE
  - In CORE, the cardiovascular data are further complicated due to significant differences in baseline CV risk factors between the patients who enrolled in CORE compared to those who chose not to enroll:
    - The patients who did not enter CORE were more often diabetic and were more likely to take CV medications (including lipid-lowering agents, anti-hypertensives, β-blocking agents, diuretics, and aspirin).
    - This point is further illustrated by the incidence rates of MI and stroke in the two populations. The rates of MI and stroke are significantly higher (1.9-fold, $p<0.001$ for MI and 2.7-fold, $p<0.001$ for stroke) among patients who chose not to enter CORE compared with patients who did enroll.

7.1.10 Immunogenicity

- Not applicable: raloxifene is not a therapeutic protein.

7.1.11 Human Carcinogenicity

Concern with increased risk of cancers with raloxifene use was heightened because of an increased risk of uterine endometrial cancer seen with the other approved SERM—tamoxifen. This has been discussed in other sections. Based on the available data:

- No increase in the risk of endometrial or other cancers is seen with raloxifene use.
- Raloxifene provides no protection against the non-invasive breast cancers; however, raloxifene does not increase the risk of non-invasive breast cancers (based on the available data).
- Raloxifene provides no protection against ER negative breast cancer; however, it does not increase the risk of ER negative breast cancers (based on the available data).

7.1.12 Special Safety Studies

- See the discussion above under 7.1.11

7.1.13 Withdrawal Phenomena and/or Abuse Potential

- The data available form the placebo-controlled studies and the post-marketing data do not signal an abuse potential or withdrawal phenomenon associated with raloxifene use.

Reviewer Comments: *In fact, compliance may be a more important issue.*

7.1.14 Human Reproduction and Pregnancy Data

- Raloxifene has been studied in postmenopausal women only, and it is approved for use by the postmenopausal women only.

7.1.15 Assessment of Effect on Growth

- Raloxifene has been studied in postmenopausal women only, and it is approved for use by the postmenopausal women only.
- Raloxifene is not for use in the pediatric population.

7.1.16 Overdose Experience

- The approved raloxifene dose is 60 mg/day.
- Raloxifene has also been studied at a dose of 120 mg/day in the MORE trial.
- No information of concern has emerged since its approval in terms of an overdose potential.

7.1.17 Postmarketing Experience

- Raloxifene has been approved for prevention and treatment of osteoporosis in postmenopausal women for several years. No signals of particular concern have emerged.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The three raloxifene placebo-controlled trials are the primary clinical data source for this review. The following table shows the patient populations and median ages that were exposed to raloxifene in raloxifene placebo-controlled trials.

Table 32 Patient populations exposed in the three raloxifene placebo-controlled trials.

Trial	N	Patient Population (Postmenopausal women)	Median Age (Years)
RUTH (Raloxifene Use for The Heart)	10,101	With or at risk of adverse coronary events**	68
MORE (Multiple Outcomes of Raloxifene Evaluation)	7,705	With osteoporosis	67
CORE (Continuing Outcomes Relevant to Evista)	4,011	With osteoporosis	71

*Modified Gail score $\geq$ 1.66 or history of LCIS treated by excision only

** Cardiovascular risk score $\geq$ 4
Abbreviation: BMD: bone mineral density

7.2.1.1 Study type and design/patient enumeration

Study types and designs are shown in the table below. The number of patients in each raloxifene placebo-controlled study has been shown above in 7.2.1.

Table 33 Study designs of raloxifene placebo-controlled trials.

TRIAL	TREATMENT ARMS	IMPORTANT EXCLUSIONS
RUTH	o Raloxifene 60 mg o Placebo	MI, PCI, or CABG within 3 months, Hx of VTE
MORE	o Raloxifene 60 mg o Raloxifene 120 mg o Placebo	Hx VTE, CVA within 10 yrs
CORE	o Raloxifene 60 mg o Placebo	Same as MORE except prior CVA not excluded

7.2.1.2 Demographics

- Only postmenopausal women were eligible for raloxifene placebo-controlled trials.

RUTH

Age and breast cancer risk information is shown in the following table.

Table 34 Table xxx RUTH: Breast cancer risk and demographics

Characteristics	Placebo N=5,057	Raloxifene N=5,044	Total N=10,101
5-year predicted breast cancer risk (%)			
# of patients	5056	5044	10100
Mean	1.73	1.73	1.73
Standard deviation	0.77	0.76	0.76
Median	1.54	1.55	1.55
Minimum	0.52	0.50	0.50
Maximum	9.57	14.15	14.15
5-yr predicted breast cancer risk ≥ 1.66			
# of patients (%)	5056	5044	10100
Yes	2091 (41.2)	2101 (41.65)	4192 (41.50)
No	2975 (58.8)	2943 (58.35)	5919 (59.50)
Age (yrs.)			
# of patients (%)	5057	5044	10101
≤ 60	944 (16.69)	926 (16.38)	1670 (16.53)
> 60-≤ 65	1033 (20.43)	1029 (20.39)	2061 (20.40)
> 65-≤ 70	1213 (23.99)	1260 (24.98)	24.73 (24.48)
> 70-≤ 75	1291 (25.53)	1251 (29.90)	25.42 (25.17)
>75	676 (13.37)	679 (13.46)	1355 (13.41)
Age at menarche			
# of patients	5039	5025	10064
Mean	13.47	13.51	13.49
Standard deviation	1.75	1.79	1.77
Median	13.00	13.00	13.00
Minimum	8.00	6.00	6.00
Maximum	20.00	23.00	23.00
Age at first live birth			
# of patients	4520	4500	9020
Mean	23.34	23.43	23.38
Standard deviation	4.53	4.37	4.45
Median	23.00	23.00	23.00
Minimum	12.00	13.00	12.00
Maximum	54.00	44.00	54.00
# live births			
# of patients (%)	5056	5043	10099
0	521 (10.30)	529 (10.49)	1050 (10.40)
1	800 (15.82)	916 (16.18)	1616 (16.00)
2	1396 (27.61)	1439 (29.51)	2934 (29.06)
≥ 3	2339 (46.26)	2260 (44.81)	4599 (45.54)

Characteristics	Placebo N=5057	Raloxifene N=5044	Total N=10101
# 1st degree relatives with breast cancer			
# of patients (%)	4584	4600	9184
0	4139 (90.29)	4149 (90.17)	8287 (90.23)
1	402 (8.77)	418 (9.09)	820 (8.93)
2	36 (0.79)	28 (0.61)	64 (0.70)
≥ 3	7 (0.15)	6 (0.13)	13 (0.14)
# Of prior breast biopsies			
# of patients (%)	5041	5027	10068
0	4574 (90.74)	4611 (91.72)	9185 (91.23)
1	372 (7.38)	343 (6.82)	715 (7.10)
2	65 (1.29)	58 (1.15)	123 (1.22)
≥ 3	30 (0.60)	15 (0.30)	45 (0.45)
Prior breast biopsies with dx of invasive breast cancer			
# of patients (%)	390	345	725
Yes	1 (0.26)	0	1 (0.14)
No	379 (99.74)	345 (100)	724 (99.86)
Prior breast biopsies with dx of DCIS			
# of patients (%)	380	345	725
Yes	0	2 (0.59)	2 (0.29)
No	380 (100)	343 (99.42)	723 (99.72)
Prior breast biopsies with dx of LCIS			
# of patients (%)	380	345	725
Yes	0	0	0
No	380 (100)	345 (100)	725 (100)
Prior breast biopsies with dx of atypical hyperplasia			
# of patients (%)	380	345	725
Yes	8 (2.11)	4 (1.16)	12 (1.66)
No	372 (97.99)	341 (98.84)	713 (98.34)
Prior breast biopsies with dx of other breast conditions			
# of patients (%)	386	349	735
Yes	379 (98.19)	343 (98.28)	722 (98.23)
No	7 (1.81)	6 (1.72)	13 (1.77)

MORE

The following table shows demographics of patients enrolled in MORE.

Table 35 MORE: Demographics of the enrolled patients.

Patient origin

Variable	PLACEBO (N=2576)	RLX060 (N=2557)	RLX120 (N=2572)	Total (N=7705)	p-Value
ORIGIN					
No. Patients	2576	2557	2572	7705	.228*
African Descent	6 (0.2)	6 (0.2)	14 (0.5)	26 (0.3)	
Western Asian	6 (0.2)	1 (0.0)	4 (0.2)	11 (0.1)	
Caucasian	2465 (95.7)	2455 (96.0)	2452 (95.3)	7372 (95.7)	
East/Southeast A	48 (1.9)	41 (1.6)	48 (1.9)	137 (1.8)	
Hispanic	44 (1.7)	48 (1.9)	41 (1.6)	133 (1.7)	
Other	7 (0.3)	6 (0.2)	13 (0.5)	26 (0.3)	

Age

Variable	PLACEBO (N=2576)	RLX060 (N=2557)	RLX120 (N=2572)	Total (N=7705)	p-Value
AGE: (yrs)					
No. Patients	2576	2557	2572	7705	.337**
Mean	66.60	66.48	66.91	66.67	
Median	66.93	66.86	66.73	66.85	
Standard Dev.	7.07	6.99	7.13	7.06	
Minimum	35.68	31.08	35.99	31.08	
Maximum	80.96	80.94	80.91	80.96	

Height

Variable	PLACEBO (N=2576)	RLX060 (N=2557)	RLX120 (N=2572)	Total (N=7705)	p-Value
HEIGHT: (cm) (VISIT: 1)					
No. Patients	2575	2557	2571	7703	.010**
Mean	158.95	158.93	159.38	159.08	
Median	159.00	159.00	159.51	159.10	
Standard Dev.	6.57	6.60	6.68	6.61	
Minimum	133.00	117.00	133.95	133.95	
Maximum	185.00	192.20	178.00	192.20	
Unspecified	0	0	1	1	

Weight

Variable	PLACEBO (N=2576)	RLX060 (N=2557)	RLX120 (N=2572)	Total (N=7705)	p-Value
WEIGHT: (kg) (VISIT: 1)					
No. Patients	2575	2556	2571	7703	.364**
Mean	63.64	63.58	63.96	63.73	
Median	62.88	62.60	63.00	62.88	
Standard Dev.	10.51	10.35	10.73	10.53	
Minimum	33.81	34.00	35.30	33.81	
Maximum	131.31	111.00	130.75	131.31	
Unspecified	0	1	0	1	

BMI and smoking status

Variable	PLACEBO (N=2576)	RLX060 (N=2557)	RLX120 (N=2572)	Total (N=7705)	p-Value
BMI: (kg/m2) (VISIT: 2)					
No. Patients	2575	2557	2571	7703	.989**
Mean	25.24	25.23	25.21	25.23	
Median	24.82	24.66	24.78	24.77	
Standard Dev.	3.99	4.01	4.02	4.01	
Minimum	13.54	14.21	14.45	13.54	
Maximum	51.59	43.16	49.56	51.59	
Unspecified	1	0	1	2	
CURRENT SMOKER (VISIT: 2)					
No. Patients	2576	2557	2572	7705	.915*
No	2134 (83.5)	2102 (83.1)	2112 (83.2)	6938 (83.3)	
Yes	430 (16.5)	429 (16.9)	425 (16.8)	1274 (16.7)	
Unspecified	32	26	35	93	

Alcohol use and years postmenopausal

Variable	PLACEBO (N=2576)	RLX060 (N=2557)	RLX120 (N=2572)	Total (N=7705)	p-Value
ALCOHOL > 3 DRINKS WKLY (VISIT: 2)					
No. Patients	2576	2557	2572	7705	.606*
No	2132 (83.8)	2089 (81.7)	2134 (83.0)	6355 (82.5)	
Unknown	4 (0.2)	2 (0.1)	2 (0.1)	8 (0.1)	
Yes	440 (17.1)	466 (18.2)	436 (17.0)	1342 (17.4)	
YEARS PMP (VISIT: 1)					
No. Patients	2576	2557	2572	7705	.262**
Mean	18.89	18.76	18.51	18.72	
Median	19.00	19.00	18.00	19.00	
Standard Dev.	8.48	8.51	8.30	8.43	
Minimum	2.00	2.00	2.00	2.00	
Maximum	54.00	67.00	48.00	67.00	

Family history of osteoporosis and breast cancer

Variable	PLACEBO (N=2576)	RLX060 (N=2557)	RLX120 (N=2572)	Total (N=7705)	p-Value
FAM. HIST. OF OSTPRS (VISIT: 1)					
No. Patients	2576	2557	2572	7705	.936*
No	1595 (61.9)	1561 (61.0)	1571 (61.1)	4727 (61.3)	
Unknown	299 (11.6)	304 (11.9)	295 (11.5)	898 (11.7)	
Yes	682 (26.5)	692 (27.1)	706 (27.4)	2080 (27.0)	
FAM. HIST. OF BREAST CANCER (VISIT: 1)					
No. Patients	2576	2557	2572	7705	.814*
No	2196 (85.3)	2190 (85.6)	2183 (84.9)	6569 (85.3)	
Unknown	67 (2.6)	55 (2.2)	65 (2.5)	187 (2.4)	
Yes	313 (12.2)	312 (12.2)	324 (12.6)	949 (12.3)	

History of hysterectomy and type of hysterectomy

Variable	PLACEBO (N=2576)	RLX060 (N=2557)	RLX120 (N=2571)	Total (N=7705)	p-Value
HYSTERECTOMY (VISIT: 1)					
No. Patients	2576	2557	2572	7705	.251*
No	1999 (77.6)	1950 (76.3)	2010 (78.1)	5959 (77.3)	
Yes	577 (22.4)	607 (23.7)	562 (21.9)	1746 (22.7)	
TYPE OF HYSTERECTOMY (VISIT: 1)					
No. Patients	2576	2557	2572	7705	.968*
Unknown	47 (8.1)	46 (7.6)	43 (7.7)	136 (7.8)	
Uterus,0-1 Ovary	278 (48.2)	305 (50.2)	277 (49.3)	860 (49.3)	
Uterus,2 Ovaries	252 (43.7)	256 (42.2)	242 (43.1)	750 (43.0)	
Unspecified	1999	1950	2010	5959	

Use of hormone replacement therapy

Variable	PLACEBO (N=2576)	RLX060 (N=2557)	RLX120 (N=2572)	Total (N=7705)	p-Value
PREV USE OF HRT (VISIT: 1)					
No. Patients	2576	2557	2572	7705	.567*
No	1833 (71.1)	1785 (69.8)	1829 (71.1)	5447 (70.7)	
Unknown	5 (0.2)	10 (0.4)	8 (0.3)	23 (0.3)	
Yes	738 (28.6)	762 (29.8)	735 (28.6)	2235 (29.0)	
PREV USE OF THIAZ DIURETICS (VISIT: 1)					
No. Patients	2576	2557	2572	7705	.174*
No	2241 (87.0)	2234 (87.0)	2249 (87.4)	6714 (87.1)	
Unknown	24 (0.9)	14 (0.5)	29 (1.1)	67 (0.9)	
Yes	311 (12.1)	319 (12.5)	294 (11.4)	924 (12.0)	

Previous systemic osteoporosis therapy

Variable	PLACEBO (N=2576)	RLX060 (N=2557)	RLX120 (N=2572)	Total (N=7705)	p-Value
PREV USE OF SYSTEMIC FLUORIDES (VISIT: 1)					
No. Patients	2576	2557	2572	7705	.847*
No	2531 (98.3)	2506 (98.0)	2523 (98.1)	7560 (98.1)	
Unknown	4 (0.2)	4 (0.2)	2 (0.1)	10 (0.1)	
Yes	41 (1.6)	47 (1.8)	47 (1.8)	135 (1.8)	
PREV USE OF BISPHOSPHONATES (VISIT: 1)					
No. Patients	2576	2557	2572	7705	.072*
No	2522 (97.9)	2482 (97.1)	2504 (97.4)	7508 (97.4)	
Unknown	1 (0.0)	7 (0.3)	2 (0.1)	10 (0.1)	
Yes	53 (2.1)	68 (2.7)	66 (2.6)	187 (2.4)	

Results of breast imaging at baseline

	Placebo (N=2576)	RLX060 (N=2557)	RLX120 (N=2572)	p-value[a]
Baseline Breast Imaging Results[b]				
Normal	1864 (72.4%)	1864 (72.9%)	1904 (74.0%)	0.387
Abnormal, Not Clinically Relevant	671 (26.1%)	653 (25.5%)	628 (24.4%)	0.388
Abnormal, Clinically Relevant	38 (1.5%)	40 (1.6%)	39 (1.5%)	0.966
Any Abnormal Result	709 (27.5%)	693 (27.1%)	667 (25.9%)	0.411

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

[b] Patients with more than one baseline breast image were classified according to their most severe result.

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

CORE

Table 36 CORE: Demographics and breast cancer risk of the enrolled patients.

Patient race, age, and height

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	

Patient weight and BMI

Variable	PLACEBO (N=1286)	RLX060 (N=2725)	Total (N=4011)	p-Value
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	25.29	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	

History of hysterectomy and type

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	

Gail score at visit 1 and age at menarche

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	

Age of first live birth

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	

Family history of breast cancer and history of breast biopsies

Variable	PLACEBO (N=1286)	RLX060 (N=2725)	Total (N=4011)	p-Value
CORE 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	

History of breast biopsy with atypical hyperplasia

Variable	PLACEBO (N=1286)	RLX060 (N=2725)	Total (N=4011)	p-Value
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	

7.2.1.3 Extent of exposure (dose/duration)

- Exposure to raloxifene in the three placebo-controlled trials is shown in the table below.

Table 37 Duration of raloxifene and placebo exposure in raloxifene placebo-controlled trials.

	RUTH		MORE		CORE	
Treatment	**Placebo**	**Evista**	**Placebo**	**Evista**	**Placebo**	**Evista**
Number of Pts.	5057	5044	2576	5129	1018[a]	2182[a]
Median (Years)	5.05	5.06	3.94	3.95	2.98	2.99
Mean (Years)	4.31	4.32	3.24	3.30	2..68	2.66
SD	2.06	2.06	1.29	1.29	0.83	0.88

[a] A total of 4,011 patients from MORE continued in CORE; however, 543 of 2,725 patients enrolled in Evista arm and 268 of 1,286 patients enrolled in placebo arm in CORE did not take the study drug. Thus the number of patients with study drug exposure is 3,200.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

- Safety and efficacy data from the NSABP Study of Tamoxifen and Raloxifene (STAR) are discussed by Dr. Cortazar in her part of the NDA review.

7.2.2.2 Postmarketing experience

- Postmarketing data have not identified any new AEs. This is not a surprise as the controlled trials have consisted of large numbers of patients.

7.2.2.3 Literature

- No other data are available in the peer reviewed literature than what has been presented in this review.
    - Review articles published under various titles refer only to the data from the MORE, the CORE, the RUTH, and the STAR trials.

7.2.3 Adequacy of Overall Clinical Experience

Overall clinical experience with raloxifene and safety evaluation can be considered adequate to grant approval:

- In the raloxifene placebo-controlled clinical trials, adequate numbers of patients were exposed to raloxifene. RUTH enrolled 10,101 patients, and MORE enrolled 7,705 patients; 4,011 patients from MORE were followed in CORE.
- All the patients enrolled in the placebo-controlled raloxifene trials were postmenopausal women—the patient population for which the proposed indication is being evaluated. Data on breast cancer risk of participating patients were collected in CORE follow-up of MORE and RUTH studies.
- Dose of raloxifene in CORE follow-up of MORE and RUTH trials was 60 mg/day, the dose being reviewed. In MORE the doses were 60 and 120 mg/day.
- Follow-up duration in is adequate. Median follow-up in RUTH is 5 years, and it is approximately 4 and 3 years in MORE and CORE, respectively. About 1,000 patients have been followed up for about 8 years (MORE/CORE combined follow-up data).
- MORE, CORE, and RUTH were placebo-controlled studies and allowed evaluation of AEs incidence compared to placebo in the relevant patient population.
- Many of the AEs associated with estrogen agonist-antagonist (SERMs) drugs are well known from long experience with tamoxifen. The incidences of endometrial and breast cancer were systematically evaluated in these trials. Risks of increased thromboembolic events with SERMs are well known data on these were collected during the trials.
- RUTH included patients who were known to be at high risk for cardiovascular events. Data on breast cancer risk was collected in RUTH and CORE.
- Patients with history of VTE and CVA were excluded from MORE and those with history of VTE were excluded form RUTH—as VTE risk was anticipated. Higher VTE risk has been noted in the raloxifene arms in the reviewed trials and will be included in the label.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

- No new animal or *in vitro* testing was submitted or reviewed in the current NDA submission.

7.2.5 Adequacy of Routine Clinical Testing

Clinical testing in raloxifene placebo-controlled trials is adequate:

- Patients in the raloxifene placebo-controlled trials underwent regularly scheduled bilateral breast mammograms.
- Serum lipids were included in the clinical lab follow-up in RUTH trial.
- ECGs were monitored in RUTH trial.
- Information on VTE events, strokes, cardiac interventions, and endometrial and other cancers was collected in raloxifene placebo controlled trials.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

- No new data were submitted or reviewed under this NDA submission.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

- Please see 7.2.3.
- Evaluation of AEs expected with an estrogen agonist-antagonist class drug has been studied adequately—based on the data reviewed in this NDA.
- No recommendations are made for further studies. However, the increased risk of thromboembolic AEs will be highlighted in the label.

7.2.8 Assessment of Quality and Completeness of Data

Complete data of adequate quality were available to allow review of raloxifene safety:

- Trials were placebo controlled
- Several thousand patients were enrolled in each trial
- Follow-up in the trial is 3 to 8 years long
- Information for many of the anticipated AEs was systematically collected and analyzed

7.2.9 Additional Submissions, Including Safety Update

- All of the placebo controlled trials reviewed in this NDA submission have had long (at least over 3 years) follow-ups. A safety update with a relatively short additional follow-up (120 days additional days of follow up) cannot be expected to provide information that would materially change the conclusions of the original review based on approximately 5, 4, and 3 years in the RUTH, MORE, and CORE trials.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The following AEs are considered clinically important and likely to be treatment related. (For further details, please see 7.1).

Venous thromboembolic event (VTE)

- A *statistically significant* increase in deep vein thrombosis (DVT), pulmonary embolism (PE), and other VTEs was observed in the raloxifene arms in RUTH (44% increase) and MORE (89% increase) trials.
- *Numerical increases* in the incidence of DVT and the incidence of PE, i.e. DVT and PE events counted separately rather than under single VTE events category, were observed in raloxifene assigned patients in RUTH, MORE, and CORE trials.
    - This increase was statistically significant for DVT in MORE.

Hot flushes, leg cramps, and peripheral edema

- There were statistically significant increases in the incidences of *hot flushes*, *leg cramps* (*muscle spasms*), and *peripheral edema* in raloxifene assigned patients in RUTH and MORE.
- There was a numerically higher incidence of hot flashes and leg cramps in CORE.

Death due to stroke

- This important safety observation was noted in RUTH only:
    - A statistically significant (p=0.0499) 49% increase in the incidence of the *death due to stroke* was observed in raloxifene (compared with placebo) assigned patients.

- No such increase was observed in MORE.
- An increase was observed in CORE but it was not statistically significant.

Cholelithiasis

- In RUTH, there was a *statistically significantly* greater incidence of *cholelithiasis* in raloxifene- compared with placebo-assigned patients (3.3% versus 2.6%).
- This increase was not statistically significant in MORE or CORE.

Important Limitations of the Data

The primary endpoints for the 3 placebo-controlled clinical trials were efficacy endpoints—accordingly, the sample size in each trial was determined based on the expected rates of efficacy events in the experimental and the control arms. Therefore:

- The risk of both type 1 and type 2 errors is high.

- Statistical significance testing of the safety events is neither reliable nor conclusive.

Conclusions

- Safety conclusions were made considering the above limitations of the analyses.
- The applicant agreed to include the information on VTE, death due to stroke, and cholelithiasis risk in the label.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The data from MORE, CORE, and RUTH were **not pooled** for this safety review. The following considerations entered this decision.

- Each of the placebo-controlled trials enrolled somewhat different patient population
  - All patients in RUTH were at high risk for a cardiovascular event as all of them had a high cardiovascular risk score.
  - Patients in MORE and CORE had osteoporosis
  - CORE was a continuation of MORE

The differences noted above could obscure differences in AEs among different patient populations. Moreover, as each trial was placebo-controlled, had several thousand patients, and had considerable follow-up, the opportunity to detect AEs occurring at a clinically important frequency was there.

7.4.1.2 Combining data

- Not applicable. See 7.4.1.1

7.4.2 Explorations for Predictive Factors

No specific factor that was predictive of VTE, stroke, or death due to stroke risk was found.

- In RUTH, a higher incidence of death due to stroke was noted, and it was statistically significant.
  - There was a higher incidence of strokes, but it was not statistically significant.
  - Several factors, eg atrial fibrillation, were explored further to see if they were predictable.
  - There were no conclusive predictive factors of death due to stroke.
- As the trials enrolled only postmenopausal women—no sex differences are there.

- All trials enrolled only postmenopausal women—no association with menopausal status can be elicited.
- In RUTH all women had a high CV risk score.

7.4.2.1 Explorations for dose dependency for adverse findings

No dose dependency for AEs was found.

- In RUTH and CORE, only one dose was used: 60 mg/day.
- In MORE, doses of 60 and 120 mg/day were used, but as there was no improvement in efficacy for osteoporosis prevention or treatment, the approved dose is 60 mg/day.
- The protocols required discontinuation of study drugs in the event of significant AEs, there was o provision four using lower than 60 mg/day doses.

7.4.2.2 Explorations for time dependency for adverse findings

No time dependency has been noted for AEs, i.e., there was no remarkable increase or decrease in the incidence of an AE with time.

- Follow-up in the studies has ranged form 3 to 5 years. A subset of patients has been followed up for more than 8 years—but it must be stated that only the patients who are tolerating the drug are likely to continue taking it.
- The increased risk of VTE events is observed throughout the study periods.

7.4.2.3 Explorations for drug-demographic interactions

- See 7.4.1.1 and 7.4.2 above; all patients enrolled in raloxifene trials were postmenopausal women.

7.4.2.4 Explorations for drug-disease interactions

- It is likely that a higher incidence of VTE would have been observed if women with history of DVT and PE were not excluded from the trials.
- As women in RUTH trial had high CV risk scores, and in the RUTH trial the risk of **death due to stroke** was found to be higher (and statistically significant), it is possible that raloxifene increases the risk of fatal strokes in patients with CV risk factors.
  - Raloxifene IR = 2.20 per 1000 patient-years
  - Placebo IR = 1.47 per 1000 patient-years
- Note that numerically there were more **strokes** in the raloxifene arm in RUTH, although the increase was to statistically significant.
  - Raloxifene IR = 9.46 per 1000 patient-years
  - Placebo IR = 8.60 per 1000 patient-years

7.4.2.5 Explorations for drug-drug interactions

- No new data were available for drug-drug interaction exploration.
- Possible interactions with cholestyramine, warfarin, and highly protein bound drugs (eg diazepam, diazoxide, and lidocaine) are already included in the label.

7.4.3 Causality Determination

Ability to determine causality is limited due to the following reasons:

- The primary endpoints of all of the controlled clinical trials reviewed in this NDA were efficacy endpoints—accordingly, the sample size in each trial was determined based on the expected rates of efficacy events in the experimental and the control arms.
- Therefore, statistical significance testing of safety events is not highly reliable and conclusive: risk of both type 1 and type 2 errors is high.
- Safety conclusions must be considered given these limitations of the analyses.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Recommended raloxifene dose:

- The recommended dose is one 60 mg EVISTA tablet daily, which may be administered any time of day without regard to meals.

Recommendation for additional supplementation with calcium and vitamin D

- Intake of 1500 mg/day of **elemental calcium** is recommended.
  - Total daily intake of calcium above 1500 mg has not demonstrated additional bone benefits while daily intake above 2000 mg has been associated with increased risk of adverse effects, including hypercalcemia and kidney stones.
- Recommended intake of **vitamin D** is 400-800 IU daily.
  - Patients at increased risk for vitamin D insufficiency (e.g., over the age of 70 years, nursing home bound, or chronically ill) may need additional vitamin D supplements.
  - Patients with gastrointestinal malabsorption syndromes may require higher doses of vitamin D supplementation and measurement of 25-hydroxyvitamin D should be considered.

- 60 mg/day dose of raloxifene has been studied adequately in the placebo-controlled trials
  - A dose of 120 mg/day has also been studied. It did not improve the efficacy, and no worsening of the toxicities was observed. Both the approved and widely used recommended dose is 60 mg/day.

Raloxifene use in patients with hepatic or renal impairment:

- Raloxifene should be used with caution n patients with hepatic or renal impairment.

- **Renal Impairment**
  - In the osteoporosis treatment and prevention trials, raloxifene concentrations in women with **mild** renal impairment are similar to women with normal creatinine clearance.
  - When raloxifene was administered to individuals with **moderate or severe** renal impairment, plasma raloxifene concentrations were 122% higher than those in healthy volunteers.

- **Hepatic Impairment**
- In subjects with **mild** hepatic impairment (Child-Pugh Class A; total bilirubin 0.6 to 2 mg/dL):

- Clearance of raloxifene was reduced 56%; the half-life of raloxifene was not altered.
- Plasma raloxifene concentrations were approximately 150% higher than those in healthy volunteers and correlated with total bilirubin concentrations.

- The pharmacokinetics of raloxifene has not been studied in patients with **moderate or severe** hepatic impairment.

8.2 Drug-Drug Interactions

Cholestyramine and other anion exchange resins

- Cholestyramine, an anion exchange resin, causes a 60% reduction in the absorption and enterohepatic cycling of raloxifene after a single dose.
- Although not specifically studied, it is anticipated that other anion exchange resins would have a similar effect.

Warfarin

- In vitro, raloxifene did not interact with the binding of warfarin.
- The concomitant administration of raloxifene and warfarin, a coumarin derivative, has been assessed in a single-dose study. In this study, raloxifene had no effect on the pharmacokinetics of warfarin. However, a 10% decrease in prothrombin time was observed in the single-dose study.
- In the osteoporosis treatment trial, there were no clinically relevant effects of warfarin co-administration on plasma concentrations of raloxifene.

Other Highly Protein-Bound Drugs

- In the osteoporosis treatment trial, there were no clinically relevant effects of co-administration of other highly protein-bound drugs (e.g., **gemfibrozil**) on plasma concentrations of raloxifene.
- In vitro, raloxifene did not interact with the binding of **phenytoin**, **tamoxifen**, or **warfarin**.

Ampicillin and Amoxicillin

- Peak concentrations of raloxifene and the overall extent of absorption are reduced 28% and 14%, respectively, with co-administration of ampicillin. These reductions are consistent with decreased enterohepatic cycling associated with antibiotic reduction of enteric bacteria. However, the systemic exposure and the elimination rate of raloxifene were not affected.
- In the osteoporosis treatment trial, co-administration of amoxicillin had no discernible differences in plasma raloxifene concentrations.

Antacids

- Concomitant administration of calcium carbonate or aluminum and magnesium hydroxide-containing antacids does not affect the systemic exposure of raloxifene.

Corticosteroids

- The chronic administration of raloxifene in postmenopausal women has no effect on the pharmacokinetics of methylprednisolone given as a single oral dose.

Digoxin

- Raloxifene has no effect on the pharmacokinetics of digoxin.

Cyclosporine

- Concomitant administration of raloxifene with cyclosporine has not been studied.

Lipid-Lowering Agents

- Concomitant administration of raloxifene with lipid-lowering agents has not been studied.

8.3 Special Populations

Pregnancy

Raloxifene is approved for use by postmenopausal women only. Raloxifene should not be used in women who are or may become pregnant.

Nursing Mothers

- Raloxifene is approved for use by postmenopausal women only. It should not be used by lactating women. It is not known whether this drug is excreted in human milk.

Geriatric Use

- Of the total number of patients in placebo-controlled clinical studies of raloxifene, 61% were 65 and over, while 15.5% were 75 and over.
- No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
- Based on clinical trials, there is no need for dose adjustment for geriatric patients.

Renal Impairment

- Raloxifene should be used with caution in patients with moderate or severe renal impairment.
- See 8.1.

Hepatic Impairment

- Raloxifene should be used with caution in patients with hepatic impairment.
- See 8.1.

8.4 Pediatrics

- Raloxifene is for use in postmenopausal women only.
- Neither pharmacokinetics nor safety and effectiveness of raloxifene in pediatric patients have been evaluated.

8.5 Advisory Committee Meeting

- On the 24th of July 2007, the FDA presented its review of raloxifene NDA for the indication of reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and for reduction in risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer.
- Benefits and risks of raloxifene treatment were presented and discussed by the Oncology Drugs Advisory Committee (ODAC).
- For the first indication, the ODAC recommended approval of raloxifene by a vote of 8 to 6.
- Concerns with the increased risks of thromboembolism and death due to stroke were felt to be important and boxed warning and med-guide were the recommended methods to provide the information in this risk.

8.6 Literature Review

Peer reviewed literature highlights the following:

- Tamoxifen reduces the incidence of both invasive and non-invasive (DCIS) breast cancer in both pre- and post- menopausal women.
- Raloxifene decrease the incidence of invasive breast cancer only and only in postmenopausal women.
- The observed reduction in the incidence f breast cancer is driven by reduction in the occurrence of ER positive breast cancer.

- Increased risk of thromboembolic events is expected with drugs like tamoxifen and raloxifene—mixed estrogen agonist-antagonists/SERMs.
- Continued mammographic exams of women on treatment with tamoxifen or raloxifene are required as the risk of breast cancer development is not eliminated, it is only reduced.
- No survival benefit from tamoxifen or raloxifene has been seen so far in the prevention trials.
- Tamoxifen provides a benefit that persists well beyond the time of stopping administration of tamoxifen. This has not been shown with raloxifene.
- Most of the breast cancers, both on the treatment and control arms in tamoxifen and raloxifene trials have been early stage cancers.
- See the References Section for the relevant recent literature.

8.7 Postmarketing Risk Management Plan

- Raloxifene label will include a Black Box Warning on venous thromboembolism and death due to stroke.
- A Medication Guide will be provided and patients will be instructed to read the "Medication Guide that comes with Evista" before taking raloxifene and each time they refill the prescription.

8.8 Other Relevant Materials

9 OVERALL ASSESSMENT

9.1 Conclusions

- Efficacy of raloxifene in reducing the risk of invasive breast cancer in postmenopausal women has been demonstrated in placebo-controlled trials—raloxifene reduces this risk modestly.
- A large number of women must be treated to prevent one early stage ER positive breast cancer.
    - The number of generally healthy women needed to treat for one year to prevent one breast cancer (NNT) is over 862 based on the results of the RUTH trial, and the NNT is over 300 based on the results of MORE and CORE trials.
- Raloxifene increased the risk of VTE events in the placebo controlled trials—sometimes statistically significant and sometimes not statistically significant; however, the tests for statistical significance cannot be considered highly informative in the setting of the trials designed and powered to look at other endpoints—the risk of both type 1 and type 2 errors is high and remains unknown.
- Risks and benefits of treatment with raloxifene must be carefully weighed by the patients with the help of their prescribing physicians.
- The patients need to be aware of the risks and benefits of raloxifene treatment.

9.2 Recommendation on Regulatory Action

Raloxifene should be approved for the reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

- Raloxifene label must include a Black Box Warning to clearly state the increased risk of venous thromboembolism and increased risk of death due to stroke.
- A Medication Guide to detail the risks and benefits of treatment with raloxifene (in easily understandable language) must be provided to the patients taking raloxifene.

9.3.2 Required Phase 4 Commitments

- None.

9.3.3 Other Phase 4 Requests

- None.
-

9.4 Labeling Review

- Labeling review is ongoing.
-

9.5 Comments to Applicant

- Comments to the applicant have been provided throughout the review, at the ODAC meeting on the 24th of July 2007, and during the labeling review.
- Comments regarding safety have focused on the need to provide safety information to the patients in a clear language with appropriate prominence in the label.
- Comments on efficacy have focused on correctly stating the modest benefits of raloxifene.