Adverse Reactions (12.2.2.2.)

Adverse reactions are AEs which were deemed by the investigator to be reasonably, possibly related to either study drug administration or protocol procedures. Table GGIO.14.48 presents adverse reactions by SOC, High-level Term, and Preferred Term.

- The proportion of patients with ≥1 adverse reaction was significantly higher in the raloxifene group than in the placebo group.

The following adverse reactions at the Preferred Term level were reported significantly more frequently by patients in the raloxifene group than in the placebo group (in decreasing frequency): **muscle spasms, hot flushes, oedema peripheral, hyperhidrosis, breast pain,** and **palpitations**.

Discontinuations due to adverse reactions:

- Twenty patients discontinued study drug due to **hyperhidrosis** (9 in placebo, 11 in raloxifene); none of the events were considered serious. Although not known with certainty, hyperhidrosis may have been synonymous with excessive flushing, and hot flushes are associated with use of raloxifene.
- Six patients discontinued study drug due to **breast pain** (2 in placebo, 4 in raloxifene; none were considered serious. This increased reporting of breast pain in the raloxifene group is inconsistent with the observation of no between-treatment group differences in the analysis of breast pain using a special search category (SSC). Therefore, the adverse reaction of breast pain was not deemed clinically relevant.
- Two patients assigned raloxifene discontinued study drug due to **palpitations**; none of the events were considered serious. Palpitations were not considered clinically relevant.

Deaths, Serious Adverse Events, and Other Notable Adverse Events (12.3.)

The analysis of SAEs presented in this report is based on **the reporting database** and include randomized patients who reported an AE that met any of the protocol-defined serious criteria, whether or not the event was judged to be related to study drug, and any study endpoint considered a SAE.

Protocol defined deaths and SAEs were also collected in the **Lilly Safety System (LSS).** The listing of SAEs from the LSS may differ from the reporting database. The LSS contains SAEs that **occurred after the patient discontinued from the study** and were judged by the investigator to be potentially related to study drug.
The reporting database contains protocol-defined SAE information collected only when the patient was participating in the study. Additionally, the protocol definition of an SAE resulted in the reporting database containing a more comprehensive set of data with respect to clinical events. For example, the LSS contains only those deaths defined in the protocol as SAEs;

whereas, the reporting database contains all deaths. At the time of the database lock, the reporting database and the LSS were consistent with respect to protocol specifications for SAEs. Therefore, **analysis of SAEs in the LSS database is not presented in this report.**

See Section 14.4.3 for narratives on the patients meeting the following criteria as agreed upon with the Division of Drug Oncology Products at the US FDA (pre-NDA meetings 25 May 2005 and 15 November 2005):

1. **Patients who died on-study**

2. **Patients who experienced one of the following SAEs:**

a. Study Endpoints – Any patient who experienced an endpoint event meeting criteria for an SAE. All VTEs were SAEs.
b. Cancers – Any patient diagnosed with one of the following cancers: breast, endometrial, ovarian, or gastrointestinal cancer.
c. A patient who experienced postmenopausal bleeding reported as an SAE.
d. A patient who experienced an SAE of resuscitated cardiac arrest.
e. A patient who experienced an SAE of ventricular arrhythmia, including ventricular tachycardia, ventricular fibrillation or flutter, or torsade de pointe.
f. A patient who experienced an SAE of syncope or dizziness.
g. A patient who experienced an SAE of rhadomyolysis.
h. A patient who experienced a hematological or other laboratory abnormality, or an allergic reaction, reported as an SAE.
i. A patient who experienced an SAE deemed by the investigator as related to study drug or protocol procedures not listed above.

3. Patients who discontinued study drug due to an AE: Study medication may have been temporarily or permanently discontinued if a patient experienced an AE, became immobilized, or had other reasons warranting discontinuation of treatment, such as the diagnosis of a VTE or a breast cancer. However, patient follow-up was to have continued while off-treatment.

- Table GGIO.14.56 presents a by-patient listing for patients who experienced an AE resulting in discontinuation of study medication (including a VTE or a breast cancer), without evidence that study medication was ever resumed again throughout her participation in the study.
- See Section 14.4.2 for by-patient listings of all patients who died (Table GGIO.14.54) or experienced other SAEs (Table GGIO.14.55).
- Individual CRFs for patients who had breast cancer during this study are available from the sponsor upon request (Appendix 16.3.2).

Deaths (12.3.1.)

Refer to Section 11.4.4.4 for results of the all-cause mortality endpoint.
Table GGIO.14.54 presents a by-patient listing of all patients who died.

Other Serious Adverse Events (12.3.2.)

An SAE was defined as any event that met at least one of the following criteria:

- Life-threatening
- Severely or permanently disabling
- Cancer
- Significant for any other reason

The table below presents SAEs reported during the study by SOC, High-level Term, and Preferred Term. (The primary and secondary endpoint events may or may not have been reported as an SAE depending on whether the protocol definition of an SAE in GGIO was met.)

- There was no significant difference between treatment groups in the proportion of patients who reported ≥1 SAE.

- Significantly more patients in the raloxifene group than in the placebo group reported SAEs categorized under the Preferred Terms of **pulmonary embolism** and **bladder cancer.**
  - Pulmonary embolism is a known SAE associated with use of raloxifene and therefore this is not an unexpected finding.
  - Although the Preferred Term "bladder cancer" was reported more frequently in the raloxifene group compared with the placebo group as an SAE, there was no significant difference between treatment groups at the High-level Term "bladder neoplasms malignant" to which this Preferred Term maps.

In review of TEAEs, 14 events mapped to the High-level Term "bladder neoplasms malignant" and 14 bladder cancers were identified using the SSC for all cancers.

- There were no between-treatment group differences in either of these analyses; however, the proportion of patients reporting bladder cancer was greater in the raloxifene group compared with the placebo group.
- Bladder cancer has not been reported in other clinical trials of raloxifene and the clinical relevance of this observation is unknown.
- Six patients discontinued study drug due to bladder cancer (1 in placebo, 5 in raloxifene).

Table GGIO.12.5. Serious Adverse Events (By System Organ Class, High-level Term, and Preferred Term; All Randomized Patients)

SOC: System Organ Class HLT: High-Level Term PT: Preferred Term	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Overall				
Patients with >=1 SAE	392(7.75)	436(8.64)	828(8.20)	.093
Patients with no SAEs	4665(92.25)	4608(91.36)	9273(91.80)	
Blood and lymphatic system disorders				
Patients with >=1 SAE	1(0.02)	4(0.08)	5(0.05)	.171
Patients with no SAEs	5056(99.98)	5040(99.92)	10096(99.95)	
Anaemias NEC	1(0.02)	3(0.06)	4(0.04)	N/A
Anaemia	0(0.00)	3(0.06)	3(0.03)	N/A
Normochromic normocytic anaemia	1(0.02)	0(0.00)	1(0.01)	N/A
Leukocytoses NEC	0(0.00)	1(0.02)	1(0.01)	N/A
Leukocytosis	0(0.00)	1(0.02)	1(0.01)	N/A
Cardiac disorders				
Patients with >=1 SAE	42(0.83)	39(0.77)	81(0.80)	.750
Patients with no SAEs	5015(99.17)	5005(99.23)	10020(99.20)	
Aortic valvular disorders	1(0.02)	0(0.00)	1(0.01)	N/A
Aortic valve stenosis	1(0.02)	0(0.00)	1(0.01)	N/A
Cardiac conduction disorders	1(0.02)	1(0.02)	2(0.02)	N/A
Adams-Stokes syndrome	0(0.00)	1(0.02)	1(0.01)	N/A
Atrioventricular block complete	1(0.02)	0(0.00)	1(0.01)	N/A
Cardiac disorders NEC	0(0.00)	1(0.02)	1(0.01)	N/A
Atrial thrombosis	0(0.00)	1(0.02)	1(0.01)	N/A
Coronary artery disorders NEC	1(0.02)	1(0.02)	2(0.02)	N/A
Coronary artery disease	1(0.02)	0(0.00)	1(0.01)	N/A
Coronary artery dissection	0(0.00)	1(0.02)	1(0.01)	N/A
Heart failures NEC	10(0.20)	8(0.16)	18(0.18)	.646
Cardiac failure	4(0.08)	4(0.08)	8(0.08)	.979
Cardiac failure acute	1(0.02)	0(0.00)	1(0.01)	N/A
Cardiac failure congestive	1(0.02)	1(0.02)	2(0.02)	N/A
Cardiogenic shock	4(0.08)	3(0.06)	7(0.07)	.700
Ischaemic coronary artery disorders	12(0.24)	17(0.34)	29(0.29)	.340
Acute coronary syndrome	3(0.06)	2(0.04)	5(0.05)	.682
Angina pectoris	2(0.04)	4(0.08)	6(0.06)	.415
Angina unstable	6(0.12)	8(0.16)	14(0.14)	.586
Myocardial infarction	3(0.06)	3(0.06)	6(0.06)	.991
Myocardial ischaemia	0(0.00)	2(0.04)	2(0.02)	N/A
Silent myocardial infarction	0(0.00)	1(0.02)	1(0.01)	N/A
Left ventricular failures	2(0.04)	0(0.00)	2(0.02)	N/A
Left ventricular failure	2(0.04)	0(0.00)	2(0.02)	N/A
Mitral valvular disorders	2(0.04)	0(0.00)	2(0.02)	N/A
Mitral valve incompetence	2(0.04)	0(0.00)	2(0.02)	N/A
Noninfectious myocarditis	1(0.02)	0(0.00)	1(0.01)	N/A
Myocarditis	1(0.02)	0(0.00)	1(0.01)	N/A
Rate and rhythm disorders NEC	1(0.02)	2(0.04)	3(0.03)	N/A
Bradyarrhythmia	1(0.02)	0(0.00)	1(0.01)	N/A
Bradycardia	0(0.00)	2(0.04)	2(0.02)	N/A
Supraventricular arrhythmias	4(0.08)	4(0.08)	8(0.08)	.996
Atrial fibrillation	1(0.02)	3(0.06)	4(0.04)	N/A
Sick sinus syndrome	2(0.04)	1(0.02)	3(0.03)	N/A
Sinus arrest	1(0.02)	0(0.00)	1(0.01)	N/A
Sinus bradycardia	1(0.02)	0(0.00)	1(0.01)	N/A
Ventricular arrhythmias and cardiac arrest	12(0.24)	8(0.16)	20(0.20)	.374
Cardiac arrest	5(0.10)	3(0.06)	8(0.08)	.478
Cardiac fibrillation	1(0.02)	0(0.00)	1(0.01)	N/A
Cardio-respiratory arrest	1(0.02)	0(0.00)	1(0.01)	N/A
Ventricular fibrillation	4(0.08)	4(0.08)	8(0.08)	.998
Ventricular tachycardia	3(0.06)	1(0.02)	4(0.04)	N/A
Ear and labyrinth disorders				
Patients with >=1 SAE	0(0.00)	1(0.02)	1(0.01)	N/A
Patients with no SAEs	5057(100.00)	5043(99.98)	10100(99.99)	
Inner ear signs and symptoms	0(0.00)	1(0.02)	1(0.01)	N/A
Vertigo	0(0.00)	1(0.02)	1(0.01)	N/A

SOC: System Organ Class HLT: High-Level Term PT: Preferred Term	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Eye disorders				
Patients with >=1 SAE	12(0.24)	12(0.24)	25(0.25)	.655
Patients with no SAEs	5044(99.74)	5032(99.76)	10076(99.75)	
Blindness (excl colour blindness)	2(0.04)	0(0.00)	2(0.02)	N/A
Blindness	1(0.02)	0(0.00)	1(0.01)	N/A
Blindness unilateral	1(0.02)	0(0.00)	1(0.01)	N/A
Cataracts (excl congenital)	1(0.02)	0(0.00)	1(0.01)	N/A
Cataract	1(0.02)	0(0.00)	1(0.01)	N/A
Choroid and vitreous haemorrhages and vascular disorders	1(0.02)	1(0.02)	2(0.02)	N/A
Vitreous haemorrhage	1(0.02)	1(0.02)	2(0.02)	N/A
Ocular bleeding and vascular disorders NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Ocular vascular disorder	1(0.02)	0(0.00)	1(0.01)	N/A
Partial vision loss	1(0.02)	0(0.00)	1(0.01)	N/A
Visual acuity reduced	1(0.02)	0(0.00)	1(0.01)	N/A
Retinal bleeding and vascular disorders (excl retinopathy)	8(0.16)	11(0.22)	19(0.19)	.482
Retinal artery embolism	1(0.02)	1(0.02)	2(0.02)	N/A
Retinal artery occlusion	0(0.00)	1(0.02)	1(0.01)	N/A
Retinal vascular thrombosis	1(0.02)	0(0.00)	1(0.01)	N/A
Retinal vein occlusion	1(0.02)	1(0.02)	2(0.02)	N/A
Retinal vein thrombosis	5(0.10)	8(0.16)	13(0.13)	.401
Retinal structural change, deposit and degeneration	1(0.02)	1(0.02)	2(0.02)	N/A
Retinal detachment	1(0.02)	1(0.02)	2(0.02)	N/A
Gastrointestinal disorders				
Patients with >=1 SAE	15(0.30)	16(0.32)	31(0.31)	.813
Patients with no SAEs	5042(99.70)	5028(99.68)	10070(99.69)	
Acute and chronic pancreatitis	0(0.00)	1(0.02)	1(0.01)	N/A
Pancreatitis acute	0(0.00)	1(0.02)	1(0.01)	N/A
Benign neoplasms gastrointestinal (excl oral cavity)	1(0.02)	0(0.00)	1(0.01)	N/A
Rectal polyp	1(0.02)	0(0.00)	1(0.01)	N/A
Colitis (excl infective)	0(0.00)	2(0.04)	2(0.02)	N/A
Colitis	0(0.00)	1(0.02)	1(0.01)	N/A
Colitis ischaemic	0(0.00)	1(0.02)	1(0.01)	N/A
Diarrhoea (excl infective)	1(0.02)	0(0.00)	1(0.01)	N/A
Diarrhoea	1(0.02)	0(0.00)	1(0.01)	N/A
Duodenal ulcers and perforation	1(0.02)	2(0.04)	3(0.03)	N/A
Duodenal ulcer perforation	1(0.02)	2(0.04)	3(0.03)	N/A
Gastric and oesophageal haemorrhages	0(0.00)	1(0.02)	1(0.01)	N/A
Mallory-Weiss syndroma	0(0.00)	1(0.02)	1(0.01)	N/A
Gastrointestinal and abdominal pains (excl oral and throat)	2(0.04)	1(0.02)	3(0.03)	N/A
Abdominal pain	0(0.00)	1(0.02)	1(0.01)	N/A
Abdominal pain lower	1(0.02)	0(0.00)	1(0.01)	N/A
Abdominal pain upper	1(0.02)	0(0.00)	1(0.01)	N/A
Gastrointestinal necrosis and gangrene (excl gangrenous hernia)	0(0.00)	1(0.02)	1(0.01)	N/A
Gastrointestinal necrosis	0(0.00)	1(0.02)	1(0.01)	N/A
Gastrointestinal stenosis and obstruction NEC	4(0.08)	1(0.02)	5(0.05)	.197
Ileus	2(0.04)	0(0.00)	2(0.02)	N/A
Intestinal obstruction	2(0.04)	1(0.02)	3(0.03)	N/A
Gastrointestinal ulcers and perforation, site unspecified	0(0.00)	1(0.02)	1(0.01)	N/A
Diverticular perforation	0(0.00)	1(0.02)	1(0.01)	N/A
Gastrointestinal vascular occlusion and infarction	0(0.00)	4(0.08)	4(0.04)	N/A
Mesenteric occlusion	0(0.00)	4(0.08)	4(0.04)	N/A
Intestinal haemorrhages	2(0.04)	0(0.00)	2(0.02)	N/A
Rectal haemorrhage	2(0.04)	0(0.00)	2(0.02)	N/A
Non-site specific gastrointestinal haemorrhages	3(0.06)	3(0.06)	6(0.06)	.997
Gastrointestinal haemorrhage	1(0.02)	3(0.06)	4(0.04)	N/A
Upper gastrointestinal haemorrhage	2(0.04)	0(0.00)	2(0.02)	N/A
Peptic ulcers and perforation	0(0.00)	1(0.02)	1(0.01)	N/A
Peptic ulcer haemorrhage	0(0.00)	1(0.02)	1(0.01)	N/A
Peritoneal and retroperitoneal disorders	2(0.04)	2(0.04)	4(0.04)	N/A
Peritonitis	2(0.04)	2(0.04)	4(0.04)	N/A
Peritoneal and retroperitoneal haemorrhages	0(0.00)	1(0.02)	1(0.01)	N/A
Retroperitoneal haematoma	0(0.00)	1(0.02)	1(0.01)	N/A
General disorders and administration site conditions				
Patients with >=1 SAE	6(0.12)	3(0.06)	9(0.09)	.321
Patients with no SAEs	5051(99.88)	5041(99.94)	10092(99.91)	
Asthenic conditions	1(0.02)	0(0.00)	1(0.01)	N/A
Asthenia	1(0.02)	0(0.00)	1(0.01)	N/A
Death and sudden death	3(0.06)	0(0.00)	3(0.03)	N/A
Sudden death	3(0.06)	0(0.00)	3(0.03)	N/A
General signs and symptoms NEC	1(0.02)	1(0.02)	2(0.02)	N/A
Multi-organ failure	1(0.02)	0(0.00)	1(0.01)	N/A
Performance status decreased	0(0.00)	1(0.02)	1(0.01)	N/A
Interactions	0(0.00)	1(0.02)	1(0.01)	N/A
Drug interaction	0(0.00)	1(0.02)	1(0.01)	N/A
Oedema NEC	1(0.02)	1(0.02)	2(0.02)	N/A
Oedema peripheral	1(0.02)	1(0.02)	2(0.02)	N/A

SOC: System Organ Class HLT: High-Level Term PT: Preferred Term	Placebo (N=5057) n (%)	Ralox (N=5046) n (%)	Total (N=10103) n (%)	p-Value*
Hepatobiliary disorders				
Patients with >=1 SAE	7(0.14)	4(0.08)	11(0.11)	.278
Patients with no SAEs	5050(99.86)	5040(99.92)	10090(99.89)	
Cholecystitis and cholelithiasis	3(0.06)	1(0.02)	4(0.04)	N/A
Cholecystitis	1(0.02)	0(0.00)	1(0.01)	N/A
Cholecystitis acute	1(0.02)	1(0.02)	2(0.02)	N/A
Cholelithiasis	1(0.02)	0(0.00)	1(0.01)	N/A
Cholestasis and jaundice	2(0.04)	0(0.00)	2(0.02)	N/A
Cholestasis	1(0.02)	0(0.00)	1(0.01)	N/A
Jaundice	1(0.02)	0(0.00)	1(0.01)	N/A
Hepatic fibrosis and cirrhosis	1(0.02)	0(0.00)	1(0.01)	N/A
Biliary cirrhosis primary	1(0.02)	0(0.00)	1(0.01)	N/A
Hepatic vascular disorders	0(0.00)	1(0.02)	1(0.01)	N/A
Hepatic vein thrombosis	0(0.00)	1(0.02)	1(0.01)	N/A
Portal vein thrombosis	0(0.00)	1(0.02)	1(0.01)	N/A
Hepatocellular damage and hepatitis NEC	1(0.02)	1(0.02)	2(0.02)	N/A
Cytolytic hepatitis	0(0.00)	1(0.02)	1(0.01)	N/A
Hepatic steatosis	1(0.02)	0(0.00)	1(0.01)	N/A
Hepatitis	1(0.02)	0(0.00)	1(0.01)	N/A
Obstructive bile duct disorders (excl neoplasms)	0(0.00)	1(0.02)	1(0.01)	N/A
Bile duct stone	0(0.00)	1(0.02)	1(0.01)	N/A
Immune system disorders				
Patients with >=1 SAE	2(0.04)	0(0.00)	2(0.02)	N/A
Patients with no SAEs	5055(99.96)	5046(100.00)	10099(99.98)	
Allergic conditions NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Hypersensitivity	1(0.02)	0(0.00)	1(0.01)	N/A
Anaphylactic responses	1(0.02)	0(0.00)	1(0.01)	N/A
Anaphylactic reaction	1(0.02)	0(0.00)	1(0.01)	N/A
Infections and infestations				
Patients with >=1 SAE	20(0.40)	14(0.28)	34(0.34)	.309
Patients with no SAEs	5037(99.60)	5030(99.72)	10067(99.66)	
Abdominal and gastrointestinal infections	2(0.04)	2(0.04)	4(0.04)	N/A
Diverticulitis	2(0.04)	0(0.00)	2(0.02)	N/A
Gastroenteritis	0(0.00)	1(0.02)	1(0.01)	N/A
Gastrointestinal infection	0(0.00)	1(0.02)	1(0.01)	N/A
Bacterial infections NEC	2(0.04)	1(0.02)	3(0.03)	N/A
Gangrene	2(0.04)	1(0.02)	3(0.03)	N/A
Bone and joint infections	1(0.02)	0(0.00)	1(0.01)	N/A
Osteomyelitis	1(0.02)	0(0.00)	1(0.01)	N/A
Hepatobiliary and spleen infections	1(0.02)	0(0.00)	1(0.01)	N/A
Gallbladder empyema	1(0.02)	0(0.00)	1(0.01)	N/A
Infections NEC	3(0.06)	0(0.00)	3(0.03)	N/A
Localised infection	1(0.02)	0(0.00)	1(0.01)	N/A
Peridiverticular abscess	1(0.02)	0(0.00)	1(0.01)	N/A
Postoperative infection	1(0.02)	0(0.00)	1(0.01)	N/A
Lower respiratory tract and lung infections	4(0.08)	3(0.06)	7(0.07)	.705
Pneumonia	4(0.08)	3(0.06)	7(0.07)	.705
Sepsis, bacteraemia and viraemia	7(0.14)	5(0.10)	12(0.12)	.576
Bacterial sepsis	0(0.00)	1(0.02)	1(0.01)	N/A
Sepsis	6(0.12)	3(0.06)	9(0.09)	.328
Septic shock	1(0.02)	1(0.02)	2(0.02)	N/A
Staphylococcal infections	1(0.02)	2(0.04)	3(0.03)	N/A
Meningitis staphylococcal	0(0.00)	1(0.02)	1(0.01)	N/A
Pneumonia staphylococcal	1(0.02)	1(0.02)	2(0.02)	N/A
Streptococcal infections	1(0.02)	1(0.02)	2(0.02)	N/A
Erysipelas	0(0.00)	1(0.02)	1(0.01)	N/A
Meningitis streptococcal	1(0.02)	0(0.00)	1(0.01)	N/A
Urinary tract infections	1(0.02)	0(0.00)	1(0.01)	N/A
Pyonephrosis	1(0.02)	0(0.00)	1(0.01)	N/A
Injury, poisoning and procedural complications				
Patients with >=1 SAE	5(0.10)	4(0.08)	9(0.09)	.741
Patients with no SAEs	5052(99.90)	5040(99.92)	10092(99.91)	
Abdominal injuries NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Splenic rupture	1(0.02)	0(0.00)	1(0.01)	N/A
Cardiovascular injuries	1(0.02)	0(0.00)	1(0.01)	N/A
Heart injury	1(0.02)	0(0.00)	1(0.01)	N/A
Cerebral injuries NEC	1(0.02)	2(0.04)	3(0.03)	N/A
Brain contusion	1(0.02)	0(0.00)	1(0.01)	N/A
Extradural haematoma	0(0.00)	2(0.04)	2(0.02)	N/A
Gastrointestinal and hepatobiliary procedural complications	1(0.02)	0(0.00)	1(0.01)	N/A
Intestinal stoma site bleeding	1(0.02)	0(0.00)	1(0.01)	N/A
Non-site specific injuries NEC	0(0.00)	1(0.02)	1(0.01)	N/A
Polytraumatism	0(0.00)	1(0.02)	1(0.01)	N/A
Site specific injuries NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Head injury	1(0.02)	0(0.00)	1(0.01)	N/A
Spinal fractures and dislocations	0(0.00)	1(0.02)	1(0.01)	N/A
Lumbar vertebral fracture	0(0.00)	1(0.02)	1(0.01)	N/A

Investigations				
Patients with >=1 SAE	2(0.04)	1(0.02)	3(0.03)	N/A
Patients with no SAEs	5055(99.96)	5043(99.98)	10098(99.97)	
Gastrointestinal and abdominal imaging procedures	1(0.02)	0(0.00)	1(0.01)	N/A
Endoscopy upper gastrointestinal tract	1(0.02)	0(0.00)	1(0.01)	N/A
Liver function analyses	1(0.02)	1(0.02)	2(0.02)	N/A
Aspartate aminotransferase increased	0(0.00)	1(0.02)	1(0.01)	N/A
Hepatic enzyme increased	1(0.02)	0(0.00)	1(0.01)	N/A

SOC: System Organ Class HLT: High-Level Term PT: Preferred Term	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Metabolism and nutrition disorders				
Patients with >=1 SAE	2(0.04)	3(0.06)	5(0.05)	.646
Patients with no SAEs	5055(99.96)	5041(99.94)	10096(99.95)	
Diabetic complications NEC	1(0.02)	2(0.04)	3(0.03)	N/A
Diabetic ketoacidosis	1(0.02)	2(0.04)	3(0.03)	N/A
Hypoglycaemic conditions NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Hypoglycaemia	1(0.02)	0(0.00)	1(0.01)	N/A
Potassium imbalance	0(0.00)	1(0.02)	1(0.01)	N/A
Hyperkalaemia	0(0.00)	1(0.02)	1(0.01)	N/A
Musculoskeletal and connective tissue disorders				
Patients with >=1 SAE	2(0.04)	1(0.02)	3(0.03)	N/A
Patients with no SAEs	5055(99.96)	5043(99.98)	10098(99.97)	
Arthropathies NEC	0(0.00)	1(0.02)	1(0.01)	N/A
Arthritis	0(0.00)	1(0.02)	1(0.01)	N/A
Intervertebral disc disorders NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Intervertebral disc protrusion	1(0.02)	0(0.00)	1(0.01)	N/A
Myopathies	1(0.02)	0(0.00)	1(0.01)	N/A
Rhabdomyolysis	1(0.02)	0(0.00)	1(0.01)	N/A
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Patients with >=1 SAE	193(3.82)	201(3.98)	394(3.90)	.652
Patients with no SAEs	4864(96.18)	4843(96.02)	9707(96.10)	
Anal canal neoplasms malignant	1(0.02)	1(0.02)	2(0.02)	N/A
Anal cancer	1(0.02)	1(0.02)	2(0.02)	N/A
B-cell small lymphocytic lymphomas	1(0.02)	0(0.00)	1(0.01)	N/A
B-cell small lymphocytic lymphoma	1(0.02)	0(0.00)	1(0.01)	N/A
Bile duct neoplasms malignant	0(0.00)	1(0.02)	1(0.01)	N/A
Bile duct cancer	0(0.00)	1(0.02)	1(0.01)	N/A
Bladder neoplasms malignant	2(0.04)	7(0.14)	9(0.09)	.096
Bladder cancer	0(0.00)	5(0.10)	5(0.05)	.025
Bladder cancer recurrent	0(0.00)	1(0.02)	1(0.01)	N/A
Bladder cancer stage I, without cancer in situ	1(0.02)	0(0.00)	1(0.01)	N/A
Metastatic carcinoma of the bladder	1(0.02)	1(0.02)	2(0.02)	N/A
Bone neoplasms malignant (excl sarcomas)	1(0.02)	0(0.00)	1(0.01)	N/A
Bone cancer metastatic	1(0.02)	0(0.00)	1(0.01)	N/A
Breast and nipple neoplasms benign	0(0.00)	1(0.02)	1(0.01)	N/A
Fibroadenoma of breast	0(0.00)	1(0.02)	1(0.01)	N/A
Breast and nipple neoplasms malignant	3(0.06)	2(0.04)	5(0.05)	.660
Breast cancer	2(0.04)	1(0.02)	3(0.03)	N/A
Breast cancer stage I	1(0.02)	1(0.02)	2(0.02)	N/A
Breast neoplasms unspecified malignancy	0(0.00)	1(0.02)	1(0.01)	N/A
Breast neoplasm	0(0.00)	1(0.02)	1(0.01)	N/A
Cardiovascular neoplasms malignant and unspecified	0(0.00)	1(0.02)	1(0.01)	N/A
Angiosarcoma	0(0.00)	1(0.02)	1(0.01)	N/A
Central nervous system neoplasms malignant NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Brain neoplasm malignant	1(0.02)	0(0.00)	1(0.01)	N/A
Cervix neoplasms malignant	3(0.06)	3(0.06)	6(0.06)	.995
Cervix carcinoma	1(0.02)	1(0.02)	2(0.02)	N/A
Cervix carcinoma stage I	1(0.02)	1(0.02)	2(0.02)	N/A
Cervix carcinoma stage II	0(0.00)	1(0.02)	1(0.01)	N/A
Squamous cell carcinoma of the cervix	1(0.02)	0(0.00)	1(0.01)	N/A
Colonic neoplasms malignant	18(0.36)	25(0.50)	33(0.33)	.606
Colon cancer	9(0.18)	7(0.14)	16(0.16)	.622
Colon cancer metastatic	1(0.02)	3(0.06)	4(0.04)	N/A
Colon cancer stage I	2(0.04)	1(0.02)	3(0.03)	N/A
Colon cancer stage II	3(0.06)	0(0.00)	3(0.03)	N/A
Colon cancer stage III	3(0.06)	3(0.06)	6(0.06)	.998
Colon cancer stage 0	0(0.00)	1(0.02)	1(0.01)	N/A
Diffuse large B-cell lymphomas	1(0.02)	2(0.04)	3(0.03)	N/A
Diffuse large B-cell lymphoma	1(0.02)	1(0.02)	2(0.02)	N/A
Diffuse large B-cell lymphoma stage I	0(0.00)	1(0.02)	1(0.01)	N/A
Endometrial neoplasms malignant	15(0.30)	16(0.32)	31(0.31)	.853
Endometrial cancer	8(0.16)	2(0.04)	10(0.10)	.059
Endometrial cancer metastatic	0(0.00)	1(0.02)	1(0.01)	N/A
Endometrial cancer stage I	5(0.10)	10(0.20)	15(0.15)	.196
Endometrial cancer stage II	1(0.02)	1(0.02)	2(0.02)	N/A
Endometrial cancer stage III	1(0.02)	2(0.04)	3(0.03)	N/A
Female reproductive neoplasms unspecified malignancy	1(0.02)	0(0.00)	1(0.01)	N/A
Borderline ovarian tumour	1(0.02)	0(0.00)	1(0.01)	N/A

SOC: System Organ Class HLT: High-Level Term PT: Preferred Term	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Gallbladder neoplasms malignant	2(0.04)	1(0.02)	3(0.03)	N/A
Gallbladder cancer	2(0.04)	1(0.02)	3(0.03)	N/A
Gastric neoplasms malignant	6(0.12)	4(0.08)	10(0.10)	.526
Gastric cancer	4(0.08)	3(0.06)	7(0.07)	.705
Gastric cancer stage I	1(0.02)	0(0.00)	1(0.01)	N/A
Gastric cancer stage IV	1(0.02)	1(0.02)	2(0.02)	N/A
Gastrointestinal neoplasms benign NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Benign pancreatic neoplasm	1(0.02)	0(0.00)	1(0.01)	N/A
Gastrointestinal neoplasms malignant NEC	2(0.04)	0(0.00)	2(0.02)	N/A
Gastrointestinal carcinoma	1(0.02)	0(0.00)	1(0.01)	N/A
Peritoneal carcinoma	1(0.02)	0(0.00)	1(0.01)	N/A
Glial tumours malignant	1(0.02)	1(0.02)	2(0.02)	N/A
Glioblastoma	1(0.02)	1(0.02)	2(0.02)	N/A
Hepatic neoplasms malignant	3(0.06)	0(0.00)	3(0.03)	N/A
Hepatic neoplasm malignant	3(0.06)	0(0.00)	3(0.03)	N/A
Hepatobiliary neoplasms malignant NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Malignant neoplasm of ampulla of Vater	1(0.02)	0(0.00)	1(0.01)	N/A
Hodgkin's disease NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Hodgkin's disease	1(0.02)	0(0.00)	1(0.01)	N/A
Hypopharyngeal neoplasms malignant and unspecified	1(0.02)	0(0.00)	1(0.01)	N/A
Hypopharyngeal cancer	1(0.02)	0(0.00)	1(0.01)	N/A
Laryngeal neoplasms malignant	1(0.02)	0(0.00)	1(0.01)	N/A
Laryngeal cancer	1(0.02)	0(0.00)	1(0.01)	N/A
Leukaemias acute myeloid	0(0.00)	1(0.02)	1(0.01)	N/A
Acute myeloid leukaemia	0(0.00)	1(0.02)	1(0.01)	N/A
Leukaemias acute NEC	2(0.04)	0(0.00)	2(0.02)	N/A
Acute leukaemia	2(0.04)	0(0.00)	2(0.02)	N/A
Leukaemias chronic lymphocytic	3(0.06)	5(0.10)	8(0.08)	.475
Chronic lymphocytic leukaemia	3(0.06)	5(0.10)	8(0.08)	.475
Leukaemias chronic myeloid	0(0.00)	1(0.02)	1(0.01)	N/A
Chronic myeloid leukaemia	0(0.00)	1(0.02)	1(0.01)	N/A
Lip and oral cavity neoplasms malignant	1(0.02)	3(0.06)	4(0.04)	N/A
Gum neoplasm malignant stage unspecified	0(0.00)	1(0.02)	1(0.01)	N/A
Lip and/or oral cavity cancer	0(0.00)	2(0.04)	2(0.02)	N/A
Tongue neoplasm malignant stage unspecified	1(0.02)	0(0.00)	1(0.01)	N/A
Lymphomas unspecified NEC	0(0.00)	2(0.04)	2(0.02)	N/A
Lymph node cancer metastatic	0(0.00)	1(0.02)	1(0.01)	N/A
Lymphoma	0(0.00)	1(0.02)	1(0.01)	N/A
Mesotheliomas benign	1(0.02)	0(0.00)	1(0.01)	N/A
Benign mesothelioma	1(0.02)	0(0.00)	1(0.01)	N/A
Metastases to specified sites	2(0.04)	1(0.02)	3(0.03)	N/A
Metastases to abdominal cavity	0(0.00)	1(0.02)	1(0.01)	N/A
Metastases to adrenals	1(0.02)	0(0.00)	1(0.01)	N/A
Metastases to spine	1(0.02)	0(0.00)	1(0.01)	N/A
Multiple myelomas	3(0.06)	4(0.08)	7(0.07)	.702
Multiple myeloma	3(0.06)	4(0.08)	7(0.07)	.702
Mycoses fungoides	1(0.02)	0(0.00)	1(0.01)	N/A
Mycosis fungoides	1(0.02)	0(0.00)	1(0.01)	N/A
Myelodysplastic syndromes	0(0.00)	1(0.02)	1(0.01)	N/A
Chronic myelomonocytic leukaemia	0(0.00)	1(0.02)	1(0.01)	N/A
Myeloproliferative disorders (excl leukaemias)	0(0.00)	1(0.02)	1(0.01)	N/A
Polycythaemia vera	0(0.00)	1(0.02)	1(0.01)	N/A
Neoplasms malignant site unspecified NEC	9(0.18)	10(0.20)	19(0.19)	.883
Metastatic neoplasm	1(0.02)	1(0.02)	2(0.02)	N/A
Neoplasm malignant	1(0.02)	0(0.00)	1(0.01)	N/A
Squamous cell carcinoma	7(0.14)	9(0.18)	16(0.16)	.601
Nervous system neoplasms malignant NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Neuroblastoma	1(0.02)	0(0.00)	1(0.01)	N/A
Nervous system neoplasms unspecified malignancy NEC	2(0.04)	0(0.00)	2(0.02)	N/A
Astrocytoma	1(0.02)	0(0.00)	1(0.01)	N/A
Meningioma	1(0.02)	0(0.00)	1(0.01)	N/A
Non-small cell neoplasms malignant of the respiratory tract cell type spec	5(0.10)	7(0.14)	12(0.12)	.556
Lung adenocarcinoma	2(0.04)	2(0.04)	4(0.04)	N/A
Lung adenocarcinoma stage II	1(0.02)	0(0.00)	1(0.01)	N/A
Lung adenocarcinoma stage IV	0(0.00)	1(0.02)	1(0.01)	N/A
Lung squamous cell carcinoma stage III	2(0.04)	0(0.00)	2(0.02)	N/A
Lung squamous cell carcinoma stage IV	0(0.00)	1(0.02)	1(0.01)	N/A
Non-small cell lung cancer	0(0.00)	1(0.02)	1(0.01)	N/A
Non-small cell lung cancer stage I	0(0.00)	1(0.02)	1(0.01)	N/A
Non-small cell lung cancer stage IIIB	0(0.00)	1(0.02)	1(0.01)	N/A
Non-Hodgkin's lymphomas unspecified histology indolent	1(0.02)	0(0.00)	1(0.01)	N/A
Non-Hodgkin's lymphoma unspecified histology indolent stage I	1(0.02)	0(0.00)	1(0.01)	N/A
Non-Hodgkin's lymphomas NEC	2(0.04)	4(0.08)	6(0.06)	.403
Non-Hodgkin's lymphoma	1(0.02)	3(0.06)	4(0.04)	N/A
Non-Hodgkin's lymphoma stage I	1(0.02)	1(0.02)	2(0.02)	N/A

SOC: System Organ Class HLT: High-Level Term PT: Preferred Term	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Ocular melanomas	1(0.02)	0(0.00)	1(0.01)	N/A
Choroid melanoma	1(0.02)	0(0.00)	1(0.01)	N/A
Oesophageal neoplasms malignant	1(0.02)	2(0.04)	3(0.03)	N/A
Oesophageal adenocarcinoma	0(0.00)	1(0.02)	1(0.01)	N/A
Oesophageal adenocarcinoma stage III	0(0.00)	1(0.02)	1(0.01)	N/A
Oesophageal cancer metastatic	1(0.02)	0(0.00)	1(0.01)	N/A
Ovarian neoplasms malignant (excl germ cell)	5(0.10)	10(0.20)	15(0.15)	.198
Ovarian cancer	1(0.02)	5(0.10)	6(0.06)	.104
Ovarian cancer metastatic	2(0.04)	1(0.02)	4(0.04)	N/A
Ovarian epithelial cancer	0(0.00)	1(0.02)	1(0.01)	N/A
Ovarian epithelial cancer stage I	0(0.00)	1(0.02)	1(0.01)	N/A
Ovarian epithelial cancer stage III	1(0.02)	2(0.04)	3(0.03)	N/A
Pancreatic neoplasms malignant (excl islet cell and carcinoid)	2(0.04)	1(0.02)	3(0.03)	N/A
Pancreatic carcinoma	1(0.02)	1(0.02)	2(0.02)	N/A
Pancreatic carcinoma metastatic	1(0.02)	0(0.00)	1(0.01)	N/A
Rectal neoplasms malignant	7(0.14)	5(0.10)	12(0.12)	.564
Rectal cancer	4(0.08)	2(0.04)	6(0.06)	.412
Rectal cancer stage II	1(0.02)	0(0.00)	1(0.01)	N/A
Rectal cancer stage III	2(0.04)	1(0.02)	3(0.03)	N/A
Rectal cancer stage IV	0(0.00)	1(0.02)	1(0.01)	N/A
Rectosigmoid cancer stage II	0(0.00)	1(0.02)	1(0.01)	N/A
Renal cell carcinomas	6(0.12)	13(0.26)	19(0.19)	.106
Renal cancer metastatic	0(0.00)	1(0.02)	1(0.01)	N/A
Renal cell carcinoma stage unspecified	3(0.06)	8(0.16)	11(0.11)	.130
Renal cell carcinoma stage I	1(0.02)	3(0.06)	4(0.04)	N/A
Renal cell carcinoma stage II	1(0.02)	1(0.02)	2(0.02)	N/A
Renal cell carcinoma stage IV	1(0.02)	0(0.00)	1(0.01)	N/A
Renal pelvis and ureter neoplasms malignant	1(0.02)	0(0.00)	1(0.01)	N/A
Ureteric cancer	1(0.02)	0(0.00)	1(0.01)	N/A
Respiratory tract and pleural neoplasms malignant cell type unspecified NE	8(0.16)	8(0.16)	16(0.16)	.992
Bronchial carcinoma	1(0.02)	2(0.04)	3(0.03)	N/A
Lung cancer metastatic	1(0.02)	2(0.04)	3(0.03)	N/A
Lung carcinoma cell type unspecified stage I	0(0.00)	1(0.02)	1(0.01)	N/A
Lung carcinoma cell type unspecified stage IV	1(0.02)	0(0.00)	1(0.01)	N/A
Lung neoplasm malignant	5(0.10)	4(0.08)	9(0.09)	.740
Respiratory tract small cell carcinomas	1(0.02)	2(0.04)	3(0.03)	N/A
Small cell lung cancer metastatic	1(0.02)	0(0.00)	1(0.01)	N/A
Small cell lung cancer stage unspecified	0(0.00)	2(0.04)	2(0.02)	N/A
Salivary gland neoplasms malignant	1(0.02)	0(0.00)	1(0.01)	N/A
Salivary gland cancer stage I	1(0.02)	0(0.00)	1(0.01)	N/A
Skin melanomas (excl ocular)	9(0.18)	7(0.14)	16(0.16)	.625
Lentigo maligna stage unspecified	2(0.04)	0(0.00)	2(0.02)	N/A
Malignant melanoma	4(0.08)	4(0.08)	8(0.08)	.995
Malignant melanoma stage I	0(0.00)	1(0.02)	1(0.01)	N/A
Malignant melanoma stage II	3(0.06)	0(0.00)	3(0.03)	N/A
Superficial spreading melanoma stage unspecified	0(0.00)	2(0.04)	2(0.02)	N/A
Skin neoplasms malignant and unspecified (excl melanoma)	58(1.15)	60(1.19)	118(1.17)	.829
Basal cell carcinoma	54(1.07)	53(1.05)	107(1.06)	.944
Bowen's disease	0(0.00)	3(0.06)	3(0.03)	N/A
Skin cancer	1(0.02)	3(0.06)	4(0.04)	N/A
Squamous cell carcinoma of skin	5(0.10)	3(0.06)	8(0.08)	.486
Soft tissue neoplasms benign NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Leiomyoma	1(0.02)	0(0.00)	1(0.01)	N/A
Thyroid neoplasms malignant	8(0.16)	3(0.06)	11(0.11)	.135
Papillary thyroid cancer	6(0.12)	1(0.02)	7(0.07)	.059
Thyroid gland cancer	2(0.04)	2(0.04)	4(0.04)	N/A
Uterine neoplasms malignant NEC	0(0.00)	4(0.08)	4(0.04)	N/A
Uterine cancer	0(0.00)	4(0.08)	4(0.04)	N/A

Nervous system disorders				
Patients with >=1 SAE	15(0.30)	15(0.30)	30(0.30)	.959
Patients with no SAEs	5042(99.70)	5029(99.70)	10071(99.70)	
Central nervous system haemorrhages and cerebrovascular accidents	8(0.16)	7(0.14)	15(0.15)	.820
Cerebral artery occlusion	0(0.00)	1(0.02)	1(0.01)	N/A
Cerebral ischaemia	0(0.00)	2(0.04)	2(0.02)	N/A
Cerebrovascular accident	5(0.10)	4(0.08)	9(0.09)	.753
Ischaemic stroke	2(0.04)	1(0.02)	3(0.03)	N/A
Subarachnoid haemorrhage	1(0.02)	0(0.00)	1(0.01)	N/A
Central nervous system vascular disorders NEC	1(0.02)	1(0.02)	2(0.02)	N/A
Carotid artery stenosis	1(0.02)	1(0.02)	2(0.02)	N/A
Coma states	3(0.06)	0(0.00)	3(0.03)	N/A
Coma	2(0.04)	0(0.00)	2(0.02)	N/A
Diabetic ketoacidotic hyperglycaemic coma	1(0.02)	0(0.00)	1(0.01)	N/A
Dementia (excl Alzheimer's type)	0(0.00)	1(0.02)	1(0.01)	N/A
Dementia	0(0.00)	1(0.02)	1(0.01)	N/A
Encephalopathies NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Anoxic encephalopathy	1(0.02)	0(0.00)	1(0.01)	N/A
Neurologic visual problems NEC	0(0.00)	1(0.02)	1(0.01)	N/A
Hemianopia	0(0.00)	1(0.02)	1(0.01)	N/A
Paraesthesias and dysaesthesias	1(0.02)	0(0.00)	1(0.01)	N/A
Hypoaesthesia	1(0.02)	0(0.00)	1(0.01)	N/A
Sensory abnormalities NEC	0(0.00)	1(0.02)	1(0.01)	N/A
Complex regional pain syndrome	0(0.00)	1(0.02)	1(0.01)	N/A
Spinal cord and nerve root disorders NEC	0(0.00)	1(0.02)	1(0.01)	N/A
Spinal cord disorder	0(0.00)	1(0.02)	1(0.01)	N/A
Transient cerebrovascular events	1(0.02)	3(0.06)	4(0.04)	N/A
Transient ischaemic attack	1(0.02)	3(0.06)	4(0.04)	N/A

SOC: System Organ Class HLT: High-Level Term PT: Preferred Term	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Psychiatric disorders				
Patients with >=1 SAE	2(0.04)	2(0.04)	4(0.04)	N/A
Patients with no SAEs	5055(99.96)	5042(99.96)	10097(99.96)	
Cognitive and attention disorders and disturbances NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Cognitive deterioration	1(0.02)	0(0.00)	1(0.01)	N/A
Delirium	0(0.00)	1(0.02)	1(0.01)	N/A
Delirium	0(0.00)	1(0.02)	1(0.01)	N/A
Depressive disorders	1(0.02)	0(0.00)	1(0.01)	N/A
Depression	1(0.02)	0(0.00)	1(0.01)	N/A
Suicidal and self-injurious behaviour	0(0.00)	1(0.02)	1(0.01)	N/A
Suicide attempt	0(0.00)	1(0.02)	1(0.01)	N/A
Renal and urinary disorders				
Patients with >=1 SAE	5(0.10)	5(0.10)	10(0.10)	.990
Patients with no SAEs	5052(99.90)	5039(99.90)	10091(99.90)	
Renal failure and impairment	5(0.10)	3(0.06)	8(0.08)	.485
Renal failure	2(0.04)	1(0.02)	3(0.03)	N/A
Renal failure acute	1(0.02)	2(0.04)	3(0.03)	N/A
Renal failure chronic	2(0.04)	0(0.00)	2(0.02)	N/A
Renal obstructive disorders	0(0.00)	1(0.02)	1(0.01)	N/A
Hydronephrosis	0(0.00)	1(0.02)	1(0.01)	N/A
Renal vascular and ischaemic conditions	0(0.00)	1(0.02)	1(0.01)	N/A
Renal vein thrombosis	0(0.00)	1(0.02)	1(0.01)	N/A
Reproductive system and breast disorders				
Patients with >=1 SAE	6(0.12)	2(0.04)	8(0.08)	.160
Patients with no SAEs	5051(99.88)	5042(99.96)	10093(99.92)	
Cervix neoplasms	1(0.02)	0(0.00)	1(0.01)	N/A
Cervical polyp	1(0.02)	0(0.00)	1(0.01)	N/A
Menopausal effects on the genitourinary tract	4(0.08)	2(0.04)	6(0.06)	.422
Postmenopausal haemorrhage	4(0.08)	2(0.04)	6(0.06)	.422
Uterine disorders NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Endometrial hyperplasia	1(0.02)	0(0.00)	1(0.01)	N/A
Uterine neoplasms	1(0.02)	0(0.00)	1(0.01)	N/A
Uterine polyp	1(0.02)	0(0.00)	1(0.01)	N/A

Respiratory, thoracic and mediastinal disorders				
Patients with >=1 SAE	56(1.07)	62(1.23)	116(1.15)	.447
Patients with no SAEs	5003(98.93)	4982(98.77)	9985(98.85)	
Breathing abnormalities	1(0.02)	1(0.02)	2(0.02)	N/A
Respiratory arrest	1(0.02)	1(0.02)	2(0.02)	N/A
Bronchospasm and obstruction	2(0.04)	1(0.02)	3(0.03)	N/A
Bronchospasm	1(0.02)	0(0.00)	1(0.01)	N/A
Chronic obstructive airways disease exacerbated	0(0.00)	1(0.02)	1(0.01)	N/A
Chronic obstructive pulmonary disease	1(0.02)	0(0.00)	1(0.01)	N/A
Coughing and associated symptoms	1(0.02)	0(0.00)	1(0.01)	N/A
Cough	1(0.02)	0(0.00)	1(0.01)	N/A
Laryngeal spasm, oedema and obstruction	1(0.02)	0(0.00)	1(0.01)	N/A
Laryngeal oedema	1(0.02)	0(0.00)	1(0.01)	N/A
Lower respiratory tract inflammatory and immunologic conditions	1(0.02)	0(0.00)	1(0.01)	N/A
Pneumonia aspiration	1(0.02)	0(0.00)	1(0.01)	N/A
Parenchymal lung disorders NEC	0(0.00)	1(0.02)	1(0.01)	N/A
Pulmonary fibrosis	0(0.00)	1(0.02)	1(0.01)	N/A
Pneumothorax and pleural effusions NEC	2(0.04)	1(0.02)	3(0.03)	N/A
Pleural effusion	2(0.04)	1(0.02)	3(0.03)	N/A
Pulmonary oedemas	16(0.32)	8(0.16)	24(0.24)	.108
Acute pulmonary oedema	3(0.06)	2(0.04)	5(0.05)	.666
Acute respiratory distress syndrome	0(0.00)	1(0.02)	1(0.01)	N/A
Pulmonary oedema	13(0.26)	5(0.10)	18(0.18)	.062
Pulmonary thrombotic and embolic conditions	31(0.61)	49(0.97)	80(0.79)	.043
Pulmonary embolism	31(0.61)	49(0.97)	80(0.79)	.043
Respiratory failures (excl neonatal)	4(0.08)	2(0.04)	6(0.06)	.406
Acute respiratory failure	1(0.02)	0(0.00)	1(0.01)	N/A
Respiratory failure	3(0.06)	2(0.04)	5(0.05)	.646
Skin and subcutaneous tissue disorders				
Patients with >=1 SAE	1(0.02)	1(0.02)	2(0.02)	N/A
Patients with no SAEs	5056(99.98)	5043(99.98)	10099(99.98)	
Panniculitides	0(0.00)	1(0.02)	1(0.01)	N/A
Erythema nodosum	0(0.00)	1(0.02)	1(0.01)	N/A
Pruritus NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Rash pruritic	1(0.02)	0(0.00)	1(0.01)	N/A

SOC: System Organ Class HLT: High-Level Term PT: Preferred Term	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Surgical and medical procedures				
Patients with >=1 SAE	6(0.12)	5(0.10)	11(0.11)	.750
Patients with no SAEs	5051(99.88)	5039(99.90)	10090(99.89)	
Abdominal therapeutic procedures NEC	0(0.00)	1(0.02)	1(0.01)	N/A
Abdominal operation	0(0.00)	1(0.02)	1(0.01)	N/A
Cardiac valve therapeutic procedures	1(0.02)	0(0.00)	1(0.01)	N/A
Mitral valve replacement	1(0.02)	0(0.00)	1(0.01)	N/A
Gastric therapeutic procedures	0(0.00)	1(0.02)	1(0.01)	N/A
Gastrectomy	0(0.00)	1(0.02)	1(0.01)	N/A
Hepatic therapeutic procedures	1(0.02)	0(0.00)	1(0.01)	N/A
Hepatectomy	1(0.02)	0(0.00)	1(0.01)	N/A
Large intestine therapeutic procedures	1(0.02)	0(0.00)	1(0.01)	N/A
Colectomy	1(0.02)	0(0.00)	1(0.01)	N/A
Limb therapeutic procedures	1(0.02)	0(0.00)	1(0.01)	N/A
Arm amputation	1(0.02)	0(0.00)	1(0.01)	N/A
Mastectomies	0(0.00)	1(0.02)	1(0.01)	N/A
Mastectomy	0(0.00)	1(0.02)	1(0.01)	N/A
Renal therapeutic procedures	0(0.00)	1(0.02)	1(0.01)	N/A
Nephrectomy	0(0.00)	1(0.02)	1(0.01)	N/A
Therapeutic procedures NEC	1(0.02)	0(0.00)	1(0.01)	N/A
Tumour excision	1(0.02)	0(0.00)	1(0.01)	N/A
Uterine therapeutic procedures	1(0.02)	1(0.02)	2(0.02)	N/A
Hysterectomy	0(0.00)	1(0.02)	1(0.01)	N/A
Hysterosalpingo-oophorectomy	1(0.02)	0(0.00)	1(0.01)	N/A

Vascular disorders				
Patients with >=1 SAE	72(1.42)	92(1.81)	164(1.62)	.110
Patients with no SAEs	4985(98.58)	4952(98.18)	9937(98.38)	
Aortic aneurysms and dissections	1(0.02)	0(0.00)	1(0.01)	N/A
Aortic aneurysm rupture	1(0.02)	0(0.00)	1(0.01)	N/A
Aortic necrosis and vascular insufficiency	1(0.02)	0(0.00)	1(0.01)	N/A
Aortic stenosis	1(0.02)	0(0.00)	1(0.01)	N/A
Arterial and aortic injuries	2(0.04)	0(0.00)	2(0.02)	N/A
Arterial rupture	2(0.04)	0(0.00)	2(0.02)	N/A
Circulatory collapse and shock	4(0.08)	1(0.02)	5(0.05)	.173
Hypovolaemic shock	1(0.02)	0(0.00)	1(0.01)	N/A
Shock	3(0.06)	1(0.02)	4(0.04)	N/A
Haemorrhages NEC	2(0.04)	0(0.00)	2(0.02)	N/A
Haematoma	1(0.02)	0(0.00)	1(0.01)	N/A
Haemorrhage	1(0.02)	0(0.00)	1(0.01)	N/A
Non-site specific embolism and thrombosis	1(0.02)	3(0.06)	4(0.04)	N/A
Embolism	0(0.00)	1(0.02)	1(0.01)	N/A
Embolism venous	0(0.00)	1(0.02)	1(0.01)	N/A
Phlebothrombosis	1(0.02)	1(0.02)	2(0.02)	N/A
Non-site specific vascular disorders NEC	0(0.00)	1(0.02)	1(0.01)	N/A
Vascular pseudoaneurysm	0(0.00)	1(0.02)	1(0.01)	N/A
Peripheral embolism and thrombosis	60(1.19)	82(1.63)	142(1.41)	.059
Arterial thrombosis limb	0(0.00)	3(0.06)	3(0.03)	N/A
Deep vein thrombosis	55(1.09)	73(1.45)	128(1.27)	.103
Iliac artery thrombosis	0(0.00)	1(0.02)	1(0.01)	N/A
Iliac vein thrombosis	0(0.00)	1(0.02)	1(0.01)	N/A
Jugular vein thrombosis	1(0.02)	0(0.00)	1(0.01)	N/A
Peripheral embolism	0(0.00)	3(0.06)	3(0.03)	N/A
Thrombophlebitis superficial	4(0.08)	2(0.04)	6(0.06)	.423
Peripheral vascular disorders NEC	0(0.00)	2(0.04)	2(0.02)	N/A
Peripheral vascular disorder	0(0.00)	2(0.04)	2(0.02)	N/A
Peripheral vasoconstriction, necrosis and vascular insufficiency	3(0.06)	2(0.04)	5(0.05)	.646
Femoral artery occlusion	1(0.02)	0(0.00)	1(0.01)	N/A
Intermittent claudication	0(0.00)	1(0.02)	1(0.01)	N/A
Necrosis ischaemic	0(0.00)	1(0.02)	1(0.01)	N/A
Peripheral ischaemia	1(0.02)	0(0.00)	1(0.01)	N/A
Peripheral occlusive disease	1(0.02)	0(0.00)	1(0.01)	N/A
Phlebitis NEC	0(0.00)	1(0.02)	1(0.01)	N/A
Phlebitis superficial	0(0.00)	1(0.02)	1(0.01)	N/A
Vascular hypotensive disorders	0(0.00)	1(0.02)	1(0.01)	N/A
Hypotension	0(0.00)	1(0.02)	1(0.01)	N/A
Vena caval embolism and thrombosis	0(0.00)	2(0.04)	2(0.02)	N/A
Vena cava thrombosis	0(0.00)	2(0.04)	2(0.02)	N/A

Abbreviations: SAE-Serious adverse event.
*p-Value is obtained from a Cochran-Mantel-Haenszel (CMH) test, stratified by country. Statistical test is not performed when the total number of patients in a category is less than 5.

Program: RMP.H3SSGGIO.SASPGM(SFCMTEAE) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(SFTSAE)

Other Notable Adverse Events (12.3.3.)

Notable AEs are AEs of potential relevance to SERMs or hormone therapy **based on (known from) previous data or literature**. Special search categories were predefined using MedDRA lower-level terms to comprehensively assess the notable AEs.

Special Search Categories (12.3.3.1.)

Table GGIO.12.6 presents the prespecified and post-hoc analyses of **benign breast changes or diseases.** There were no significant differences between treatment groups in the incidences of benign breast changes or diseases, except for breast hypertrophy. The proportion of patients who reported breast hypertrophy was significantly higher among patients in the placebo group compared with the raloxifene group, but the clinical relevance of this finding is unclear.

Table GGIO.12.6. Adverse Events: Benign Breast Changes or Diseases
All Randomized Patients

SSC: Special Search Category	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Benign breast changes or diseases	161(3.18)	148(2.93)	309(3.06)	.462
Fibrocystic breast disease	39(0.77)	34(0.67)	73(0.72)	.563
Fibroadenoma	20(0.40)	24(0.48)	44(0.44)	.548
Breast cysts	35(0.69)	37(0.73)	72(0.71)	.802
Fibroses	11(0.22)	8(0.16)	19(0.19)	.491
Sclerosing adenoses	0(0.00)	0(0.00)	0(0.00)	N/A
Dysplasia	7(0.14)	7(0.14)	14(0.14)	.995
Hyperplasia	5(0.10)	1(0.02)	6(0.06)	.104
Atypical hyperplasia	5(0.10)	1(0.02)	6(0.06)	.104
Miscellaneous and breast neoplasm benign	52(1.03)	43(0.85)	95(0.94)	.361
Breast conditions	144(2.85)	144(2.85)	288(2.85)	.977
Nipple discharge	2(0.04)	3(0.06)	5(0.05)	.649
Galactorrhea	1(0.02)	1(0.02)	2(0.02)	N/A
Intraductal papilloma	3(0.06)	2(0.04)	5(0.05)	.656
Mastitis	5(0.10)	8(0.16)	13(0.13)	.402
Mammary duct ectasia	0(0.00)	0(0.00)	0(0.00)	N/A
Breast pain or tenderness	65(1.29)	66(1.31)	131(1.30)	.913
Breast hypertrophy	11(0.22)	2(0.04)	13(0.13)	.014
Miscellaneous breast conditions	7(0.14)	11(0.22)	18(0.18)	.341
Breast lump NOS	57(1.13)	64(1.27)	121(1.20)	.517

*p-Value is obtained from a Cochran-Mantel-Haenszel (CMH) test, stratified by country. Statistical test is not performed when the total number of patients in a category is less than 5.

Program: RMP.H3SSGGIO.SASPGM(SFCTAESS)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(SFTAEBD)

Table GGIO.12.7 presents **benign gynecological conditions**. There were no significant differences between treatment groups in the incidences of any benign gynecological condition.

Table GGIO.12.7. Adverse Events: Benign Gynecological Conditions (All Randomized Patients)

SSC: Special Search Category	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Benign gynecological conditions	107(2.12)	102(2.02)	209(2.07)	.740
Cervix neoplasm (a)	4(0.10)	1(0.03)	5(0.06)	.178
Uterine neoplasm (a)	42(1.08)	42(1.08)	84(1.08)	.987
Uterine polyps (a)	13(0.33)	10(0.26)	23(0.30)	.516
Fibroid/leiomyoma/endometriosis (a)	25(0.64)	25(0.64)	50(0.64)	.997
Uterine cysts (a)	0(0.00)	1(0.03)	1(0.01)	N/A
Benign uterine neoplasm (a)	0(0.00)	1(0.03)	1(0.01)	N/A
Uterine hyperplasia (a)	6(0.15)	5(0.13)	11(0.14)	.762
Uterine hypoplasia (a)	0(0.00)	1(0.03)	1(0.01)	N/A
Other uterine neoplasm (a)	4(0.10)	3(0.08)	7(0.09)	.668
Ovarian neoplasm (b)	6(0.13)	5(0.11)	11(0.12)	.781
Vaginal neoplasm	2(0.04)	1(0.02)	3(0.03)	N/A
Vulvar neoplasm	1(0.02)	1(0.02)	2(0.02)	N/A
Postmenopausal bleeding	61(1.21)	59(1.17)	120(1.19)	.863
Other benign gynecological conditions	0(0.00)	0(0.00)	0(0.00)	N/A

*p-Value is obtained from a Cochran-Mantel-Haenszel (CMH) test, stratified by country. Statistical test is not performed when the total number of patients in a category is less than 5.
(a): only patients with intact uterus were considered as denominator, with Placebo=3882 Ralox=3900 total=7782 in analysis.
(b): only patients with at least one ovary were considered as denominator, with Placebo=4606 Ralox=4559 total=9165 in analysis.
Program: RMP.H3SSGGIO.SASPGM(SPCTARS1)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(SPTARHG)

Table GGIO.12.8 presents **cardiac arrhythmias** reported by investigators. There were no significant differences between treatment groups in the incidences of any cardiac arrhythmias.

Table GGIO.12.8. Adverse Events: Cardiac Arrhythmias (All Randomized Patients)

SSC: Special Search Category	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Ventricular arrhythmias	47(0.93)	53(1.05)	100(0.99)	.529
Supraventricular arrhythmias	449(8.88)	425(8.43)	874(8.65)	.414
Atrial fibrillation	331(6.55)	325(6.44)	656(6.49)	.836
SVAs other than atrial fibrillation	155(3.07)	128(2.54)	283(2.80)	.106
Cardiac conduction disorder	174(3.44)	165(3.27)	339(3.36)	.637
Other arrhythmias	189(3.74)	176(3.49)	365(3.61)	.499

*p-Value is obtained from a Cochran-Mantel-Haenszel (CMH) test, stratified by country. Statistical test is not performed when the total number of patients in a category is less than 5.

Program: RMP.H3SSGGIO.SASPGM(SFCTAESS)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(SFTAECH)

Table GGIO.12.9 presents **other predefined notable AEs**. Significantly more patients in the raloxifene group compared with patients in the placebo group reported hot flushes, leg cramps, peripheral edema, and gallbladder disease.

Table GGIO.12.9. Adverse Events: Other Clinically Significant Events (All Randomized Patients)

SSC: Special Search Category	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Hot flushes	244(4.82)	401(7.95)	645(6.39)	<.001
Leg cramps	341(6.74)	489(9.69)	830(8.22)	<.001
Influenza-like syndrome	31(0.61)	21(0.42)	52(0.51)	.166
Peripheral edema	610(12.06)	725(14.37)	1335(13.22)	<.001
Cataracts	391(7.73)	374(7.41)	765(7.57)	.564
Gallbladder disease (a)	186(4.52)	230(5.55)	416(5.04)	.033
Cholecystitis and cholelithiasis (a)	178(4.33)	216(5.21)	394(4.77)	.060
Gallbladder disorder / miscellaneous (a)	9(0.22)	18(0.43)	27(0.33)	.090

*p-Value is obtained from a Cochran-Mantel-Haenszel (CMH) test, stratified by country. Statistical test is not performed when the total number of patients in a category is less than 5.
(a) Patients who reported having had a cholecystectomy at baseline (and reported no subsequent gallbladder disease) were excluded. For this analysis:
N=4111 for Placebo; N=4144 for Ralox; N=8255 for Total.

Program: RMP.H3SSGGIO.SASPGM(SFCTAESS)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(SFTAEOS)

The significant difference between treatment groups in **the incidence of gallbladder disease** is a new observation; therefore, additional post-hoc analyses were conducted to investigate the clinical relevance of this finding. The predefined SSC was expanded to include gallbladder procedures. When AEs specific to gallbladder disease and procedures were assessed post hoc, significantly more patients in the raloxifene group than those in the placebo group reported events categorized as gallbladder disease and procedures; specifically, gallbladder disease and cholecystectomy. However, the incidence of cholecystectomy did not differ significantly between treatment groups.

Figure below presents Kaplan-Meier curves for the cumulative incidence of gallbladder events per 1000 patients. Although the effects of raloxifene on gallstone formation have not been examined, raloxifene binds to the estrogen receptor, and it is biologically plausible that raloxifene may in theory increase the formation of gallstones, similar to that observed with estrogen therapy.

- Therefore a treatment effect of raloxifene on gallbladder disease in postmenopausal women at risk for major coronary events may be possible.

Table GGIO.12.10. Gallbladder-Related Adverse Events (Post-Hoc Analysis, Randomized Patients with an Intact Gallbladder)

Event category	Placebo (N=4111) n (%)	Ralox (N=4144) n (%)	Total (N=8255) n (%)	p-Value*
Gallbladder disease (a) & procedures (b)	215(5.23)	263(6.35)	478(5.79)	.030
Gallbladder disease (a) & cholecystectomy (c)	213(5.18)	261(6.30)	474(5.74)	.029
Gallbladder disease (a)	186(4.52)	230(5.55)	416(5.04)	.033
Cholecystectomy (c)	100(2.43)	118(2.85)	218(2.64)	.245
Gallbladder procedures (including cholecystectomy) (b)	105(2.55)	129(3.11)	234(2.83)	.132

*p-Value is obtained from a Cochran-Mantel-Haenszel (CMH) test, stratified by country.
(a) Gallbladder disease refers to adverse events identified by the pre-specified special search category for 'Gallbladder disease'.
(b) Gallbladder procedures refers to adverse events mapped to the MedDRA high-level term of 'Biliary tract and gallbladder therapeutic procedures' (this includes events with a preferred term of Cholecystectomy).
(c) Cholecystectomy refers to adverse events mapped to the MedDRA preferred term of 'Cholecystectomy'.
Note: Only those patients who have an intact gallbladder are included in the analysis. This includes all patients who did not report having had a cholecystectomy at baseline and an additional 8 patients for whom data indicates that the patient had a cholecystactomy but also that the patient had an adverse event in the gallbladder disease special search category.

Program: RMP.H3SGGIO.SASPGM(SPCTAEG1) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(SPTAEGS1)

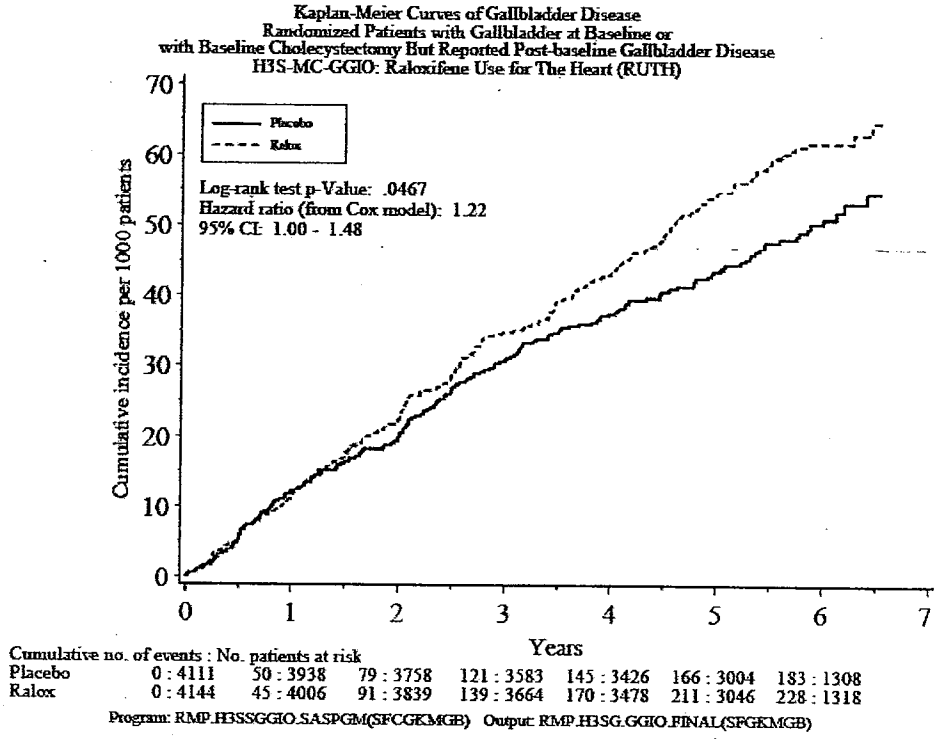


Figure GGIO.14.19. Kaplan-Meier curves for the cumulative incidence of gallbladder events for randomized patients with an intact gallbladder or with baseline cholecystectomy but reported post-baseline gallbladder disease (post-hoc analysis).

The table below summarizes of **all cancer events**.

- There was no significant difference between treatment groups in the incidence of all cancers or any specific type of cancer.

(It should be noted that for 1 patient in the placebo group (Patient 285/1124), a breast cancer endpoint was reported and adjudicated as invasive breast cancer. However, this breast cancer was not reported as an AE on the AE form. Thus, the number of patients with breast cancer shown in the placebo group in Table GGIO.12.11 (n=75), which reflects reported AEs, is one less than the number presented in Table GGIO.11.11 (n=76), which reflects adjudicated cases.)

Figure GGIO.12.1 presents Kaplan-Meier curves for the cumulative incidence of all reported cancers per 1000 patients.

Table GGIO.12.11. Adverse Events: All Cancer (All Randomized Patients)

SSC: Special Search Category	Placebo (N=5057) n (%)	Raloxifene (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Cancer	356(7.04)	339(6.72)	695(6.88)	.534
Breast cancer	75(1.48)	53(1.05)	128(1.27)	.053
Endocrine cancer	8(0.16)	3(0.06)	11(0.11)	.135
Thyroid cancer	8(0.16)	3(0.06)	11(0.11)	.135
Other endocrine cancer	0(0.00)	0(0.00)	0(0.00)	N/A
Gastrointestinal cancer	61(1.21)	61(1.21)	122(1.21)	.977
Anal cancer	2(0.04)	1(0.02)	3(0.03)	N/A
Colon cancer	25(0.49)	25(0.50)	50(0.50)	.985
Colorectal cancer	1(0.02)	2(0.04)	3(0.03)	N/A
Gastric cancer	8(0.16)	10(0.20)	18(0.18)	.636
Esophageal cancer	3(0.06)	3(0.06)	6(0.06)	.992
Pancreas cancer	11(0.22)	10(0.20)	21(0.21)	.839
Rectal cancer	8(0.16)	5(0.10)	13(0.13)	.410
Small intestine cancer	0(0.00)	0(0.00)	0(0.00)	N/A
Lip and oral cavity cancer	1(0.02)	4(0.08)	5(0.05)	.176
Salivary gland cancer	1(0.02)	1(0.02)	2(0.02)	N/A
Other gastrointestinal cancer	1(0.02)	0(0.00)	1(0.01)	N/A
Hematopoietic cancer	1(0.02)	1(0.02)	2(0.02)	N/A
Hepatic and biliary cancer	13(0.26)	11(0.22)	24(0.24)	.696
Bile duct cancer	2(0.04)	4(0.08)	6(0.06)	.409
Bladder cancer	4(0.08)	10(0.20)	14(0.14)	.109
Hepatic cancer	7(0.14)	2(0.04)	9(0.09)	.096
Other hepatic and biliary cancer	1(0.02)	0(0.00)	1(0.01)	N/A
Leukemias	12(0.24)	15(0.30)	27(0.27)	.560
Acute myeloid leukemia	3(0.06)	1(0.02)	4(0.04)	N/A
Acute lymphocytic leukemia	0(0.00)	1(0.02)	1(0.01)	N/A
Chronic myeloid leukemia	1(0.02)	2(0.04)	3(0.03)	N/A
Chronic lymphocytic leukemia	4(0.08)	6(0.12)	10(0.10)	.519
Myelodysplastic syndrome	2(0.04)	5(0.10)	7(0.07)	.255
Other leukemias	2(0.04)	0(0.00)	2(0.02)	N/A
Lymphomas	13(0.26)	12(0.24)	25(0.25)	.843
Hodgkin's disease	1(0.02)	0(0.00)	1(0.01)	N/A
Non-Hodgkin's B-cell	4(0.08)	4(0.08)	8(0.08)	.998
Non-Hodgkin's T-cell	1(0.02)	0(0.00)	1(0.01)	N/A
Non-Hodgkin's lymphomas	6(0.12)	7(0.14)	13(0.13)	.779
Other lymphomas	1(0.02)	1(0.02)	2(0.02)	N/A
Nervous system (malignant)	10(0.20)	7(0.14)	17(0.17)	.465
Ocular cancer	2(0.04)	0(0.00)	2(0.02)	N/A
Plasma cell neoplasm malignant	4(0.08)	5(0.10)	9(0.09)	.734
Plasma cell cancer	1(0.02)	2(0.04)	3(0.03)	N/A
Multiple myeloma	3(0.06)	4(0.08)	7(0.07)	.702
Renal and urinary tract cancer	16(0.32)	24(0.48)	40(0.40)	.205
Bladder cancer	4(0.08)	10(0.20)	14(0.14)	.109
Non renal cell kidney cancer	0(0.00)	0(0.00)	0(0.00)	N/A
Renal cell kidney cancer	10(0.20)	14(0.28)	24(0.24)	.408
Renal pelvis and ureter cancer	2(0.04)	0(0.00)	2(0.02)	N/A
Urinary tract cancer	0(0.00)	0(0.00)	0(0.00)	N/A
Reproductive cancer	35(0.69)	43(0.85)	78(0.77)	.364

SSC: Special Search Category	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Respiratory and mediastinal cancer	41(0.81)	34(0.67)	75(0.74)	.428
Mesothelioma	0(0.00)	0(0.00)	0(0.00)	N/A
Small cell lung cancer	2(0.04)	5(0.10)	7(0.07)	.260
Non-small cell lung cancer	11(0.22)	12(0.24)	23(0.23)	.828
Other respiratory cancer	28(0.55)	17(0.34)	45(0.45)	.105
Skeletal cancer	1(0.02)	0(0.00)	1(0.01)	N/A
Skin cancer	67(1.32)	69(1.37)	136(1.35)	.836
Melanoma	10(0.20)	8(0.16)	18(0.18)	.645
Basal cell skin carcinoma	55(1.09)	54(1.07)	109(1.08)	.945
Squamous cell skin cancer	5(0.10)	3(0.06)	8(0.08)	.488
Other skin cancer	2(0.04)	8(0.16)	10(0.10)	.056
Soft tissue cancer	0(0.00)	1(0.02)	1(0.01)	N/A
Sarcoma (other than bone and uterine)	0(0.00)	1(0.02)	1(0.01)	N/A
Miscellaneous / site unknown cancer	16(0.32)	16(0.32)	32(0.32)	.984

*p-Value is obtained from a Cochran-Mantel-Haenszel (CMH) test, stratified by country. Statistical test is not performed when the total number of patients in a category is less than 5.

Program: RMP.H3SSGGIO.SASPGM(SFCTARSS)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(SFTARCA)

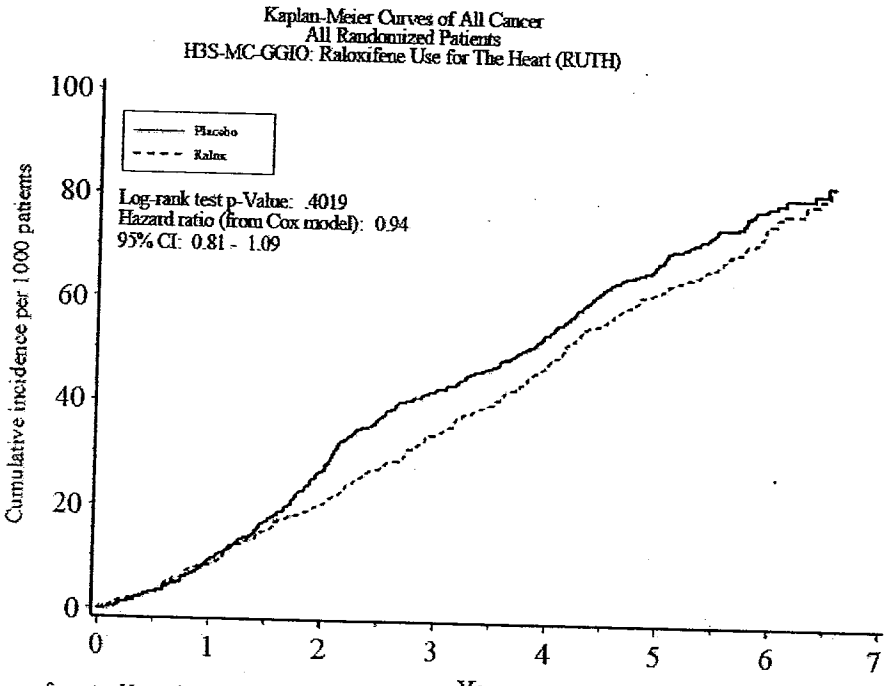


Figure GGIO.12.1. Kaplan-Meier curves of all cancer for all randomized patients.

Table GGIO.12.12 presents **reproductive cancers**.

- No significant differences in the incidences of all reproductive cancers or any individual reproductive cancer were reported between treatment groups.

The proportions of patients reporting either endometrial or uterine cancer, individually, was higher in the raloxifene group than in the placebo group, although the difference between treatment groups was not significant. Figure GGIO.14.20 presents post-hoc Kaplan-Meier curves for the cumulative incidence of endometrial or uterine cancers combined per 1000 patients.

- The post-hoc incidence rates for endometrial or uterine cancers combined were 0.83 and 1.01 per 1000 woman-years in the placebo and raloxifene groups, respectively (Table GGIO.14.49).

All cancers were identified and analyzed using a pre-specified SSC. One sarcoma was listed in the soft tissue cancer category for a patient assigned to raloxifene. Because a sarcoma is a rare cancer, all available source documents for this event were reviewed after data lock. It was subsequently identified that this was actually a uterine sarcoma.
Originally the investigator reported the event as "sarcoma uteri" but later deleted this term and reported the event as a "low malignant leiosarcoma." Using the later AE terminology, the coding of this event in MedDRA led to it being mapped to a soft tissue sarcoma. However, retrospective review of the biopsy report confirmed the diagnosis as "leiomyosarcoma uterine." Therefore, this event actually was a uterine sarcoma. The results of post-hoc sensitivity analyses (Section 9.8.2.7.3; Table GGIO.14.50) performed for all reproductive cancers and endometrial and uterine cancers including this event of "uterine sarcoma" were consistent with the prespecified analyses (Table GGIO.12.12).

Table GGIO.12.12. Adverse Events: Reproductive Cancers (All Randomized Patients)

SSC: Special Search Category	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Reproductive cancer	35(0.69)	43(0.85)	78(0.77)	.364
Cervix cancer	6(0.15)	5(0.13)	11(0.14)	.801
Endometrial and uterine cancers (a)	17(0.44)	21(0.54)	38(0.49)	.532
Endometrial cancer (a)	16(0.41)	17(0.44)	33(0.42)	.890
Uterine cancer (a)	1(0.03)	4(0.10)	5(0.06)	.174
Uterine sarcoma (a)	0(0.00)	0(0.00)	0(0.00)	N/A
Ovarian cancer (b)	10(0.22)	17(0.37)	27(0.29)	.168
Ovarian choriocarcinoma (b)	0(0.00)	0(0.00)	0(0.00)	N/A
Vaginal cancer	0(0.00)	0(0.00)	0(0.00)	N/A
Vulva cancer	0(0.00)	0(0.00)	0(0.00)	N/A
Other reproductive cancer	2(0.04)	0(0.00)	2(0.02)	N/A

*p-Value is obtained from a Cochran-Mantel-Haenszel (CMH) test, stratified by country. Statistical test is not performed when the total number of patients in a category is less than 5.
(a): only patients with intact uterus were considered as denominator, with Placebo=3882 Ralox=3900 total=7782 in analysis.
(b): only patients with at least one ovary were considered as denominator, with Placebo=4606 Ralox=4559 total=9165 in analysis.
Program: RMP.H3SSGGIO.SASPGM(SFCTAES2)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(SFTAERC1)

The proportion of patients reporting **ovarian cancer** was greater in the raloxifene group than in the placebo group, although the difference between treatment groups was not significant. Due to the higher incidence of ovarian cancer in the raloxifene group, additional post-hoc analyses (Section 9.8.2.7.5) were conducted. Figure GGIO.14.21 presents Kaplan-Meier curves for the cumulative incidence of ovarian cancer per 1000 patients and Table GGIO.14.51 shows the incidence rates.

The one-page patient summaries (OPPS) for all 27 patients diagnosed with ovarian cancer were reviewed in consultation with an independent expert in gynecological oncology. A summary of this review follows:

- The mean age of women at baseline who were diagnosed with ovarian cancer in the raloxifene group was approximately 5 years younger than the placebo group (Table GGIO.14.52).
- Most ovarian cancers were classified as serous papillary ovarian cancers, the most common type.
- Most patients were diagnosed with an advanced stage (Stage III and beyond) of ovarian cancer and many patients died within 2 months of diagnosis of ovarian cancer.
- The mean time from randomization to date of diagnosis of ovarian cancer was 2.2 years in the raloxifene group compared with 3.5 years in the placebo group (Table GGIO.14.52).

In conclusion, too few ovarian cancers were reported to draw meaningful conclusions about the observed pattern of events over time.

Adverse Events Leading to Discontinuation of Study Drug (12.3.4.)

Table GGIO.14.53 in the original CSR presents a summary of AEs leading to discontinuation of study drug by SOC, High-level Term, and Preferred Term. The table was reviewed.

- The proportion of patients who reported at least one AE leading to discontinuation of study drug was not significantly different between treatment groups.

Significantly more patients in **the raloxifene group** discontinued study drug than did those in the placebo group because of the following AEs at *the Preferred Term level* (in decreasing order of frequency): **muscle spasms, hot flush, oedema peripheral, headache, vomiting, and renal cell carcinoma stage unspecified**.

Headache and vomiting were reported by less than 1% of the raloxifene assigned patients; however, these findings may be clinically relevant.
Although the Preferred Term **"renal cell carcinoma stage unspecified"** was reported more frequently in the raloxifene group compared with the placebo group, there was no significant difference between treatment groups at the High-level Term "renal cell carcinomas" to which this Preferred Term maps. The increased reporting of the single Preferred Term, renal cell carcinoma stage unspecified, was not deemed clinically relevant.

Study drug discontinuation was reported in significantly more raloxifene-assigned patients than placebo-assigned patients *at the High-level Term* **"paralysis and paresis** (excluding congenital and cranial nerve)". However, there were no significant differences in study drug discontinuation between treatment groups in the Preferred Terms mapping to this High-level Term.

- In review of all TEAEs, there were 128 patients reporting an AE that mapped to the High-level Term "paralysis and paresis (excluding congenital and cranial nerve)".
- Significantly more patients assigned to raloxifene, compared with placebo, reported an AE mapping to the Preferred Term "paresis" contained within this High-level Term.
- 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 difference between treatment groups in the incidence of all strokes, stroke severity was not collected. Therefore, the significance of this finding is unclear.

Conversely, significantly more patients in **the placebo group** discontinued study drug than did those in the raloxifene group because of the following AEs at the Preferred Term level in decreasing frequency: **breast cancer, myalgia, alopecia, asthma, and hepatic neoplasm malignant**.

Clinical Laboratory Evaluation (12.4.)

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

Appendix 16.2.8 (in the original CSR) contains a listing of all laboratory measurements by patient with abnormal results indicated as low or high compared to relevant reference ranges

Evaluation of Each Laboratory Parameter (12.4.2.)

Laboratory Values over Time (12.4.2.1.)

Analyses of fasting glucose and HgbA1c were performed separately on patients with and without diabetes mellitus at baseline.

Table GGIO.12.13 presents change from baseline to endpoint for AST, total bilirubin, BUN, and creatinine.

- AST: there was no difference between treatment groups.
- Total bilirubin: decreased over time in both treatment groups and the magnitude of change was greater in the raloxifene group. This difference between treatment groups was significant but not considered clinically relevant.
- BUN: increased over time in both groups and the magnitude of change were greater in the placebo group. This difference between treatment groups was significant but not deemed clinically relevant.
- Creatinine: increased in both groups; however, the difference between groups was not significant.

Table GGIO.12.13. Clinical Laboratory Measurements Change from Baseline to Endpoint (All Randomized Patients)

Lab	Unit	Therapy	N**	Baseline Mean	Baseline STD	Endpoint Mean	Endpoint STD	Change to Endpoint Mean	Change to Endpoint STD	p-Value* Therapy
AST	U/L	1) Placebo	4608	23.31	16.28	22.77	10.28	-0.53	16.65	.806
		2) Ralox	4642	23.44	10.82	23.67	16.14	0.23	17.58	
T.BILI	umol/L	1) Placebo	4605	8.55	3.68	7.32	3.92	-1.23	3.54	<.001
		2) Ralox	4640	8.57	3.72	6.75	4.07	-1.82	4.08	
BUN	mmol/L	1) Placebo	4685	6.19	2.03	7.38	3.22	1.19	2.73	.020
		2) Ralox	4700	6.14	2.00	7.22	3.23	1.09	2.75	
CREAT	umol/L	1) Placebo	4685	97.01	18.49	111.14	35.13	14.13	28.77	.649
		2) Ralox	4700	96.97	17.82	112.11	41.48	15.14	35.48	

Abbreviations: STD=standard deviation; AST=aspartate transaminase;
BUN=blood urea nitrogen; CREAT=serum creatinine; T.BILI=total bilirubin.
*p-Value is obtained from a ranked ANOVA model: ranked response=therapy.
**N is the number of patients having both a baseline and an endpoint measurement.

Note: Baseline and endpoint measurements are determined using the last observation carried forward (LOCF) principle in the baseline and postbaseline period, respectively.

Program: RMP.H3SSGGIO.SASPGM(SFCMLAB1)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.LABS Output: RMP.H3SO.GGIO.FINAL(SFTABCT)

Summary statistics, presented by visit for the following: AST (Table GGIO.14.57), total bilirubin (Table GGIO.14.58), BUN (Table GGIO.14.59), and serum creatinine (Table GGIO.14.60), were reviewed.

Change from baseline: fasting glucose and Hgb A1c in patients without diabetes

Table GGIO.12.14 presents change from baseline to endpoint for fasting glucose and HgbA1c among patients *without* diabetes mellitus. No significant differences between treatment groups were noted for patients without diabetes mellitus.

Table GGIO.12.14. Glucose and Hgb A1c Change from Baseline to Endpoint (Randomized Patients without Diabetes Mellitus at Baseline; All Randomized Patients)

				Baseline		Endpoint		Change to Endpoint		p-Value*
Lab	Unit	Therapy	N**	Mean	STD	Mean	STD	Mean	STD	Therapy
FGLU	mmol/L	1) Placebo	2543	5.67	0.88	5.80	1.23	0.13	1.13	.195
		2) Ralox	2544	5.66	0.87	5.80	1.33	0.14	1.22	
HGBA1C	%	1) Placebo	2386	6.17	0.55	6.08	0.70	-0.09	0.55	.591
		2) Ralox	2399	6.18	0.52	6.08	0.66	-0.09	0.55	

Abbreviations: STD=standard deviation; FGLU=fasting glucose; HGBA1C=hemoglobin A1c.
*p-Value is obtained from a ranked ANOVA model: ranked response=therapy.
**N is the number of patients having both a baseline and an endpoint measurement.

Note: Baseline and endpoint measurements are determined using the last observation carried forward (LOCF) principle in the baseline and postbaseline period, respectively.

Program: RMP.H3SSGGIO.SASPGM(SFCMLAB1)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.LABS Output: RMP.H3SO.GGIO.FINAL(SFTFHDIN)

Change from baseline: fasting glucose and Hgb A1c in patients with diabetes

Table GGIO.12.15 presents change from baseline to endpoint for fasting glucose and HgbA1c among patients with diabetes mellitus.

- No significant difference between treatment groups was noted among patients with diabetes mellitus for changes in fasting glucose.
- HgbA1c decreased among diabetics in both treatment groups over time and the magnitude of change was greater in the placebo group.
- This difference was significant between treatment groups but not deemed clinically relevant.

Table GGIO.12.15. Glucose and Hgb A1c Change from Baseline to Endpoint (Randomized Patients with Diabetes Mellitus at Baseline; All Randomized Patients)

				Baseline		Endpoint		Change to Endpoint		p-Value*
Lab	Unit	Therapy	N**	Mean	STD	Mean	STD	Mean	STD	Therapy
FGLU	mmol/L	1) Placebo	2047	10.00	3.91	9.56	3.90	-0.44	4.47	.484
		2) Ralox	2086	10.03	3.94	9.50	3.85	-0.53	4.51	
HGBA1C	%	1) Placebo	1854	8.36	1.67	7.87	1.49	-0.49	1.53	.003
		2) Ralox	1928	8.31	1.64	7.95	1.49	-0.37	1.54	

Abbreviations: STD=standard deviation; FGLU=fasting glucose; HGBA1C=hemoglobin A1c.
*p-Value is obtained from a ranked ANOVA model: ranked response=therapy.
**N is the number of patients having both a baseline and an endpoint measurement.

Note: Baseline and endpoint measurements are determined using the last observation carried forward (LOCF) principle in the baseline and postbaseline period, respectively.

Program: RMP.H3SSGGIO.SASPGM(SFCMLAB1)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.LABS Output: RMP.H3SO.GGIO.FINAL(SFTFHDIA)

Summary statistics, presented by visit for the following: fasting glucose among patients with diabetes mellitus (Table GGIO.14.61) and without diabetes mellitus (Table GGIO.14.62); HgbA1c among patients with diabetes mellitus (Table GGIO.14.63) and without diabetes mellitus (Table GGIO.14.64), were reviewed.

Individual Patient Changes (12.4.2.2.)

Shift tables are presented in Section 14.4.4 showing the number and percent of patients by treatment group with changes classified as down (a decrease from baseline), up (an increase from baseline), and same (no change from baseline). In each of these tables, rows represent the baseline lab value category, and columns represent the maximum post-baseline value category. Analysis of the all randomized population was performed for the following: AST (Table GGIO.14.65), total bilirubin (Table GGIO.14.66), BUN (Table GGIO.14.67), and serum creatinine (Table GGIO.14.68). Analysis of subsets of patients with and without diabetes mellitus was performed for fasting glucose (Table GGIO.14.69 and Table GGIO.14.70) and HgbA1c (Table GGIO.14.71 and Table GGIO.14.72).

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

Vital Signs (12.5.1.)

Table GGIO.12.16 presents change from baseline to endpoint for BMI, height, weight, systolic and diastolic blood pressure, and heart rate. While significant differences between treatment groups were observed for BMI, weight, and heart rate, none of these were considered clinically relevant.

Table GGIO.12.16. Vital Signs: Change from Baseline to Endpoint (All Randomized Patients)

				Baseline		Endpoint		Change to Endpoint			p-Value*
Vital Sign	Unit	Therapy	N**	Mean	STD	Mean	STD	Mean	STD	w/in p*	Therapy
BMI	kg/m2	1) Placebo	4737	28.73	5.11	28.94	5.52	0.21	2.56	<.001	.002
		2) Ralox	4763	28.81	5.11	29.16	5.50	0.34	2.51	<.001	
Height	cm	1) Placebo	4741	156.16	6.84	157.05	6.85	-1.11	2.03	<.001	.079
		2) Ralox	4764	156.04	6.76	156.86	6.76	-1.19	2.13	<.001	
Weight	kg	1) Placebo	4750	71.90	13.80	71.41	14.70	-0.48	6.24	<.001	.014
		2) Ralox	4776	72.04	13.74	71.83	14.65	-0.21	6.00	.039	
Systolic BP	mmHg	1) Placebo	4757	145.46	20.05	140.44	19.25	-5.03	21.93	<.001	.508
		2) Ralox	4783	145.87	20.23	140.30	19.13	-5.57	22.53	<.001	
Diastolic BP	mmHg	1) Placebo	4757	82.04	10.28	77.73	10.25	-4.32	11.66	<.001	.222
		2) Ralox	4783	82.03	10.50	78.00	10.19	-4.02	11.86	<.001	
Heart Rate	bpm	1) Placebo	4750	70.84	10.36	70.46	10.68	-0.39	11.64	.001	.007
		2) Ralox	4776	70.84	10.90	71.05	11.22	0.21	12.34	.479	

Abbreviations: STD-standard deviation; BMI-body mass index; bpm-beats per minute.
*p-Value is obtained from a ranked ANOVA model: ranked response-therapy.
Within group p-Values are from Wilcoxon Signed Rank test on mean change.
**N is the number of patients having both a baseline and an endpoint measurement.

Note: Endpoint measurement is determined using the last observation carried forward (LOCF) principle in the postbaseline period.

Program: RMP.H3SSGGIO.SASPGM(SPCMVS2) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(SPTVITAL)

Electrocardiograms (12.5.2.)

ECG findings are reported in the efficacy section (Section 11.4.3.4).

Safety Conclusions (12.6.)

Exposure

- Median exposure to study drug was 5.05 years and was similar between treatment groups.

Treatment-emergent Adverse Events

There was no significant difference between raloxifene-assigned and placebo-assigned patients reporting ≥1 TEAE.

Reporting of the **Preferred Term "vaginal mycosis"** and the **High-level Term "Candida infections"** was significantly greater in the raloxifene group than in the placebo group. Similar observations have been made in other clinical trials of raloxifene and with another SERM, tamoxifen. Although the event rates of these infections were very low, a treatment effect of raloxifene is possible.

The following TEAEs, reported by ≥2% of raloxifene-assigned patients at the Preferred Term level, were reported significantly **more frequently by raloxifene-assigned patients** than by placebo-assigned patients (in decreasing order of frequency): oedema peripheral, muscle spasms, hot flush, dyspepsia, cholelithiasis, arthritis, and intermittent claudication.

- **Peripheral edema, muscle spasms** and **hot flushes** are known to be associated with use of raloxifene and therefore the increased reporting in patients assigned raloxifene was not unexpected.
- **Cholelithiasis** is discussed below.
- The clinical relevance of the increased reporting of **dyspepsia** and **arthritis** is unknown.
- Given that raloxifene had no effect on coronary or cerebrovascular events, or lower extremity revascularizations or amputations (Section 12.2.2.1), there is no obvious biologically plausible explanation for the increased reporting of **intermittent claudication** in patients assigned raloxifene.

The following TEAEs reported by ≥2% of raloxifene-assigned patients were reported significantly **more frequently by placebo-assigned patients** than raloxifene-assigned patients: **osteoporosis, constipation,** ACS, and **anxiety**.

Adverse Reactions

The following ***adverse reactions*** **at the Preferred Term level** were reported significantly more frequently by patients in the raloxifene group than in the placebo group (in decreasing order of frequency): muscle spasms, hot flush, oedema peripheral, hyperhidrosis, breast pain, and palpitations. Hyperhidrosis may be biologically plausible if it was synonymous with excessive flushing, as hot flushes are a known AE associated with use of raloxifene. Breast pain and palpitations were not considered clinically relevant.

Deaths, Serious Adverse Events, and Other Notable Adverse Events

Deaths

There was no significant difference between treatment groups for all-cause mortality.
See Section 11.4.4.4 for further discussion.

Serious Adverse Events

There was no significant difference between treatment groups in the proportion of patients who reported ≥1 SAE.
Significantly more patients in the raloxifene group than in the placebo group reported SAEs categorized under the Preferred Terms of **pulmonary embolism** and **bladder cancer**.

- **Pulmonary embolism** is a known SAE associated with the use of raloxifene and was required to be reported as such per the protocol. See Section 11.4.4.3 for further discussion.
- **Bladder cancer** has not been reported in other raloxifene clinical trials and its clinical relevance is unknown, especially since bladder cancer is more often diagnosed in older, white males, smokers, or persons exposed to certain chemical substances such as rubber or certain dyes.

Notable Adverse Events

Special search categories were predefined to evaluate notable AEs of interest to SERMS or hormone therapy. There was no difference between treatment groups in the reporting of **benign breast or gynecological conditions**, including **breast pain**, **uterine polyps** or **postmenopausal bleeding**.
Hot flushes, **leg cramps** (ie, muscle spasms), and **peripheral edema** were reported significantly more frequently in patients assigned raloxifene compared with those assigned placebo, consistent with the known safety profile of raloxifene.
An increased reporting of **flu-like syndrome** has been observed in patients treated with raloxifene in prior clinical trials; however, there was no difference between treatment groups with respect to this event in the GGIO population.

The incidence of **gallbladder disease**, specifically **cholecystitis** and **cholelithiasis**, was reported significantly more frequently in patients assigned raloxifene compared with the placebo group; however, there was no between-treatment group difference in the reporting of cholecystectomy. This is a new finding. In an osteoporosis treatment trial comparing raloxifene with placebo, a

post-hoc analysis showed no difference between treatment groups in the incidence of gallbladder disease including surgery (Grady et al. 2004). Estrogen therapy has been associated with an increased incidence of cholelithiasis and gallbladder surgery (Simon et al. 2001; Cirillo et al. 2005). Although the effects of raloxifene on gallstone formation have not been examined, raloxifene binds to the estrogen receptor, and it is biologically plausible that raloxifene may in theory increase the formation of gallstones. Therefore, a treatment effect of raloxifene on gallbladder disease in women at risk for major coronary events may be possible.

The incidences of **all cancers** or **any specific type of cancer** did not differ significantly between treatment groups.
Specifically, **endometrial** and **uterine cancers** *combined* did not differ significantly between treatment groups. This finding is consistent with observations from prior clinical trials with raloxifene.
There was no significant difference in the incidence of **ovarian cancer** between treatment groups; however, the proportion of patients reporting ovarian cancer was greater in the raloxifene-assigned group compared with the placebo-assigned group. In a prior cumulative assessment of seven clinical trials with raloxifene, 16 cases of ovarian cancers were reported: 8 women (79.4/100,000 patient-years) on placebo and 8 (37.4/100,000 patient-years) on pooled raloxifene doses. The relative risk of ovarian cancer associated with raloxifene therapy was 0.50 (95% CI 0.19, 1.35) (Neven et al. 2002). In conclusion, in GGIO, too few ovarian cancers were reported to draw meaningful conclusions about the observed pattern of events over time.

AEs Leading to Discontinuation of Study Drug

The proportion of patients who reported at least one AE leading to discontinuation of study drug was not significantly different between treatment groups. Significantly more patients in the raloxifene group discontinued study drug than did those in the placebo group due to the following AEs at the Preferred Term level (in decreasing order of frequency):

- Muscle spasms
- Hot flush
- Peripheral oedema
- Headache
- Vomiting
- Renal cell carcinoma-stage unspecified

- **Headache** and **vomiting** were infrequently reported events but may be clinically relevant.
- The specific Preferred Term **"renal cell carcinoma stage unspecified"** was not deemed clinically relevant.
- All other events are known to be associated with the use of raloxifene.
- Study drug discontinuation was reported in significantly more raloxifene-assigned patients than placebo-assigned patients at the High-level Term **"paralysis and paresis (excluding congenital and cranial nerve)"**. In review of all TEAEs, significantly more patients assigned to raloxifene, compared with placebo, reported an AE mapping to this High-level Term and the majority of these patients had an investigator-reported **stroke**

event during the trial. Although there was no difference between treatment groups in the incidence of all strokes, stroke severity was not collected. Therefore, the significance of this finding is unclear.

Significantly more patients in the **placebo group** discontinued study drug than did those in the raloxifene group due to the following AEs at the Preferred Term level (in decreasing order of frequency): breast cancer, myalgia, alopecia, asthma, and hepatic neoplasm malignant.

Laboratory Parameters and Vital Signs

Significant differences between treatment groups were observed for total bilirubin and BUN, but not for AST or creatinine. These differences were not considered clinically relevant.
Significant differences between treatment groups were observed for BMI, weight, and heart rate but these differences were not deemed clinically relevant. No significant differences were observed for height, or systolic or diastolic blood pressure.

Discussion and Overall Conclusions (13.)

GGIO was a Phase 3, placebo-controlled study to determine if raloxifene HCl 60 mg/day would reduce the incidence of:
1. The combined endpoint of coronary death, nonfatal (including silent) MI, or hospitalized ACS other than MI
2. Invasive breast cancer in postmenopausal women at risk for major coronary events

- A total of 10,101 patients were randomly assigned to either placebo (N=5057) or raloxifene HCL 60 mg/day (N=5044).
- The study completed after **the last randomized patient** had been followed for 5 years.
- The **median follow-up** was 5.6 years.

Efficacy

Raloxifene significantly reduced the incidence of invasive breast cancer in postmenopausal women at risk for major coronary events. This significant reduction in incidence of invasive breast cancer was primarily due to a significant reduction in ER-positive invasive breast cancer.

- The **absolute risk reduction** was 1.2 cases of invasive or 1.2 cases of **ER-positive invasive** breast cancer per 1000 woman-years.
- The effect of treatment with raloxifene on invasive breast cancer risk reduction **did not differ by age** *or* **by 5-year predicted risk for invasive breast cancer**
- Raloxifene had no effect on the incidence of **ER-negative invasive** or **noninvasive** breast cancer.

The effect of raloxifene on the incidence of invasive breast cancer has been assessed in **other clinical trials**.

- In **the placebo group**, the incidence rate of invasive breast cancer was 2.66 cases per 1000 woman-years. This rate is lower than that observed in the placebo group (ie, 4.7 to 5.2 cases per 1000 woman-years) of clinical trials assessing the effect of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis.
  - However, the statistically significant reduction in relative risk observed in GGIO has been consistently observed in these other raloxifene clinical trials.
- The lack of effect of raloxifene on the incidence of ER-negative invasive or noninvasive breast cancer in GGIO is also consistent with results from the other raloxifene clinical trials.

Raloxifene had no effect on the incidence of the **combined coronary primary endpoint events** of coronary death, nonfatal MI, or hospitalized ACS other than MI.
Changes in **lipid parameters** and **fibrinogen levels** occurring in the raloxifene group were not large enough to translate into a clinical coronary benefit, as evidenced by the null effect of raloxifene on the incidence of the primary coronary endpoint events.

Raloxifene did not significantly affect the incidences of all **revascularizations**, including myocardial or non-coronary arterial revascularizations, of non-traumatic lower extremity amputations or of the combined CV endpoint comprised of CV death, nonfatal MI, hospitalized ACS other than MI, stroke, or myocardial revascularization.

In the raloxifene group, there was a significant increase in the incidence of **VTE** (absolute risk increase of 1.2 VTEs per 1000 woman-years). This finding was expected as VTE has been shown in prior clinical trials to be a serious, but uncommon, AE associated with the use of raloxifene.

Raloxifene had no effect on the incidences of **all strokes** or **overall mortality**, including **CV mortality**.

A 49% increase in the incidence of **death due to stroke** was observed in women assigned to raloxifene, which translates into an absolute risk increase of 0.7 deaths due stroke per 1000 woman-years. After Year 3 there was an increased incidence of death due to stroke in the raloxifene group compared with placebo; this increased incidence persisted thereafter, becoming statistically significant in Year 7.

This is a new finding not previously seen in prior clinical trials with raloxifene and is perplexing given that no significant increase in the incidence of all strokes was observed in women assigned raloxifene in GGIO. Stroke is a leading cause of functional impairment however, in this study, stroke morbidity was not collected.

Since the statistical significance of the increased incidence of death due to stroke was relatively weak ($p=0.0499$), this observation may be due to chance or may be real. Exploratory post-hoc analyses were performed for all strokes and deaths due to stroke. No single risk factor could be identified from statistical modeling that would predict which women treated with raloxifene might experience a stroke and subsequently die from it.

Given that the postmenopausal women enrolled in GGIO either had established CHD or risk factors for CHD, that most of these CHD risk factors are also stroke risk factors, that these risk factors were well treated based on the substantial concomitant CV medication usage, and that there was no difference between treatment groups in the incidence of all strokes, it is not surprising that the statistical modeling failed to identify a single risk factor predictive of stroke or death due to stroke. The low number of deaths due to stroke in this large cohort of postmenopausal women also limited the ability to identify any predictive risk factors.

A woman who has already had a stroke has an increased risk of having another stroke, in comparison to a woman who has never had a stroke (Fuster et al. 2001). Atrial fibrillation and transient ischemic attack (TIA) are also known stroke risk factors (Friberg et al. 2004; Marini et al. 2005; Goldstein et al. 2006; Sacco et al. 2006). The exploratory analyses did provide limited evidence suggesting that these risk factors might have contributed to the increased incidence of death due to stroke in this population of women assigned raloxifene. Therefore, postmenopausal women at risk for major coronary events who also have a history of stroke, atrial fibrillation, or

TIA may be at increased risk of having a stroke and possibly dying from it; thus, the benefits and risks of raloxifene therapy should be carefully considered in these postmenopausal women. .

In clinical trials assessing the effects of **raloxifene in postmenopausal women with osteoporosis**, raloxifene did not significantly increase the incidences of stroke or overall mortality, including deaths due to coronary or cerebrovascular etiologies (Barrett-Connor et al. 2002; Ensrud et al. 2006). On retrospective assessment, the prevalence of CHD or CHD risk factors was lower in these postmenopausal women with osteoporosis and, therefore, they were likely to be at lower risk for stroke or death due to stroke, in comparison to the women enrolled in GGIO (Barrett-Connor et al. 2002; Ensrud et al. 2006). In conclusion, **this increased incidence of death due to stroke has only been observed in one study of raloxifene in postmenopausal women at risk for major coronary events.**

Raloxifene significantly reduced clinical **vertebral fracture incidence** (absolute risk reduction of 1.3 clinical vertebral fractures per 1000 woman-years) and did not significantly affect the incidences of **non-vertebral fractures** including hip/femur or wrist fractures. These findings are consistent with the known skeletal efficacy profile of raloxifene.

Safety

Overall, raloxifene treatment appeared to be well tolerated during the study as the AEs reported during the trial were generally consistent with the known safety profile of raloxifene, except for the new finding of an increased incidence of deaths due to stroke in women assigned to raloxifene.

Hot flushes, muscle spasms (ie, leg cramps), and peripheral edema were reported more frequently in the raloxifene group and are known to be associated with raloxifene use.

The reporting of flu-like syndrome did not differ between treatment groups; however, in prior clinical trials, an increased reporting of flu-like syndrome has been observed in postmenopausal women with osteoporosis treated with raloxifene.

There was a significant increase in the incidence of gallbladder disease in the raloxifene group; however, there was no difference in the rate of cholecystectomy. This is a new finding and was not seen in a raloxifene osteoporosis treatment trial. The effects of raloxifene on gallstone formation have not been examined; however, because raloxifene binds to the estrogen receptor, it is biologically plausible that raloxifene may in theory increase the formation of gallstones, similar to the effect of estrogen, in postmenopausal women at risk for major coronary events. Raloxifene had no effect on the incidence of all cancers. Endometrial and ovarian cancer did not differ significantly between treatment groups; however, the proportion of women reporting these events was greater in the raloxifene-assigned group compared with the placebo group.

Benefit Risk Conclusion

In postmenopausal women at risk for major coronary events, ie, with established CHD or with multiple risk factors for CHD, raloxifene treatment reduced the incidence of invasive breast cancer and had no effect on the incidence of coronary death, nonfatal MI, or hospitalized ACS other than MI combined. Raloxifene reduced clinical vertebral fracture incidence and increased the risk of venous thromboembolism. Raloxifene had a neutral effect on the incidences of combined CV events, stroke, or overall deaths. An increased incidence in death due to stroke was observed in the raloxifene group in this population; the clinical significance of this finding, which has not been observed in previous raloxifene trials, remains unclear. The benefits and risks of raloxifene therapy should be carefully considered in any postmenopausal woman at risk for major coronary events who also has a history of stroke, atrial fibrillation, or TIA as these conditions are associated with an increased stroke mortality risk.

In summary, in postmenopausal women at risk for major coronary events, the benefits of raloxifene in reducing the incidences of invasive breast cancer and clinical vertebral fracture must be weighed against the increased risk of VTE and the possible increased risk of death due to stroke.

Summary 2 MORE Clinical Study Report

Clinical Study Report: Comparison of Raloxifene Hydrochloride and Placebo in the Treatment of Postmenopausal Women with Osteoporosis

Eli Lilly and Company Protocol H3S-MC-GGGK(g)

First patient enrolled:	16 December 1994
Last patient completed:	31 August 1999
Interim report:	28 March 1997
Interim report:	11 March 1999
Date report approved by Lilly Medical:	18 October 2002

- This was a Phase 3, multicenter, parallel, placebo-controlled, randomized, double-blind study with a completed 36-month core treatment phase and a completed 12-month extension phase.
- Patients were randomly assigned to placebo, raloxifene hydrochloride 60 mg/day, or raloxifene hydrochloride 120 mg/day.

Clinical Study Synopsis
Study H3S-MC-GGGK

Title of Study: Comparison of Raloxifene Hydrochloride and Placebo in the Treatment of Postmenopausal Women with Osteoporosis

Investigator(s): This multicenter study included 181 principal investigators in 25 countries.

Study Center(s): This study was conducted at 125 study centers.

Length of Study: 4 years

Date of first patient enrolled: 16 December 1994

Date of last patient completed: 31 August 1999

Phase of Development: 3

Objectives:

Primary:
To compare raloxifene HCl with placebo on:
1) The rate of new vertebral fractures
2) Lumbar spine and femoral neck bone mineral density (BMD)
3) Safety

Secondary:
To compare raloxifene HCl with placebo on:
1) Total body bone mineral content (BMC) and radial BMD
2) Rates of new nonvertebral fractures alone and of nonvertebral and vertebral fractures combined
3) Biochemical markers of bone metabolism
4) Serum lipids and other laboratory markers of cardiovascular risk
5) Health outcomes and quality of life
6) Cognitive and neuropsychomotor function, risk of cardiovascular disease and risks of breast and endometrial cancers
7) Alzheimer's disease,
8) Dementia

Methodology: Double-blind, placebo-controlled, randomized trial consisting of two parallel sub studies in separate populations.

Number of Patients:

Planned:	2167 raloxifene 60 mg/day, 2167 raloxifene 120 mg/day, 2167 placebo
Randomized:	2557 active drug, 2572 comparator, 2576 placebo
Completed:	1737 active drug, 1822 comparator, 1849 placebo

Diagnosis and Main Criteria for Inclusion:
- Ambulatory, postmenopausal women with primary osteoporosis, ≤ 80 years old, were enrolled.
- For Substudy I, women with femoral neck or lumbar spine BMD measurements ≤ 2.5 standard deviations below normal bone mass for healthy, premenopausal women were eligible.

- For Substudy II, women with either a minimum of one moderate or two mild vertebral fractures in the presence of low BMD or a minimum of two moderate vertebral fractures, regardless of BMD, were eligible.

Test Product, Dose and Mode of Administration, Batch Number: Raloxifene HCl: tablets of 60 mg/day or 120 (60 x 2) mg/day given orally; see Appendix 16.1.10 for a listing of clinical trial materials used in this study.

Duration of Treatment: 4 years (36 months with 12-month extension)

Reference Therapy, Dose and Mode of Administration, Batch Number: Placebo: tablets matching in appearance to test product and given once daily; see Appendix 16.1.10 for a listing of clinical trial materials used in this study.

Criteria for Evaluation:

Efficacy: Mammograms or breast ultrasonography; clinical breast examinations; breast cancer events; spinal radiographs; dual x-ray absorptiometry measurements at the femoral neck, lumbar spine, and radius; total body bone mineral content; biochemical markers of bone metabolism; bone biopsies (subset); biochemical markers of cardiovascular risk; and neuropsychometric tests.

Safety: Adverse events; laboratory tests; vital signs; 12-lead electrocardiograms; clinical pelvic exams; uterine ultrasounds (subset; patients with uterine bleeding or endometrial thickening observed on scheduled uterine ultrasound underwent follow-up physical and gynecological exams); Papanicolaou tests; endometrial cancer events; cardiovascular events and procedures.

Pharmacokinetic: Plasma concentrations.

Health Outcomes: Medical resource utilization and quality of life data.

Statistical Methods: Continuous data were analyzed using analysis of variance (ANOVA), and binary data were analyzed using Pearson's chi-square test and Fisher's Exact test. All safety and efficacy analyses were performed on the entire study cohort (pooled substudies). In addition, primary efficacy analyses were performed separately on each substudy. All substudy analyses were performed based on the assignment made at randomization. Unless otherwise stated, all hypotheses were tested at the 0.05 (two-sided) level of significance. No adjustments were made for multiple comparisons.

Summary and Conclusions: Treatment with raloxifene for 48 months with raloxifene is effective for the treatment of postmenopausal osteoporosis, as evidenced by a significant decrease in the rate of new vertebral fractures and significant increases in BMD. In addition, treatment with raloxifene in this patient population resulted in a statistically significant reduction in the incidence of breast cancer. The significant reduction was also seen for cases of invasive breast cancer, estrogen receptor (ER)-positive breast cancer, and invasive ER-positive breast cancer.

Raloxifene has an excellent safety profile with venous thromboembolism the only serious adverse event of clinical significance. Furthermore, raloxifene was not associated with endometrial cancer or clinically relevant effects on the endometrium and was associated with beneficial or neutral effects on biochemical markers of cardiovascular risk and no increase in major cardiovascular events. There were no clinically relevant vital signs or safety laboratory changes or effects on cognition.

The sponsor concludes that 48 months of raloxifene treatment is well tolerated, effectively treats osteoporosis, and substantially reduces the risk of breast cancer in postmenopausal women with osteoporosis.

List of Abbreviations and Definitions of Terms (4.)

Adverse event (Used as category; no definition.)

Clinical trial adverse event

An adverse event is any undesirable experience, unanticipated benefit, or pregnancy that occurs after informed consent for the study has been obtained, without regard to the possibility of a causal relationship and without regard to treatment group assignment, even if no study drug has been taken.

Clinical trial serious adverse event

Any adverse event from a clinical study that includes one of the following criteria:

- Death
- Initial or prolonged inpatient hospitalization
- Life-threatening
- Severe or permanent disability
- Cancer (other than cancers diagnosed prior to enrollment in studies involving patients with cancer)
- Congenital anomaly
- Significant for other reason

Spontaneous adverse event

A spontaneous adverse event is any untoward happening, failure of expected pharmacological action, unanticipated benefit, or pregnancy in a patient after the onset of therapy or upon withdrawal with a Lilly/Dista product, without regard to the possibility of a causal relationship.

Unanticipated benefit

An unanticipated event that may be considered of benefit to the study participant. An event that is considered an unanticipated benefit is reported to Lilly in the same manner as an adverse event.

Automated clinical data output

ACDO

Standardized computer summary tables, listings, and graphics designed with options that can help customize study data output.

Blinding, unblinding (Used as category; no definition.)

Double-blind study

A study in which neither the study participant nor the investigator is aware of the treatment received. Studies in which Lilly personnel are blinded (in addition to the study participant and the investigator) are also considered double-blind studies (sometimes called triple-blind studies).

Unblinding

The act of providing visual or verbal access to study participant treatment information obtained from secured random number tables, or emergency identification envelopes.

Unblinding at the group level

Unblinding of the randomization scheme such that summary results are identified by treatment group, but any results for individual study participants do not include treatment-group assignment.

Unblinding at the individual level

Unblinding of the randomization scheme such that the actual treatment of an individual study participant is known.

Clinical report form (*CRF*)

The form used for recording study participants' data during a clinical study, as required by the established clinical study protocol. The form operates as a direct report to the sponsor. An electronic version of this form may be used. Sometimes called case card or case report form.

Coding Symbol and Thesaurus for Adverse Reaction Terms (*COSTART*)

A dictionary developed by the US Food and Drug Administration (FDA) that is used to describe, catalog, analyze, and report all adverse events.

Curriculum vitae (*CV*)

A document that contains a person's educational and professional background. Clinical research investigators' curriculum vitae (CVs) are collected to ensure that the investigators are qualified and have experience in the appropriate research area.

Data analysis group (*DAG*)

A group of Lilly personnel (for example, pharmacokineticists, clinical laboratory medicine personnel, medical science writers, regulatory scientists, systems analysts, statisticians) who have unblinded access to clinical study data during the study. The members of the data analysis group (DAG) perform functions such as providing interim reports to the data monitoring board (DMB), testing and validating data management programs, and developing pharmacokinetic models. The members of this group are not in contact with the study sites during the study and cannot access data to make changes or corrections to it.

Declaration of Helsinki

An international standard for the conduct of clinical trials that has been adopted as legally enforceable by many countries and jurisdictions.

Enroll/Randomize

The act of assigning a patient to a treatment. Patients who were enrolled in the trial are those who had been assigned to a treatment.

Enter/Consent

The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible to participate in the clinical trial. Patients entered into a trial were those who signed the informed consent document directly or through their legal representatives.

Ethical review board (*ERB*)

A board or committee (institutional, regional, or national) composed of medical professionals and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects or patients participating in a clinical trial are protected. Sometimes called *institutional review board* (IRB) or *independent ethics committee*.

Informed consent document *(ICD)*

An official document that is used to obtain informed consent for a clinical study from potential study participants. See *enter, enroll, screen.*

Intent-to-treat analysis

An analysis of study participants by the groups to which they were assigned by random allocation, even if the study participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Such an analysis is sometimes stated analyze as randomized.

Interim analysis

An analysis of clinical trial data that is conducted before the final analysis. The analysis compares relative treatment effects. For example, a direct comparison in a parallel or crossover study, a historical comparison, a selection of the better treatment(s) in a study, or, the separation of treatment groups in order to assess outcomes in a small number of many treatment groups (variability assessments).

Investigational new drug application *(IND)*

An application to the US Food and Drug Administration (FDA) to allow testing of a new drug in humans.

Multicenter study or trial

A study conducted simultaneously by several investigators at different locations, with identical methods and following the same protocol. The aim of this type of study is to collect data as rapidly as possible, for a combined analysis leading to a single report.

Note to file

A narrative summary that documents significant decisions, rationale, actions, protocol variations, additional instructions provided to a site during the course of a study, and any other issues or situations not adequately documented by other means.

Protocol

A document that states the background, rationale, and objectives of a clinical trial and describes its design, methodology, and organization. This document also includes statistical considerations and conditions under which the study is to be performed and managed.

Protocol addendum

The addition of special procedures being done by one or a few investigators in a large multicenter study using a single protocol.

Protocol amendment

A change in the content of a protocol that affects all investigators. An amended protocol must be provided to regulatory agencies when required.

Protocol attachments

Documents attached to the protocol to provide greater detail or explanation, such as clinical report forms (CRFs) or examples of efficacy measures.

Protocol signatures

Documentation that the investigator has read the protocol and understands it, agrees to work according to the protocol and to specific ethical principles and guidelines for good clinical practices, accepts the monitor's overseeing of the study, and will abide by the agreed-upon publication plan.

Protocol violation

Any instance in a clinical trial where the current approved protocol is not followed explicitly.

Randomization

In clinical trials, the assignment of a study participant to a treatment group in such a way that all possible treatment group assignments are equally probable, subject to certain constraints imposed by stratification or blocking (see randomization block, below), serving to avoid the introduction of known or unknown bias (for example, assignment of study participants who may be ill to the new drug).

Randomization block size

- A specified number of study participants grouped in a block to achieve the desired ratios of study participants in each treatment group. After randomization occurs for the participants within a block, the desired ratios will be achieved within that block.
- The block size selected must be a multiple of the sum of the allocation ratios (for example, if the study participants are allocated to the low dose, high dose, and control groups in ratios of 2:2:1; the block size would be a multiple of 5).
- The block size should be large enough to aid in preserving the blinding (for example, if the ratio is 1:1, a block size of 2 would not preserve blinding; because if a study participant was unblinded for an adverse event, both study participants in that block would be unblinded). Usually, each study site is assigned its own blocks in order to preserve the desired allocation within each site.
- The overall plan for blocking is called the *blocking scheme*.

Randomization codes

The identification of random treatment assignments for study participants in a clinical study. For blinded studies, the treatment assignment for an individual study participant is sealed (for example, in an envelope), and access to this information is carefully controlled. Unblinding before the completion of the study and creation of the final reporting database must be documented.

Randomization table (or random table)

The entire list of randomization codes for a study.

Screen

- The act of determining if an individual meets the minimum requirements to become part of a pool of potential candidates for participation in a clinical trial.
- In this study, screening involved invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws)].
- For this type of screening, informed consent for these screening procedures and/or tests was obtained; this consent may have been separate from obtaining consent for the study.

AD	Alzheimer's disease
AE	adverse event
ALT	alanine transaminase
ANCOVA	analysis of covariance

ANOVA	analysis of variance
A/P	anterior-posterior
ARB	adjudication review board
AST	aspartate transaminase
ATC	anatomic therapeutic class
BCPT	breast cancer prevention trial
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BSAP	bone-specific alkaline phosphatase
BSQ	binary semi-quantitative
BUN	blood urea nitrogen
CABC	Clinical Assessment of Breast Cancer
CBC	complete blood count
CI	confidence interval
CIA	clinical investigative assistant
CIB	clinical investigator's brochure
CK	creatine kinase
CK-MB	creatine kinase myocardial band
CMH	Cochran-Mantel-Haenszel test
CORE	Continuing Outcomes of Raloxifene Evaluation
CPK	creatine phosphokinase
CRA	clinical research administrator
CRO	contract research organization
CRP	clinical research physician
CS	clinically significant
CSR	clinical study report
CT	clinical trial or computed tomography
CV	cerebrovascular disease or coefficient of variation
D&C	dilatation and curettage
DDE	Dementia Diagnostic Evaluation
DMB	data monitoring board
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis or thrombophlebitis
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
EFFO	European Foundation for Osteoporosis Quality-of-Life Assessment (same as QualEFFO)
EQ-5D	formerly EuroQol
ER	estrogen receptor
ERT	estrogen replacement therapy
ET	endometrial thickness
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FTA	fluorescent treponemal antibody
GCP	good clinical practices
GGGF	Study H3S-MC-GGGF
GGGG	Study H3S-MC-GGGG
GGGH	Study H3S-MC-GGGH
GGGK	Study H3S-MC-GGGK
GGGV	Study H3S-MC-GGGV
GGHR	Study H3S-MC-GGHR
GGT	gamma-glutamyl transferase
HbA1c	hemoglobin A1c (glycosylated hemoglobin)
HCl	hydrochloride

HDL-C	high-density lipoprotein cholesterol
HRQOL	health-related quality of life
HRT	hormone replacement therapy
ICD-9-CM	International Classification of Diseases, 9th revision, clinical modification
ITT	intention to treat
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MHA-TP	microhemagglutination – *Treponema pallidum*
MHUI	McMaster Health Utilities Index
MI	myocardial infarction
MORE	Multiple Outcomes of Raloxifene Evaluation
MRI	magnetic resonance imaging
MVA	motor vehicle accident
N/A	not applicable
NCS	not clinically significant
NHP	Nottingham Health Profile
NONMEM	nonlinear mixed-effects model
NOS	not otherwise specified
NSABP	National Surgical Adjuvant Breast and Bowel Project
NTT	needed-to-treat
OC	osteocalcin
OPAQ	Osteoporosis Assessment Questionnaire
OPPS	one-page patient summaries
OSTPRS	osteoporosis
OUS	outside the United States
PE	pulmonary embolus
PEPI	Postmenopausal Estrogen/Progestin Intervention trial
PI	principal investigator
PICP	carboxy-terminal propeptide of type-I procollagen, carboxy-terminal collagen propeptide
PMP	postmenopausal
PTCA	percutaneous transluminal coronary angioplasty
PTH	parathyroid hormone
QM	quantitative morphometry
QualEFFO	European Foundation for Osteoporosis Quality-of-Life Assessment, questionnaire of the European Foundation for Osteoporosis (formerly EFFO)
RBC	red blood cell(s)
RLX	raloxifene HCl
RLX060	raloxifene HCl 60 mg/day
RLX120	raloxifene HCl 120 mg/day
RR	relative risk
RVT	retinal vein thrombosis
SAE	serious adverse events
SAS	Statistical Application Software
SCA	scientific communications associate
SD	standard deviation(s)
SEETUS	spurious elevation of endometrial thickness of undetermined significance
SERM	selective estrogen receptor modulator
SGOT	serum glutamic oxaloacetic transaminase (same as AST)
SGPT	serum glutamic pyruvic transaminase (same as ALT)
SIS	saline-infusion sonohysterography
SOF	Study of Osteoporotic Fractures

SQ	semiquantitative
SS	subject-provided words recalled as subject-provided words
ST	subject-provided words recalled as tester-provided words
T3	triiodothyronine
T4	thyroxine
TESS	treatment-emergent signs and symptoms
THIAZ	thiazide
TRHP	total raloxifene in hydrolyzed plasma
TS	subject-provided words
TSH	thyroid-stimulating hormone
TVU	transvaginal ultrasound or transvaginal ultrasonography
US	United States
VAS	visual analog scale
VS	versus
VTE	venous thromboembolic event(s) or venous thromboembolism
WBC	white blood cell(s)
WHI	Women's Health Initiative
WHO	World Health Organization
WHOART	World Health Organization Adverse Reactions Terminology

5. Ethics

5.1. Ethical Review Boards (ERBs)

Ethical Review Boards provided written approval of the study protocol and the informed consent document (ICD). The study was initiated after the principal investigator (PI) at each site obtained approval documents and copies were received by Lilly. Reports on the progress of the study were made by the PIs to the ERBs in accordance with the applicable government regulations and in agreement with policy established by Lilly.
The PI provided documentation that the ERB had approved revisions to the ICD and amendments (a) through (g) to the protocol.
Appendix 16.1.9 provides the name and address of each PI's ERB, and the name of the chairperson of each ERB.

5.2. Ethical Conduct of the Study

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

5.3. Patient Information and Consent

A properly executed, signed ICD, in compliance with the International Council on Harmonization (ICH) guideline on GCP, was obtained from each patient. The PI at each site was responsible for preparing the ICD. The PI used information provided in the most current version of the Clinical Investigator's Brochure (CIB) to prepare the ICD. The ICD was used to explain, in simple terms, the risks and benefits of the study to the patient and/or legal representative. A copy of the ICD was submitted by the PI to the ERB for review and approval prior to the initiation of the study.

The PI was responsible for obtaining informed consent from each patient or legal representative and for obtaining the appropriate signatures on the ICD prior to the performance of any protocol procedures and prior to the administration of study drug.
The PI provided a copy of the signed ICD to the patient and a copy was maintained at the investigative site.

6. Investigators and Study Administrative Structure

This multicenter study was conducted by 181 investigators at 125 study sites.
Appendix 16.1.3 contains a list of investigators. Table GGGK.6.1 lists all vendors, laboratories, and contract research organizations (CROs) used by Eli Lilly and Company during the conduct of this study. All statistical analyses were performed by Eli Lilly and Company.

The sponsor's medical officer responsible for the content of this clinical study report was Dr. Per Cantor, Eli Lilly and Company.
The coordinating investigator for this study was Dr. Steven R. Cummings of the University of California San Francisco.
Appendix 16.1.4 lists the authors of this clinical study report.

Table GGGK.6.1. Contracted Services

Organization	Role

b(4)

7. Introduction

Raloxifene, a benzothiophene selective estrogen receptor modulator (SERM) with estrogen agonist effects in bones. It has been approved for the prevention and treatment of postmenopausal osteoporosis.

- MORE was a 3-year study to support raloxifene use for the treatment of osteoporosis.
- A 1-year extension phase was added after the trial was initiated.
- Predefined secondary endpoints included the effect of raloxifene on lipids, cardiovascular disease, and breast and endometrial cancers.

This report serves to support an indication of the use of raloxifene for the prevention of breast cancer in postmenopausal women with osteoporosis. Therefore, breast cancer results from the 4th year of follow-up will be emphasized and analyses from other objectives (both primary and secondary) will be presented as supportive data.

Although women with osteoporosis are at lower risk for breast cancer than women without osteoporosis, presumably due to lower overall estrogen exposure, breast cancer is still a significant disease in this population (Zhang et al. 1997; Cauley et al. 1996). The **overall rate of breast cancer in postmenopausal women with osteoporosis in the Study of Osteoporotic Fractures (SOF) was 4.3 per 1000 patient years** and **was similar to that observed for white women aged 65 years and older in the United States** (Cauley et al. 1996). Postmenopausal women with osteoporosis have limited or no pharmacologic agents available to prevent breast cancer.

Tamoxifen, a SERM, has been studied in both the treatment and prevention of breast cancer among women at high risk for the disease but is only currently approved for prevention of breast cancer in the United States.

- Among the women treated with tamoxifen for a median of 3.5 years in the tamoxifen Breast Cancer Prevention Trial (BCPT, NSABP P-1), the risk of **invasive breast cancer** incidence was reduced by 49% and the risk of **noninvasive breast cancer** was reduced by 50%. For estrogen receptor (ER)-positive tumors, the occurrence was reduced by 69%; however, no significant reduction was found for ER-negative tumors.
- Tamoxifen was also found to have beneficial effects on the skeleton in postmenopausal women.
- However, tamoxifen has been found to have a stimulatory effect on the uterus, and patients who received tamoxifen in the P-1 trial had a 2.53-times greater risk of developing endometrial cancer than did women given placebo.
- Other adverse events that were increased by treatment with tamoxifen included stroke, pulmonary embolism, deep-vein thrombosis, and cataracts (Fisher et al. 1998).

Hormone replacement therapy (HRT) is prescribed to ease the symptoms of menopause, but many women continue the therapy after major menopausal symptoms disappear for its purported skeletal and cardiovascular benefits. Recently, data from a study of HRT versus placebo

conducted by the Women's Health Initiative (WHI) provided the first empirical data that HRT therapy does not provide cardiovascular protection and increased the incidence of coronary heart disease, stroke, and pulmonary embolism. Further, women who received HRT had in increased incidence of invasive breast cancer compared with placebo. These data have prompted many patients to reconsider hormone therapy, despite its confirmed benefits for the skeleton and colon.

Raloxifene effectively prevents and treats postmenopausal bone loss without increasing the incidence of cardiovascular disease or endometrial cancer. Because it also reduces the risk of breast cancer, raloxifene is an important therapy for postmenopausal women with osteoporosis who are concerned about their risk of breast cancer.

8. Study Objectives

8.1. Primary Objective

The primary objectives of this clinical trial were as follows:

- To establish the effect of long-term treatment with raloxifene, compared with placebo, on the rate of new vertebral fractures in osteoporotic postmenopausal women with and without prevalent vertebral fractures
- To establish the safety of chronic administration of raloxifene in postmenopausal women with osteoporosis
- To establish the effect of long-term treatment with raloxifene compared with placebo on lumbar spine and femoral neck bone mineral density (BMD) in postmenopausal women with osteoporosis.

8.2. Secondary Objectives

The secondary objectives of this clinical trial were as follows:

- To establish the effect of long-term treatment with raloxifene, compared with placebo, on total body bone mineral content (BMC) and radial BMD in postmenopausal women with osteoporosis
- To establish the effect of long-term treatment with raloxifene, compared with placebo, on the rates of new nonvertebral fractures alone and of nonvertebral and vertebral fractures combined in postmenopausal women with osteoporosis
- To establish the effect of long-term treatment with raloxifene, compared with placebo, on biochemical markers of bone metabolism in postmenopausal women with osteoporosis
- To establish the effect of long-term treatment with raloxifene, compared with placebo, on serum lipids and other laboratory markers of cardiovascular risk in postmenopausal women with osteoporosis
- To quantify medical resources used by patients treated with raloxifene so that a subsequent incremental cost-effectiveness analysis could be performed
- To assess the impact of raloxifene on quality of life in osteoporotic women with prevalent vertebral fractures

- To assess the possible impact of long-term treatment with raloxifene on cognitive and neuropsychomotor function, risk of cardiovascular disease, and risks of breast and endometrial cancer
- To determine the effect of long-term treatment with raloxifene on the prevalence of Alzheimer's disease (AD) in postmenopausal women with osteoporosis
- To determine the effect of long-term treatment with raloxifene on the prevalence of dementia associated with cerebrovascular (CV) disease in postmenopausal women with osteoporosis
- To determine the effect of long-term treatment with raloxifene on the prevalence of all causes of dementia in postmenopausal women with osteoporosis.

9. Investigational Plan

9.1. Overall Study Design and Plan: Description

- This was a **Phase 3, multicenter, double-blind, placebo-controlled, randomized clinical trial that enrolled 7705 postmenopausal women with osteoporosis.** For the purpose of the primary endpoints, women were enrolled in two separate substudies. **These sub-studies were considered together for the analysis of the breast cancer endpoint.**
- **Substudy I** included postmenopausal women with a low BMD (BMD 2.5 standard deviations [SD] or more below normal peak bone mass for healthy, premenopausal women either at the femoral neck or at the lumbar spine), and
- **Substudy II** enrolled postmenopausal women with at least one moderate or at least two mild vertebral fractures in the presence of low BMD (as specified above) or at least two moderate vertebral fractures without regard to BMD.

Patients were enrolled at an approximate ratio of 2 (to Substudy I) to 1 (to Substudy II) and randomly assigned to one of three treatment groups:

- Raloxifene HCl 60 mg/day
- Raloxifene HCl 120 mg/day
- Placebo

- All patients were supplemented with calcium and vitamin D.

The study consisted of 4 phases:

- Screening phase
- Enrollment phase
- Double-blind core treatment phase of 36 months
- Double-blind extension phase of 12 months

(Figure GGGK.9.1 presents the study design).

- From the beginning of the enrollment phase to the start of the core treatment phase, all patients received placebo in a single blind manner.

- All patients in all groups received daily calcium and vitamin D supplementation throughout the study from the enrollment phase through the extension phase. Patients received double-blind study materials (either raloxifene or placebo) daily for 48 months (4 years).
- Visits occurred at screening (Visit 888), enrollment (Visit 1), baseline (Visit 2), Months 3, 6, and 12 of the first year (Visits 3, 4, and 5, respectively), and every 6 months thereafter (Months 18 through 48, corresponding to Visits 6 through 11).

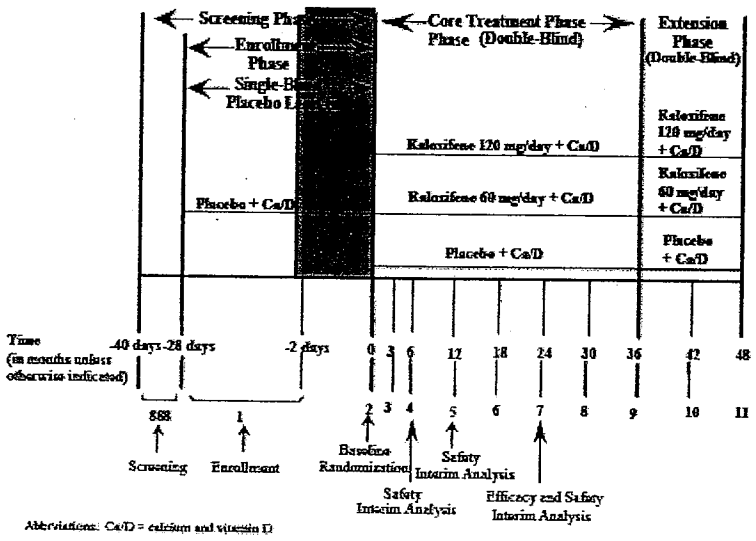


Figure GGGK.9.1. Study design for study H3S-MC-GGGK.

All patients enrolled in Study GGGK underwent **screening mammography** within 12 months prior to study entry (screening), followed by an optional mammography after 1 year of treatment (Visit 5) and mandatory annual mammography screenings thereafter (Visits 7, 9, and 11).

Mammograms were read by radiologists for the local investigative sites; serial mammograms from **all identified cancer cases** were **re-read centrally by a radiologist with expertise in mammography**. The central reader first assessed the baseline films for each case without knowledge of diagnosis, treatment group assignment, or follow-up film findings. A number of non-cancer controls were included in this review process to reduce ascertainment bias. The central reader read the follow-up films for each case, and these readings, compared with the baseline central readings, were used to ascertain whether cases had evidence of being preexisting or were de novo. *To reduce ascertainment bias, retrospective identification of a "preexisting" lesion not initially identified by either local or central mammographic review was not used to classify lesions as preexisting.*
Finally, an independent, blinded adjudication board convened periodically to confirm pathologic diagnosis (for example, confirm breast cancer diagnosis and judge whether the pathology

represents invasive or noninvasive breast cancer) and make clinical judgments to determine whether the breast cancer was likely preexisting or de novo on clinical and/or radiographic grounds.

In cases where local or central mammographic review indicated that **a baseline suspicious mammographic lesion** was present, the adjudication panel confirmed that this radiographic lesion was, in fact, related to the subsequently identified cancer. Only in cases where this correlation was identified was a case listed as "preexisting." In some cases, the panel could not identify with certainty whether a case was preexisting or de novo; these cases were listed as "indeterminate." Section 11.4.3.2 describes the adjudication process used for cases of breast cancer.

Vertebral fracture prevalence was assessed by spinal x-rays at screening, and incident vertebral fractures were assessed at Visits 7, 9, and 11 (years 2, 3, and 4, respectively).
The rate of **nonvertebral fractures** alone and the pooled rate of vertebral and nonvertebral fractures were secondary endpoints. Nonvertebral fractures were assessed when clinically indicated, and diagnosis was confirmed by a radiologist's written report or by x-ray.

Femoral neck BMD was measured at the screening visit. Women with a femoral neck BMD measurement between 2.5 and 2.0 SD below normal peak bone mass for healthy, premenopausal women had a lumbar spine BMD measurement performed also at the screening visit.

A gynecological examination was performed in all patients at Visit 1 and was optional at all other annual visits. A pelvic examination and uterine ultrasound were performed in a subset of patients at Visits 1, 5, 7, 9, and 11.

The incidence of newly occurring, clinically apparent **cardiovascular disease** and **endometrial cancer** was assessed at Visits 2 through 11. **Other safety information**, such as vital signs and adverse events, was assessed at the time of all return visits and at the time of initial reports.

Interim analyses were performed near the time when all active patients had completed Visit 4 (6 months), Visit 5 (12 months), and Visit 7 (24 months) (Section 9.7.1.7). The first and second analyses assessed safety measures only, and the 24-month analysis evaluated the safety and efficacy of raloxifene.

After 36 months (3 years), patients were allowed to continue on the same treatment into **an extension phase**.

9.2. Discussion of Study Design, Including the Choice of Control Groups

The occurrence of breast cancer was assessed because estrogen antagonist action of raloxifene on reproductive tissue is expected to have a protective effect with respect to this disease. Because

full-dose, cyclical estrogen therapy could not be used as the comparator in a long-term, truly blinded study, placebo was chosen as the comparator.

- This study was double-blinded to ensure that the expectations of the patients and physicians did not influence the assessment of clinical response.
- Randomization was chosen to minimize bias.

9.3. Selection of Study Population

Patients were **enrolled based on bone criteria** to fulfill the primary endpoints.

- Patients with known history of carcinoma of the breast were not allowed to enter; however, women **were *not* enrolled based on any increased risk for developing breast cancer.**

All patients were postmenopausal women with primary osteoporosis.

- Postmenopausal status was established by a history of amenorrhea for at least 2 years.
- For women with indeterminate menopause because of hysterectomy, postmenopausal status was confirmed by serum estradiol <73 pmol/L or <20 pg/mL and follicle-stimulating hormone (FSH) >30 IU/L or >30 mIU/mL.

In **Substudy I**, the presence of osteoporosis was established by a femoral neck or lumbar spine BMD of 2.5 SD or more below the normal range of peak bone mass for healthy, premenopausal women.

In **Substudy II**, the presence of osteoporosis was established **either** by the presence of at least one moderate or at least two mild vertebral fractures and by a femoral neck or lumbar spine BMD measurement 2.5 SD or more below the normal range of peak bone mass **or** by the presence of at least two moderate vertebral fractures, regardless of BMD.

9.3.1. Inclusion Criteria

Study patients were enrolled based on **BMD and fracture criteria; baseline breast cancer risk was *not* an inclusion criterion for this study.**

The study patients were ambulatory postmenopausal women, up to 80 years of age, inclusive. All women were free of severe or chronically disabling conditions, had a life expectancy of at least 5 years, were expected to remain ambulatory throughout the entire study, and were expected to return for follow-up visits.

- All women had their last menstrual period at least 2 years before beginning the study. Postmenopausal status was verified in women who had a hysterectomy before menopause (serum estradiol <73 pmol/L or <20 pg/mL and FSH >30 IU/L or >30 mIU/mL).
- Women with a femoral neck or lumbar spine T-score ≤ 2.5 were entered into Substudy I.
- If a woman had either 1) at least one moderate or at least two mild vertebral fractures and a femoral neck or lumbar spine T-score ≤ 2.5, or 2) at least two moderate vertebral fractures, regardless of BMD, she was entered into Substudy II.

9.3.2. Exclusion Criteria

- Patients were excluded if they had known current bone disorders other than primary osteoporosis, such as hyperparathyroidism, Paget's disease, renal osteodystrophy, or osteomalacia.
- Also, patients experiencing clinically severe postmenopausal symptoms at the beginning of the study that required estrogen-replacement therapy (ERT) were excluded.
- Patients could not enter if they had known, suspected, or history of carcinoma of the breast or estrogen-dependent neoplasia (except for hysterectomized patients with a history of carcinoma in situ of the uterus) or if they had any history of cancer within the previous 5 years (except for excised superficial lesions such as basal cell carcinoma and squamous cell carcinoma of the skin).
- Patients could not have pathologic fractures and could not be entered if a satisfactory baseline thoracic and lumbar x-ray could not be obtained.
- Certain hormonal medications, osteoporosis medications, and steroids were not allowed within a predefined time prior to study entry. Other exclusion criteria included abnormal uterine bleeding; history of deep venous thrombosis (DVT), thromboembolic disorders, or cerebral vascular accident within the past 10 years; endocrine disorders requiring pharmacologic therapy except for type II diabetes; not biochemically euthyroid; acute or chronic liver disease; impaired kidney function; active renal lithiasis; and known malabsorption syndromes.

9.3.3. Removal of Patients from Therapy or Assessment

Patients were discontinued from the study in ALL of the following cases:

- The patient died.
- The patient was lost to follow-up (that is, patients who, after having missed one visit, did not return by the time of the following visit).
- The patient withdrew her informed consent to further participate in any study procedures.

If a patient who did not meet criteria for enrollment was inadvertently enrolled, she should have been discontinued from the study unless there was an ethical reason to have her remain in the study. In these cases, the investigator obtained specific approval for the patient to continue in the study from the Lilly clinical research physician (CRP).

9.4. Treatments

9.4.1. Treatments Administered

- No study materials were taken during the initial **screening phase**.
- Starting at Visit 1, the **enrollment phase**, patients were instructed to take open-label supplements of approximately 500 mg/day calcium and approximately 400 to 600 IU/day of vitamin D. (If a patient was unable to tolerate either of these supplements, the

investigator could decide to reduce or discontinue the supplementation. However, the patient continued to participate in the study.) In addition, all patients received a single-blind placebo throughout the enrollment phase.

- During the **core treatment phase** (beginning at Visit 2), patients were instructed to take two double-blinded study medication tablets each morning. Each tablet contained either 60 mg of raloxifene or placebo.
- During the **extension phase** (beginning at Visit 9), patients continued to take two double-blinded study medication tablets each morning. Calcium and vitamin D supplements were taken throughout the core treatment and extension phases as instructed by the investigator.

At Visit 2, a medication kit number was assigned after a patient qualified for the study in accordance with the inclusion and exclusion criteria. Both the medication kit numbers and the patient numbers were assigned in sequence, beginning with the lowest numbers available.

9.4.2. Identity of Investigational Product(s)

Placebo material for the enrollment phase (single-blind placebo lead-in) was provided in separate kits.
The randomized study material for the core treatment and extension phases were packaged according to a random-number table in numbered kits. At each visit, the patient returned unused study medication so that the remaining tablets could be counted. The number of tablets remaining was recorded.

9.4.2.1. Primary Study Material

Raloxifene HCl was provided as oral tablets, each containing 60 mg of drug.

- A dose of 60 mg of raloxifene HCl is equivalent to 55.71 mg of raloxifene.
- A dose of 120 mg of raloxifene HCl is equivalent to 111.42 mg of raloxifene.

9.4.2.2. Placebo Study Material

Placebo was provided in tablets identical in appearance to the raloxifene tablets.

9.4.2.3. Supplements

- Approximately 500 mg/day elemental calcium was provided as open-label calcium tablets containing approximately 250 or 500 mg of elemental calcium per tablet.
- A vitamin D supplement containing approximately 400 to 600 IU of vitamin D was also provided.

9.4.3. Method of Assigning Patients to Treatment Groups

- Upon entry into the screening phase, a patient number was assigned to each participant who had any screening procedure performed.
- At Visit 2, patients were randomly assigned to one of three treatment groups: placebo, raloxifene HCl 60 mg/day, or raloxifene HCl 120 mg/day.

9.4.4. Blinding

This was a double-blind study.

- Emergency codes, generated by a computer drug-labeling system, were available to the PI. These codes, which revealed the patient's treatment group when opened, could be opened during the study only if the choice of follow-up treatment depended on the patient's therapy assignment. The PI was instructed to make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment.
- If a patient's treatment assignment was unblinded, the Lilly CRP was to be notified immediately by telephone. After the study, the PI was to return all sealed and any opened codes.
- If a PI, site personnel performing assessments, or patient was unblinded, the patient was to be discontinued from the study unless there were ethical reasons to have the patient remain in the study. In these special cases, the PI was to obtain specific approval from Lilly's CRP for the patient to continue in the study.
- The following Lilly personnel were also blinded to treatment assignments: CRPs, clinical research administrators (CRAs), clinical investigative assistants (CIAs), and their management.
    - However, **if a serious adverse event occurred**, the CRPs, the CRAs, and/or CIAs were unblinded to the patient's treatment in order to enter the drug name into the Lilly safety database. In these instances, the investigator and the patient remained blinded.
- To maintain the blinding of this study to Lilly personnel and to permit interim analyses to be conducted without affecting study integrity, a data monitoring board was created.
- After all clinical data from the first 24 months of the core treatment phase were received and any known data inconsistencies were resolved, Lilly personnel were unblinded in a manner to minimize bias.

9.4.5. Prior and Concomitant Therapy

- With noted exceptions, none of the excluded medications listed as exclusion criteria was allowed during the studies. However, patients who received protocol-excluded concomitant therapy were not necessarily discontinued from the study.
- Concomitant use of other osteoporosis medications, including bisphosphonates, calcitonin, or fluorides, **was allowed as clinically indicated *during the extension phase*** (Visits 9 through 11). Use of these medications during the extension phase did not require approval by a Lilly CRP. Patients taking these medications could continue concomitant use of the double-blind study medication.

- Patients who began taking sex hormones and related compounds (such as systemic estrogens, combined hormone replacement therapy (HRT), phyto-estrogens, anabolic androgens or any sex hormone agonists/antagonists), other than estriol up to 2 mg/day or intra-vaginal estrogen up to three times per week, were instructed to stop the double-blind study medication immediately. They could resume the double-blind study medication as soon as they discontinued treatment with the above-mentioned compounds.
- All medications (other than study medication) taken during the study were recorded on the case report form (CRF). Any use of excluded medication (except as indicated during the extension phase) was a violation of the protocol and was documented. Section 10.2 provides a discussion of significant protocol violations.

9.4.6. Treatment Compliance

Investigators assessed compliance with study medication at each visit. Compliance was assessed by counting returned medication. All unused medication was returned to Lilly.

9.5. Efficacy and Safety Variables

9.5.1. Efficacy and Safety Measurements Assessed and Study Schedule

The following efficacy measures were collected at the times shown in Table GGGK.9.1 (Study Schedule). Appendix 16.1.2 contains a sample CRF.

- **Mammograms** were obtained at baseline (within 12 months of randomization) and at regular intervals throughout the study. If a mammogram was not acceptable to a patient, an ultrasound of the breast was performed instead.
- **Femoral neck BMD** determinations were performed at screening and at some follow-up visits (Table GGGK.9.1). Women with a femoral neck BMD measurement *between 2.5 and 2.0 SD below normal* peak bone mass also had a **lumbar spine BMD** measurement performed at screening to determine their eligibility.
    - Women with a femoral neck BMD *less than 2.0 SD below normal* peak bone mass may have had a lumbar spine BMD performed only if historical BMD data documented that the patient's lumbar spine BMD was 2.5 SD or more below normal peak bone mass.
    - Patients with a femoral neck or lumbar spine BMD 2.5 SD or more below the mean peak bone mass for healthy, premenopausal women were eligible for further screening.
- Patients were interviewed for any clinically evident **vertebral and nonvertebral fractures** that occurred before entering the studies. At each follow-up visit, patients were interviewed for clinically evident fractures that might have occurred since the most recent visit. All fractures were documented with the radiologist's written report or the x-ray films.

- At screening, lateral and anterior-posterior (A/P) **thoracic and lumbar spinal x-ray films** were taken to determine the presence of vertebral fractures at baseline (prevalent vertebral fractures). Depending on the absence or presence of prevalent vertebral fractures, eligible patients were enrolled either in Substudy I or in Substudy II. To determine the rate of incident vertebral fractures and deformities, lateral x-ray films of the thoracic and lumbar spine were repeated as indicated in the study schedule (Table GGGK.9.1).
- **Total body bone mineral content (BMC)** and **radial BMD** were assessed in a subset of patients.
- **Biochemical markers of bone metabolism** (osteocalcin, bone-specific alkaline phosphatase, type I collagen fragment, carboxy-terminal pro-peptide of type I pro-collagen [PICP], urinary calcium excretion, and urinary creatinine) were measured in a subset of patients. Aliquots of serum and urine from a subset of patients are being stored for 5 years beyond the end of the study to allow the future assessment of additional parameters. To rule out persisting deficiency of calcium or vitamin D, parathyroid hormone and 25-hydroxyvitamin D were measured in all patients.
- **Biochemical markers of cardiovascular risk** (serum lipids, fibrinogen, and HbA1c) were measured at Visits 2, 4, 5, 7, 9, and 11 in a subset of patients. (Serum lipids included apolipoprotein A1, apolipoprotein B, total cholesterol, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and triglycerides.)
- A standardized, sensitive battery of **neuropsychometric tests** was administered to assess cognitive and neuro-psychomotor function. This battery consisted of the Short Blessed to determine if dementia develops; the Trail Making Test A and B to measure psychomotor speed; the Word Fluency Test for the assessment of verbal production and semantic memory; the Word List Memory and Word List Recall Test for the assessment of memory of recently acquired information; and the Affective Rating Scale for the self-assessment of mood. In addition, muscle strength and balance were assessed using standardized methods. The neuropsychometric tests were only performed in those countries in which translation and validation had occurred.

The following safety measurements were collected at the times shown in Table GGGK.9.1 (Study Schedule).

- During the study, **adverse events** were collected at every visit, regardless of relationship to study medication. These events were captured as actual terms and coded to COSTART terms by blinded Lilly clinical personnel.
- All **concomitant medications** taken during the study were recorded.
- During the study, standard laboratory tests, including chemistry, hematology, and urinalysis panels, were collected at regular intervals. Total cholesterol, HDL-C, LDL-C, triglycerides, FSH, estradiol, thyroxine, triiodothyroxine resin uptake (or equivalent), and TSH tests were completed at baseline.
- During the study, vital signs, including blood pressure (systolic and diastolic), heart rate, weight, and height, were collected at regular intervals.
- During the study, physical examinations, including gynecological exams, pelvic exams (subset), and uterine ultrasounds (subset) were conducted at regular intervals.

- An electrocardiogram (ECG) was collected at baseline and at regular intervals throughout the study.

Table GGGK.9.1. Study Schedule

Visit:	Screening	Enrollment	Core Treatment								Extension	
	888	1	2	3	4	5	6	7	8	9	10	11
Activity Month:	≤40 days before baseline	≤28 days before baseline	0	3	6	12	18	24	30	36	42	48
Sign informed consent document–screening phase[a]	X											
Sign informed consent document–enrollment phase[a]		X										
Clinical Assessments[b]												
Weight, blood pressure, and pulse		X	X	X	X	X	X	X	X	X	X	X
Height		X			X	X		X		X		X
History	X											
Physical examination		X										
Gynecological examinations[c]		X				X[d]		X[d]		X[d]		X[d]
Pelvic examination and uterine ultrasound, subset[e]		X				X		X		X		X
Assessment of cardiovascular and gynecological disease		X	X	X	X	X	X	X	X	X	X	X
Record of adverse event reporting[f]			X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[b]												
CBC, chemistry screen, routine urinalysis with microscopic examination		X				X		X		X		X
Additional enrollment laboratory tests[g]		X										
Biochemical bone markers, all patients[h]		X	X		X							
Biochemical bone markers, subset[i,j]			X		X	X		X		X		

Laboratory Assessments[b] (cont'd)												
Markers of cardiovascular risk, subset[k]			X		X	X		X		X		X
Study drug plasma concentration, subset				X	X	X	X	X		X		X
Technical Assessments[b]												
Femoral neck BMD determinations[l]	X	X[m]				X		X		X		X
Lumbar spine BMD determinations[l]		XX[n]				X		X		X		X
Total body bone mineral content and radial BMD determinations, subset			X					X				
Spinal x-ray films[l,o]	X[l]							X[o]		X[o]		
Assessment of clinical fractures		X	X	X	X	X	X	X	X	X	X	X
Chest x-ray[p]		X[q]										
Mammogram[r]		X				X[s]		X		X		X
ECG		X						X				X
Cognitive/Neuropsychomotor assessment			X		X	X		X		X		X
Dementia Diagnostic Evaluation											<-X[t]->	
Resource utilization, Substudy II			X	X	X	X	X	X	X	X		
Quality of life, Substudy I, subset[u]			X									
Quality of life, Substudy II[u]			X			X		X		X		
Miscellaneous[b]												
Patient number assigned	X											
Randomization[v]			X									
Study drug administration[w]			<--------									--------->

a At some sites, a single ICD may have been used for both screening and enrollment phases. At these sites, patients would have only needed to sign the ICD at screening.
b When a patient discontinued the study after Visit 2 and before Visit 11, all procedures required for Visit 11 were performed, if appropriate in the opinion of the investigator or sponsor. (Spinal radiographs were repeated only if more than 6 months had elapsed since the last x-ray). In addition, patients who discontinuing prior to Visit 11 had safety laboratories performed, and those in the defined subset sites had study drug plasma concentration and cardiovascular markers obtained.
c Included pelvic and breast examinations and Papanicolaou's test. If pelvic examination and Papanicolaou's test had been performed less than 3 months before the enrollment, these tests did not have to be repeated provided that the investigational site received a record of the results.
d The gynecological exams at Visits 5, 7, 9, and 11 were optional.
e An abdominal ultrasound of the uterus may have been performed *only* if an intra-vaginal uterine ultrasound was not acceptable to a patient. If the ultrasound showed abnormal results, please refer to protocol Section 3.9.4.4 (in Appendix 16.1.1).
f Any event suggesting the presence of a newly occurred fracture must have been followed by an x-ray assessment. (See also assessment of clinical fractures in the Study Schedule.)
g Enrollment laboratory tests included total cholesterol, HDL-C, LDL-C, triglycerides, FSH, estradiol, thyroxine, triiodothyroxine resin uptake (or equivalent), and TSH.
h Biochemical markers of bone metabolism measured in all patients included parathyroid hormone and 25-hydroxyvitamin D.
i Whenever serum and urine were collected for biochemical bone marker assays, an additional 7 mL of serum and 13 mL of urine were collected for storage.
j Biochemical markers of bone metabolism measured in a subset of patients includes osteocalcin, bone-specific alkaline phosphatase, type I collagen fragment,
carboxy-terminal propeptide of type I procollagen (PICP), urinary calcium excretion, and urinary creatinine.
k Biochemical markers of cardiovascular risk factors included apolipoprotein A1, apolipoprotein B, total cholesterol, HDL-C, LDL-C, triglycerides, fibrinogen, and HbA1c.
l If the femoral neck or lumbar spine BMD determinations or the spinal x-rays had been performed within the 14 days before the patient entered the screening phase, these tests did not have to be repeated provided the investigative site received a record of these test results and the original x-ray film before Visit 1.
m The second femoral neck BMD determination may have been performed any time during the period beginning with Visit 1 and ending with Visit 2.
n Two lumbar spine BMD determinations were performed between the period beginning with Visit 1 and ending with Visit 2, unless a patient had a lumbar spine BMD determination performed at screening. These determinations may have been performed on the same date. If a lumbar spine BMD measurement was performed at screening, only one lumbar spine BMD determination was performed during the period beginning with Visit 1 and ending with Visit 2.
o Lateral and A/P thoracic and lumbar spinal x-ray films were performed at screening. At the follow-up visits, only lateral x-ray films were performed.
p If any of these tests had been performed no more than 1 year before beginning Visit 1, the test did not have to be repeated provided the investigational site received a record of the results before Visit 2.
q The chest x-ray at Visit 1 was optional.
r If a mammogram was not acceptable to a patient, an ultrasound of the breast may have been performed instead. If a mammogram or breast ultrasound (sonogram) had been performed no more than 3 months before beginning Visit 1, the procedure did not have to be repeated provided the investigational site received a record of the results before Visit 2.
s Mammogram at Visit 5 was optional. Mammograms at Visits 1, 7, 9, and 11 were mandatory. If a mammogram was not acceptable to a patient, an ultrasound of the breast may have been performed instead.
t The Dementia Diagnostic Evaluation (DDE) was performed on patients with evidence of a cognitive deficit.
u The quality-of-life instruments were to be administered after laboratory tests were drawn but prior to any other visit procedures.
v Randomization occurred after specimens for all baseline laboratory tests were obtained.
w Based on the 2-year results and ethical considerations, the DMB could recommend that patients in ineffective treatment groups be re-randomized to effective treatment at 3 years.

9.5.2. Appropriateness of Measurements

- Efficacy assessment methods used in this protocol have been described in the literature and are generally regarded as reliable, accurate, and relevant.
- The quality-of-life questionnaires have been validated and tested for reliability, sensitivity to change, and for cross-cultural differences. Lilly had obtained legal permission to use each instrument from the appropriate authors.

9.5.3. Breast Cancer Efficacy Variable

- Breast cancer was a **predefined secondary endpoint** for this study.
- Analyses of breast cancer data were **originally conducted to determine the safety profile of raloxifene in the breast**; however, these analyses showed significantly fewer cases of breast cancer in raloxifene-treated patients compared with those who received placebo. Therefore, further analyses to determine risk reduction of breast cancer were performed and are presented in this report.

9.5.4. Drug Concentration Measurements

- Blood was collected from all patients at selected sites during Visits 3, 4, 5, 6, 7, 9, and the early discontinuation visit (when applicable) to measure raloxifene concentrations in a subset of patients receiving raloxifene.
- Dates and times for the last and penultimate doses of study drug prior to blood collection plus the date and time of blood collection were recorded.

9.6. Data Quality Assurance

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

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

A central laboratory was used to maintain consistency of methods and to combine laboratory data across study sites and/or across studies (see Section 12.4.2 for a discussion of lab analyses; see Appendix 16.1.12 for reference ranges).

To assure the safety of participants in the study and to assure accurate, complete, and reliable data, the investigator kept records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study.

Lilly or its representative periodically checked a sample of the patient data recorded against source documents at the study site.

9.7. Statistical Methods and Determination of Sample Size

9.7.1. Statistical and Analytical Plans

The protocol for this study was approved on 27 July 1994 and was amended was amended 7 times, with the latest amendment approved on 01 September 1998. Section 9.8 provides further details about protocol amendments. This section addresses the planned statistical analyses prior to unblinding as described in the protocol and other efficacy analyses that are relevant for this report (specifically, for breast cancer).

Data in this report represent 48 months of follow-up from the study: 36 months of the double-blind treatment phase plus a 12-month double-blind extension phase. The analyses presented in this report are based on data contained in the reporting databases, archived production databases used for analysis purposes that contain data collected on CRFs. The reporting database for all data except adjudicated breast cancer cases was validated and locked for analysis on 20 November 1999. The reporting database for breast cancer was locked on 6 July 2002.

Three interim analyses were performed after approximately 6, 12, and 24 months of follow-up had been completed. The final analysis of the double-blind treatment phase was conducted after 36 months of follow-up and has previously been reported.

9.7.1.1. Analyses of Breast Cancer Data

- **All non-bone secondary endpoint** treatment comparisons were performed at the two-sided 0.05 level of significance.
- The statistical significance of any pair-wise comparisons was dependent on the significance of the overall treatment comparison.
- To confirm the parametric results, the data were then ranked and reanalyzed.
- For the breast cancer endpoint, these analyses showed a statistical reduction in breast cancer incidence among patients who received raloxifene compared with patients assigned to placebo. Thus, further analyses were performed to determine the treatment effect of raloxifene (if any) on the breast. The methods used for these analyses are described throughout the discussion of breast cancer efficacy (Section 11.4.3).

9.7.1.2. Analyses of Protocol-Specified Primary Endpoints

The **primary efficacy measures** were the **changes in lumbar spine and femoral neck BMD** *and* the **rate of newly occurring vertebral fractures.**

- The **BMD measures** were analyzed using an analysis of variance (ANOVA) model on the change from baseline to endpoint including terms for treatment and geographical region.
- The steering committee for the study defined the regions to be used in the analysis. The treatment-by-region interaction was removed from the model if it was not significant at a 0.10 level. Treatment effects were tested at a 0.05 level in each of the studies.
- Significance of pair-wise comparisons of raloxifene groups with placebo depended on the overall significance.

- The **primary fracture analyses** compared the fracture rates of the three treatment groups, where fracture rate was defined as the total number of new fractures divided by the total time in the studies (up to the last visit). The fracture rates were analyzed using a weighted ANOVA model incorporating the effects of treatment, region, and substudy (for the pooled analyses). The individual fracture rates may have been transformed to stabilize the variance and approximate normality (for instance, a square root transformation in the case of Poisson fractures). The method proposed by Box and Cox (Box and Cox 1964) could find such a transformation, if necessary. Each individual's transformed rate would then be weighted by her time in a substudy to reduce variance.
- Because of the low fracture rate, it may have been necessary to pool sites into geographic regions to assess treatment by site interaction in the ANOVA model. If this interaction was not significant at a 0.10 level, it was excluded from the model. If an interaction was significant, the nature of the interaction was explored descriptively. A secondary analysis on the fracture data compared the proportion of patients with at least one new fracture in each active treatment group to placebo using Pearson's chi-square test.
- The primary efficacy variable was the rate of new vertebral fractures, which was tested for a trend ($p<0.2$) in each study and at a two-sided 0.05 level of significance pooled across both studies, using study as a blocking factor.

9.7.1.3. Analyses of Protocol-Specified Secondary Endpoints

Secondary efficacy variables included the rate of **new nonvertebral fractures** as well as the rate of **vertebral fractures and nonvertebral fractures combined** and were analyzed as described for the primary endpoints (Section 9.7.1.2). Secondary BMD efficacy measures (lumbar spine, femoral neck, radial, and total) as well as the other secondary efficacy measures (that is, biochemical markers of bone metabolism and of cardiovascular risk such as lipids) and safety measures (that is, laboratory data and vital signs) were analyzed using an ANOVA model with treatment and investigator as described earlier. The fracture endpoints were tested for trends ($p<0.2$) within each study.

9.7.1.3.1. Analysis of Cognitive Assessments

- All treatment comparisons were intent-to-treat between raloxifene and placebo or among treatment arms. Primary analyses were based on outcome assessments made by the Dementia Adjudication Committee. For each patient, **the primary outcome variable was diagnosis of AD** (a binary [yes/no] variable), as defined by the Dementia Adjudication Committee.
- To relate the risk of AD with the other potential risk factors, generalized linear modeling technique was used. The relative risk of AD for each raloxifene group compared with placebo was computed controlling for known extraneous sources of variation, such as country of origin. The results of this analysis were presented in terms of relative risks and 95% confidence intervals of the relative risks.
- As an additional analysis, the prevalence of AD was analyzed using a Pearson chi-square test statistic on the proportion of patients with AD in each of the three treatment groups. In this analysis, dose-response trend was analyzed using a gamma statistic. Similar analyses of the prevalence of AD were performed after removing the patients with evidence of preexisting dementia, as identified by the Dementia Adjudication Committee.
- The effect of raloxifene on the prevalence of dementia associated with cardiovascular disease, and on the prevalence of all causes of dementia, was determined using the categorical analyses methods described above.

9.7.1.3.2. Health Outcomes/Quality of Life Analyses

- The primary health outcomes analyses were the frequencies and percentages of patients having at least one **specified overnight hospitalization** or **osteoporotic fracture**.
    - Comparison among the treatment groups was made by using Pearson's chi-square tests, when applicable. For each patient, the number of specified overnight hospitalizations or osteoporotic fractures per exposure time (30 days) was calculated as well as corresponding descriptive statistics.

- Univariate analyses (t-tests and/or Pearson's chi-square tests) by therapy were performed for patient characteristics and **primary reasons for discontinuation**.

- The **quality-of-life parameters measured on a continuous scale** were summarized for each visit and treatment group. Also, changes in total score from baseline (Visit 2) and each visit were computed. Finally, an endpoint value was obtained for each parameter that was the last measurement observed for each patient. Significant demographic and clinical variables were used to evaluate within-group changes in quality-of-life scores over time. Depending on final sample sizes and distributed characteristics of quality-of life measures, nonparametric tests may have been used to evaluate treatment group differences.

9.7.1.3.3. Pharmacokinetic/Pharmacodynamic Analysis

- Plasma concentrations of raloxifene were determined from blood samples obtained from a subset of patients receiving raloxifene treatment. Plasma concentrations of **total raloxifene in hydrolyzed plasma** were also measured. Total raloxifene in hydrolyzed plasma represents the combined concentrations of raloxifene and the three glucuronide conjugates (raloxifene-4'-glucuronide, raloxifene-6-glucuronide, and raloxifene-6,4'-di-glucuronide).
- Plasma concentration data were pooled and analyzed by means of descriptive statistics. Raloxifene plasma concentration data were also analyzed using a population pharmacokinetic program (nonlinear mixed-effects model [NONMEM]).
- Population pharmacokinetic parameters, as well as effects of demographic values (for example, age and weight) on the parameters, were examined. Detailed information regarding population pharmacokinetics and pharmacodynamic analyses is located in the report titled "Study H3S-MC-GGGK (36-Month Data) Raloxifene Hydrochloride and Placebo in the Treatment of Postmenopausal Women with Osteoporosis: Population Analyses".

9.7.1.3.4. Safety Analyses

The incidence of adverse events was analyzed using the Cochran-Mantel-Haenszel set of techniques, stratifying on investigator.

9.7.1.3.5. Subgroup Analyses

The literature has suggested that response to treatment for osteoporosis may differ for several factors. The following is a list of potential subgroups which were analyzed for differential treatment effects. The analysis of these subgroups was exploratory in nature; therefore, no confirmatory results will be presented.

- Initial number of vertebral fractures
- Initial bone turnover rate (type I collagen fragment)
- Initial BMD
- Body mass index
- Number of years postmenopausal
- Family history of osteoporosis (Yes, No)
- Smoking status (Yes, No)
- Race
- Age
- Prior or concomitant medications (thiazide diuretics, estrogen use, bisphosphonate use)

These subgroups were appropriately categorized for the purposes of analysis. Analysis of the categorized subgroups used ANOVA with treatment, investigator, and subgroup as fixed effects. The primary interest was in the significance of the subgroup-by-treatment interaction term, which was tested at the nominal 0.10 level of significance for all subgroups. If an interaction was significant, the nature of the interaction was explored descriptively.

9.7.1.4. Patient Disposition

9.7.1.4.1. Early Discontinuation

Every effort was made to keep participating patients in the trial. Patients who discontinued study drug temporarily or permanently for personal reasons did not necessarily have to be discontinued from the study, provided they were willing to return for follow-up visits and to comply with the diagnostic study procedures. These patients may have followed a modified visit schedule. Early discontinuation from the study may have occurred because of request of patient, decision of the investigator, or decision of the sponsor. Acceptable reasons that may, but did not necessarily, lead to early discontinuation included the following:

- Adverse events
- Development of exclusion criteria during the course of the study
- Severe noncompliance or protocol violation

The following patients were discontinued from the studies in ALL cases:

- Patients who died
- Patients who were lost to follow-up
- Patients who withdrew their informed consent to further participate in any study procedures

When a patient discontinued the study after Visit 2 and before Visit 11, the following occurred:

- She was seen as soon as possible by the investigator
- All procedures required for Visit 11 were performed if appropriate in the opinion of the investigator or sponsor. Spinal radiographs were repeated only if more than 6 months had elapsed since the last x-ray. In addition, patients who discontinued prior to Visit 11 had safety laboratories performed, and those in the defined subset sites had study drug plasma concentration and cardiovascular markers obtained.
- If a patient discontinued after Visit 7 (Month 24), she had an ECG performed

These data were recorded in the Early Termination Visit. A Patient Summary was also completed

9.7.1.4.2. Study Completion

A patient was considered to have completed the study if either of the following occurred:

- Completion of the final visit
- A predefined study endpoint that indicated lack of therapeutic efficacy was reached

The following criteria were predefined as **study endpoints indicative of a lack of efficacy**:

- Accelerated loss of lumbar spine or femoral neck BMD in 1 or 2 years, defined as follows:

	▪ Lumbar Spine BMD	Femoral Neck BMD
o	At 1 year: >7%	>10%
o	At 2 years: >11%	>14%

- At 3 years: >11% >14%
- At 4 years >11% >14%

- More than two new vertebral fractures during participation in the study

If a patient met either of these criteria, she was considered to have met the requirements of the protocol and was discontinued from the study. A patient summary was completed.
After the core treatment phase (during the extension phase), because skeletally active drugs except for estrogens or estrogen-like compounds were allowed, no bone endpoint completion rules applied.

9.7.1.4.3. Qualifications for Analysis

- All adverse events reported at or after Visit 1 were included in the safety reports.
- All patients who were randomly assigned and had at least one visit after randomization were analyzed for efficacy.

9.7.1.4.4. Study Extensions

A 1-year, double-blind, placebo-controlled extension was added to the study.

9.7.1.5. Treatment Compliance

For purposes of analysis, several definitions of "compliant" were used: at least 70% of medication taken, at least 75% of medication taken, etc.

- Patients were categorized as "severely noncompliant" if they took less than 70% of drug during two separate visit intervals.

9.7.1.6. Concomitant Therapy

Osteoporosis medications were allowed per the protocol *during the extension phase*. Use of these agents made the interpretation of the fourth year of bone data more difficult than during the core double-blind treatment phase. Thus, the primary focus of analyses during the extension phase were those endpoints (e.g., cognitive, cardiovascular, breast, and uterine) that were less likely to be affected by these possible confounders.

9.7.1.7. Interim Analyses and Data Monitoring

Planned interim analyses were conducted under the auspices of the DMB assigned to this study. Only the DMB was authorized to review the completely unblinded interim efficacy and safety analyses, and, if necessary, to disseminate those results. The DMB disseminated interim results in a manner that minimized bias.
Before any data from this study was analyzed, the DMB was created. Members of the data monitoring board consisted of Lilly and non-Lilly personnel who were not directly involved with monitoring the study (for example, non-study related Lilly physician, physician external to Lilly, study statistician). Personnel directly involved with monitoring the study were not part of the

DMB, nor were they completely unblinded to any results at any time during the progress of the study without approval of the DMB.

Two planned interim analyses were conducted under the auspices of the DMB assigned to this study.

- A 12-month interim analysis was conducted that focused on general safety as well as specific safety measurements such as the uterine ultrasound assessments and the tests of cognitive function.
- A 24-month interim analysis was conducted that concentrated on the primary efficacy endpoints (incident vertebral fracture rates and BMD [total lumbar spine and femoral neck]) in addition to safety measures.
    - All analyses were conducted at the 0.05 level for statistical significance and the 0.20 level for trends.
    - No statistical adjustments were made because, regardless of the efficacy results of the 24-month interim analysis, the study was planned to and did continue for the third year in a double-blind fashion with the original study design.

Results of the 12-month interim safety analysis were discussed by the DMB in a conference call on December 5, 1997 which was attended by 9 DMB (5 members were employed by the sponsor). The main recommendation of the board was unanimous and read as follows:

- There are no overriding safety concerns which need to be explored prior to the 24-month interim analysis which will address the safety and efficacy of raloxifene in the treatment population.

This recommendation was presented to the sponsor's senior management.

Results of the 24-month interim analysis were discussed by the DMB on March 5, 1998. This meeting was attended by 9 data monitoring board members (5 members were employed by the sponsor), and two additional study statisticians (also employed by the sponsor) who helped prepare the report.

- The unanimous recommendation of the board was that the 24-month data was sufficient to demonstrate efficacy in a treatment population.
- In addition, the board recommended that the study continue to the 36-month time point.
- The board also approved the dissemination of efficacy results in publications and presentations.

These recommendations were presented to the sponsor's senior management and, upon its approval, the sponsor was unblinded to begin preparation of regulatory submissions. A subsequent decision was made by the sponsor to include 36-month data in the regulatory documents to meet global requirements with one submission.
In addition to the interim analyses, ongoing monitoring was performed on serious adverse events which were unblinded.

9.7.2. Determination of Sample Size

This study was designed to enroll approximately 6500 patients. A total of 7705 patients were enrolled. This deviation from the planned study size was not intentional, but was due to a large number of sites and inadequate tracking of the enrollment rate by the sponsor.

- The **primary comparisons** (which drive sample size) in these studies were **the difference in vertebral fracture rates** between the raloxifene treatment groups and the placebo group. ***The sample size was not determined based on expected breast cancer incidence.***

- Assuming an average age of 65 years, the rate of osteoporotic vertebral fractures was estimated to be 24 fractures/1000 patient-years for the population of Substudy I, and 65 fractures/1000 patient-years for the population of Substudy II. Calcium and vitamin D supplementation was expected to further reduce this rate by approximately 12% to 15%. Under these assumptions and an assumed 40% reduction in vertebral fracture rates in the raloxifene treatment groups compared with placebo, a sample size of 2100 patients per arm (1400 from Substudy I and 700 from Substudy II) provided over 80% power to detect a significant treatment effect in the vertebral fracture rate, pooled across the two studies, at the 24-month interim analysis (Gail 1974).
- This calculation assumed a 20% drop-out rate at 24 months, and a two-tailed 0.05 significance level.
- This sample size also provided over 90% power to detect a significant decrease in vertebral fracture rates, pooled across the two studies, at the end of the third year. Each study was powered at over 90% to detect a 2% increase in lumbar spine and femoral neck BMD at the end of 24 months, when comparing treated groups with placebo. Each study was also powered at over 80% to show a 40% reduction in vertebral and nonvertebral fractures combined at the end of 24 months.

9.8. Changes in the Conduct of the Study or Planned Analyses

9.8.1. Changes in the Conduct of the Study

Protocol H3S-MC-GGGK was initially approved by the sponsor on 27 July 1994. It was amended 7 times; with the latest amendment approved on 01 September 1998.

9.8.1.1. Protocol Amendment (a)

Amendment (a) was approved by the sponsor on 8 November 1994 for the following significant reasons:

- Instead of two informed consent documents being administered as indicated in the protocol, some sites used a single informed consent document at both the screening and enrollment phases.
- Figure GGGK.1 incorrectly referred to the enrollment phase as being 2 to 26 days before baseline. The enrollment phase actually occurred 2 to 28 days before baseline. A statement was also added to the figure legend to clarify that the 2-day period before the baseline visit allowed time for laboratory results to be returned.
- Some countries were not able to administer quality-of-life instruments because of language restrictions.
- In the subset of patients who had pelvic examinations and uterine ultrasonography performed throughout the study, the pelvic examination and uterine ultrasonography performed at Visit 11 was deleted and a pelvic examination and a uterine ultrasonography was added at Visit 5 (Month 12) for this subset of patients. The pelvic examination and uterine ultrasonography originally scheduled at Visit 7 (Month 24) was instead performed sometime between Visits 7 (Month 24) and 9 (Month 36). The timing of this pelvic examination and uterine ultrasonography was determined after the 1-year interim analysis.
- ECGs at Visits 5 (Month 12) and 11 (Month 48) were deleted. The ECG originally scheduled at Visit 9 (Month 36) was instead performed sometime between Visits 9 and 11. The timing of this ECG was determined after the 2-year interim analysis.
- Chest radiographs at Visits 1 and 11 were made optional.

9.8.1.2. Protocol Amendment (b)

Amendment (b) was approved by the sponsor on 10 March 1995 for the following significant reasons:

Study Design

- Figure GGGK.1, study design, mistakenly omitted indicators of "days" on the enrollment and screening time periods. These units were added to the figure.

Entry Procedures and Criteria for Enrollment

- Patients with a history of deep venous thrombosis, thromboembolic disorders, or cerebral vascular accident within the past 10 years were excluded from the study *except* for patients with a history of deep venous thrombosis due to accidents. The exception was not noted in Amendment (a).
- Patients with known, severe untreated malabsorption syndromes (loss of fat greater than 10 g/day in the feces) were excluded from the study.
- Patients who were treated with therapeutic doses of systemic corticosteroids for more than 1 month during the 12 months before beginning the study were excluded. However, occasional symptomatic use of inhaled, intranasal, or local steroids was permitted.
- Women were permitted to have used systemic estrogen and progestin for up to 1 cycle (28 days) during the 6 months before beginning the study. However, no systemic estrogen or progestin use was allowed within the 2 months before study entry. Use of topical estrogens up to three times per week was permitted.
- Patients who violate entry criteria were not discontinued from the study if there were ethical reasons for them to remain in the study.

Schedule of Events

- A third baseline BMD measurement was *not* performed, even if the first two measurements differed by more than 4% for the spine or 6% for the femoral neck.

Safety Evaluations

- Laboratory values that fell outside a clinically accepted reference range or values that differed significantly from previous values were evaluated and commented on by the investigator.

Patient Disposition Criteria

- To encourage long-term study participation, patients who missed one visit (except for their final study visit) were permitted to return for the missed visit if the appointment was kept before the next regularly scheduled appointment for the next visit.
- Additional study endpoints were defined by which a patient could discontinue from the study. These additional endpoints included accelerated bone loss and two new fractures within 2 years.

Data Analysis

- For the 2-year interim analyses, all efficacy parameters were analyzed separately within each substudy, as well as pooled across both substudies. Fracture endpoints within each study were tested for trends at the two-sided 0.20 level of significance.

Attachments

- A site-by-site listing of neuropsychometric tests was included as an attachment because these tests were only performed in those countries in which translation and validation had occurred.
- The quality-of-life questionnaires were updated to reflect the most recent versions.

9.8.1.3. Protocol Amendment (c)

Amendment (c) was approved by the sponsor on 11 January 1996 for the following significant reasons:

Primary Objectives

- One study endpoint, previously defined as "secondary", was included as a primary objective in addition to the previous primary endpoints of vertebral fractures and safety.
  - This addition was incorporated for the purposes of meeting regulatory requirements in the United States (US) and complying with the existing draft guidelines of the FDA.
  - The endpoint that was moved to the primary objectives was the effect of raloxifene on lumbar spine and femoral neck BMD.

Summary of Study Design

- The two substudies within the protocol were redefined as two separate studies to meet regulatory requirements in the US, and to comply with the existing draft guidelines of the FDA. Wording throughout the protocol was changed to reflect this. Whenever the two studies were referred to in the protocol, in general "studies" was used. If either study was referred to specifically, "Substudy I" or "Substudy II" was used.
- An additional interim analysis of safety data was added after the completion of the last patient's visit at 6 months. This recommendation was issued by the raloxifene data monitoring board DMB after reviewing the 6-month interim data of three other ongoing raloxifene studies for the prevention of osteoporosis (Studies H3S-MC-GGGF, -GGGG, and -GGGH). While the data monitoring board had no safety concerns with these studies and unanimously recommended their continuation, the data monitoring board also advised making the safety review process more uniform across the large long-term studies of raloxifene. This implied the addition of a safety interim analysis at 6 months that was not provided in the previous protocol version.

Sample Size

- Power calculations for the added primary endpoints (lumbar spine and femoral neck BMD) and for the most important secondary endpoint (combined incidence of vertebral fractures and nonvertebral fractures) were added to this section.

Efficacy Measures

- Type I collagen fragment was the actual test being measured rather than urinary pyridinoline crosslinks. The type I collagen fragment test was performed using the CrossLaps™ Assay, which may have been more sensitive than the cross links test in detecting a decrease in bone resorption induced by estrogen treatment.

Clinical Adverse Events

- Of all possible established risk factors for development of deep venous thrombosis and/or pulmonary embolism, the most common one identified in the studies of raloxifene (up to the point of this amendment) was a period of prolonged immobilization occurring immediately prior to the event. To minimize any potential risk from therapy in all study treatment groups, study participants were asked to discontinue their study medication temporarily, as detailed in the protocol amendment, if they became immobilized due to concurrent illness or surgical procedure.

Clinical Laboratory Tests

- Routine urinary microscopic examination of the sediment was added to allow for more effective differentiation of apparent abnormalities in the semi quantitative urinalysis, which proved to be common during the enrollment period.

Uterine Surveillance Procedures

- A procedure for the follow-up of patients with uterine bleeding or abnormal uterine ultrasound findings was added to the protocol to standardize the additional assessments worldwide. Although the available data from previous and ongoing clinical studies of raloxifene at the time of this amendment did not indicate any safety hazard of the drug with respect to the reproductive organs, it was felt that the (relatively nonspecific) recommendations given in the previous version of the protocol were not sufficient to ensure consistency in the necessary diagnostic procedures across all investigational sites. It was the aim of this amendment to achieve this consistency. These algorithms provided the investigator with clinical criteria essential for determining which diagnostic procedures were necessary.

Other Safety Measures

- A breast examination, pelvic examination, and Papanicolaou screening smear were offered to all study patients annually on an optional basis.

Visit Definitions

- The number of days allowed for patients to complete a visit was changed from ±28 to ±30 days from the actual visit date, to match the numbering system in the remote data entry edits.

Interim Analyses and Data Monitoring Boards

- An additional interim analysis of safety data was added after the completion of the last patient's visit at 6 months. This recommendation was issued by the raloxifene data monitoring board after reviewing the 6-month interim data of three other raloxifene studies in the prevention of osteoporosis (Studies H3S-MC-GGGF, -GGGG, and -GGGH). While the data monitoring board had no safety concerns with these studies and unanimously recommended their continuation, the data monitoring board also advised making the safety review process more uniform across the large long-term studies of raloxifene. This implied the addition of a safety interim analysis at 6 months that was not provided in the previous protocol version.
- The safety interim analysis of 12 months was extended to include additional safety measures such as uterine and cognitive safety data.

Attachment GGGK.2

- A superscript was needed for optional gynecological examinations at Visits 5, 7, 9, and 11. The letter "d" was used, and all subsequent superscripts were re-lettered to accommodate this change.

Attachment GGGK.5

- The Affective Rating Scale sample was updated to reflect the actual form used in the Cognitive and Neuro psychomotor Test Battery.

Attachment GGGK.12

- Two algorithms were included regarding the gynecological (uterine) surveillance procedures. The first addressed procedures to be followed on all patients who have scheduled TVU. The second addressed procedures to be followed on all patients who experienced uterine bleeding.

Miscellaneous

- Reference styles were changed from numbered in-text references to the author-year reference system.

9.8.1.4. Protocol Amendment (d)

Amendment (d) was approved by the sponsor on 24 October 1996 for the following significant reasons:

- The process by which vertebral fractures was assessed at the central reading site was defined.

- The third pelvic examination and uterine ultrasonography were performed at Visit 7 (24 months) to ensure that adequate uterine safety data were captured. Subsequent pelvic examination(s) and uterine ultrasonography were performed based on review of existing uterine safety data.
- In Attachment GGGK.2, Schedule of Events, the line for physical and gynecological examinations was changed to correct an error that was made in amendment (c). Inadvertently, the physical and gynecological examination lines were merged, giving the incorrect impression that the physical examination was required at more than Visit 1. The physical examination was always required only at Visit 1. The performance of physical examinations after Visit 1 remained at the discretion of the investigator; however, these data were not captured in the remote data entry system. Optional yearly gynecological examinations were added in amendment (c) and will continue.
- Because the study was extended to 48 months, the third ECG was performed at Visit 11 (48 months). There were no safety reasons that warranted obtaining an earlier ECG.

9.8.1.5. Protocol Amendment (e)

Amendment (e) was approved by the sponsor on 3 June 1997 for the following significant reasons:

- A decision was made **to extend the GGGK study into the 4th year.** The study continued with a placebo-controlled design, with patients taking the same study medication as in Years 1 through 3. Concomitant medication guidelines were modified to allow use of additional osteoporosis medications as clinically indicated, including bisphosphonates, calcitonin, and fluorides. Use of contraindicated estrogens, androgens, and progestins was discouraged. The Early Completion rules for the Year 3 visit were identical to that at Year 2.
- The main reason for this decision to extend the GGGK study into the 4th year was to collect more data about extra skeletal endpoints of the study, while continuing to assess key bone endpoints.

Changes to the procedures outlined in the schedule of events were as follows:

1. A pelvic examination and uterine ultrasonography were obtained in the subset of patients at Visits 9 and 11.
2. Biochemical bone markers were removed from the schedule of events for the subset of patients at Visit 11.
3. Quality of life was removed from the schedule of events for the Substudy II patients at Visit 11.
4. Resource utilization was removed from the schedule of events for the Substudy II patients at Visits 10 and 11.

- In order to allow for the possibility of further extension of the GGGK study at a future date, wording was added to the protocol regarding the continuation of the study in a

blinded or open fashion beyond 4 years, based on the decision of the data monitoring board or the sponsor.

- The optional mammography scheduled at Visit 9 (end of Year 3) was changed to mandatory. It was identified that only 50% of the patients at Visit 5 underwent an optional mammography. Because Visit 9 corresponds to the completion of the core treatment phase and because breast safety was such an important consideration in studies using selective estrogen receptor modulators, it was important to require a breast safety assessment at the end of Year 3. More extensive breast safety data enabled a timelier and appropriate response if potential new risks or benefits of raloxifene on the breast were to be identified. The protocol continued to allow for a breast ultrasonography (sonogram) to be performed instead of mammography, if mammography was not acceptable to a patient.
- Due to data handling and logistic issues, the 6- and 12-month interim analyses occurred concurrently.

9.8.1.6. Protocol Amendment (f)

Amendment (f) was approved by the sponsor on 1 December 1997. The significant purpose of this amendment was to define the effect of raloxifene on various types of dementia. The Cognitive and Neuro-psychomotor Test Battery and MAPS Battery (for two US sites) were being used in GGGK to assess overall cognitive function. However, additional cognitive testing was necessary to more fully assess the effects of raloxifene on various types of dementia. The specific objectives of this amendment were as follows:

- To determine the effect of long-term treatment with raloxifene on the prevalence of AD in postmenopausal women with osteoporosis.
- To determine the effect of long-term treatment with raloxifene on the prevalence of dementia associated with CV disease in postmenopausal women with osteoporosis.
- To determine the effect of long-term treatment with raloxifene on the prevalence of all causes of dementia in postmenopausal women with osteoporosis.
- No patient had completed the DDE algorithm as of Visit 9 (36 months), and therefore no DDE data will be included in this report.

9.8.1.7. Protocol Amendment (g)

Amendment (g) was approved by the sponsor on 1 September 1998. The significant reason for this amendment was a decision **to extend the study through the 6th year.**
However, the decision was made to stop the trial after the 4th year, and **patients were invited to enroll in a follow-up study, the Continuing Outcomes of Raloxifene Evaluation (CORE; Study H3S-MC-GGJY).**

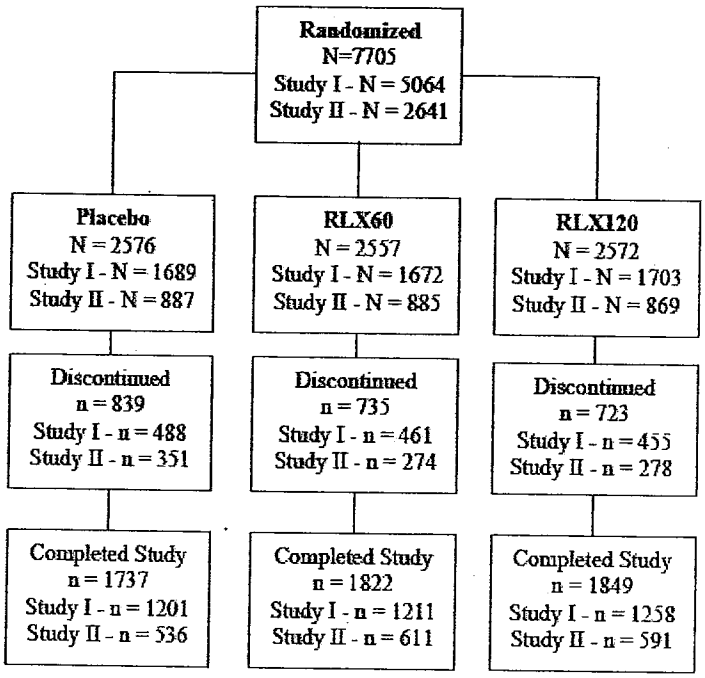
9.8.2. Changes in the Planned Analyses

The incidence of breast cancer was predefined as a secondary safety endpoint in the protocol. Analyses of breast cancer incidence for the safety endpoint indicated a significant reduction in the risk of breast cancer in this patient population. Thus, this report presents further analyses into breast cancer incidence that were not prespecified in the protocol. Breast cancer analyses are discussed briefly in Section 9.7.1.1 and are described throughout the presentation of the efficacy data (Section 11.4.3).

10. Study Patients

10.1. Disposition of Patients

A total of 7,705 patients are included in this final 48-month analysis. Of these 7,705 patients, 2,576 were randomly assigned to placebo, 2,557 to raloxifene hydrochloride (HCl) 60 mg/day, and 2,572 to raloxifene HCl 120 mg/day.



Abbreviations: N = number randomized; n = number observed.

Figure GGGK.10.1. Patient disposition.

10.1.1. Early Discontinuations in Pooled Sub-studies

During the 48-month study, 2,297 (29.8%) of the 7,705 randomly assigned patients discontinued early:

- 839 (32.6%) in the placebo group
- 735 (28.7%) in the raloxifene 60-mg group
- 723 (28.1%) in the raloxifene 120-mg group

Compared with the placebo group, there was an overall, statistically significant, *increase* among the three treatment groups and in the pooled raloxifene group, in % of enrolled **patients who completed the study** at normal end ("regular completed").

- 71.3% patients in the raloxifene 60-mg group, 71.9% in the raloxifene 120-mg group, and 67.4% in the placebo group completed the study.

Compared with the placebo group, there was a statistically significant *reduction,* overall and in the pooled raloxifene group, in early protocol completion due to lack of efficacy. **Early completion** was defined in the protocol as lack of therapeutic efficacy based on more than two new vertebral fractures observed during participation in the study or accelerated loss of bone mineral density (BMD).

- Raloxifene 60-mg group had 1.3%, raloxifene 120-mg group 0.9%, and placebo group 4.2% early completers.

Significantly fewer patients were **lost to follow-up** in the pooled raloxifene group compared with the placebo group, with the lowest incidence reported in the raloxifene 60-mg group (0.9%). No other **reasons for discontinuation** (for example, adverse event, personal conflict or patient decision, death) were different among the three treatment groups.

A total of 910 (11.8%) of the 7,705 randomly assigned patients **discontinued due to an adverse event:** 285 (11.1%) in the placebo group, 327 (12.8%) in the raloxifene 60-mg group, and 298 (11.6%) in the raloxifene 120-mg group. There were no significant differences in discontinuation due to an adverse event among the three treatment groups or in the pooled raloxifene group compared with the placebo group. Statistically significant differences in discontinuations due to adverse events are discussed in (Section 12.3.3.7).

Table GGGK.10.2 shows the time course of early study discontinuation by visit interval and also indicates the number of patients and reasons for discontinuation between any two successive visits.

- 528 (6.9%) of the randomly assigned patients discontinued prior to Visit 4 (the 6-month visit).
- Patients discontinuing in the next six 6-month periods (considering only those patients who were continuing at the start of each period) were 244 (3.4%), 278 (4.0%), 274 (4.1%), 196 (3.1%), 304 (4. 9%), and 189 (3.2%).

Table GGGK.10.1. Reasons for Study Discontinuation (All Randomly Assigned Patients, H3S-MC-GGGK 48-Month Data)

Primary Reason for Discontinuation	Placebo (N= 2576)	Rlx060 (N= 2557)	Rlx120 (N= 2572)	Overall p-Value	Pooled Rlx p-Value
Total Discontinued	2576 (100.0%)	2557 (100.0%)	2572 (100.0%)		
Regular completed	1737 (67.4%)	1822 (71.3%)b	1849 (71.9%)c	<.001	<.001
Adverse Event	285 (11.1%)	327 (12.8%)	298 (11.6%)	.146	.150
Personal conflict or other patient decision	252 (9.8%)	220 (8.6%)	223 (8.7%)	.231	.097
Early completed	106 (4.2%)	36 (1.3%)c	21 (0.8%)c	<.001	<.001
Protocol variance	35 (1.4%)	49 (1.9%)	50 (1.9%)	.194	.070
Death	36 (1.4%)	23 (0.9%)	41 (1.6%) d	.077	.584
Unable to contact patient (lost to follow-up)	41 (1.6%)	22 (0.9%)a	29 (1.1%)	.051	.023
Protocol entry criteria not met	37 (1.4%)	31 (1.2%)	21 (0.8%)a	.109	.102
Patient moved	28 (1.1%)	21 (0.8%)	26 (1.0%)	.608	.472
Patient completed protocol, but had an adverse event	16 (0.6%)	8 (0.3%)	12 (0.5%)	.270	.160
Total Continuing	0 (0.0%)	0 (0.0%)	0 (0.0%)		

NOTE: Chi-square tests were used when total count >= 10, else Fisher's exact test was used.
a - pairwise comparison statistically significant (p < 0.05) different from placebo
b - pairwise comparison statistically significant (p < 0.01) different from placebo
c - pairwise comparison statistically significant (p < 0.001) different from placebo
d - pairwise comparison of RLX060 statistically significant (p < 0.05) different from RLX120
Data: RMP.SAS.H3SM.MCGGGISC.Final
Source: RMP.H3SSK4YR.SASPGM(DC0000S2) 95761 15NOV00
Output: RMP.H3SO.GGGK.FINAL(DC0000S2N)

Table GGGK.10.2. Time Course of Early Discontinuation (All Randomly Assigned Patients, H3S-MC-GGGK 48-Month Data)

Visit/ Months	Number of Subjects Continuing	Number of Subjects Discontinued	Reason Discontinued	PLACEBO	RLX060	RLX120
2 Baseline	7705					
		327	Death	1	5	7
			Adverse event	41	58	55
			Entry crit. not met	24	19	15
			Lost to follow-up	6	1	2
			Patient moved	5	3	0
			Personal conflict	24	24	26
			Protocol variance	3	4	4
3 3 Month	7378					
		201	Death	0	0	4
			Adverse event	25	42	39
			Entry crit. not met	2	1	5
			Lost to follow-up	3	1	5
			Patient moved	2	1	4
			Personal conflict	17	18	20
			Protocol variance	2	4	6
4 6 Month	7177					
		244	Death	7	2	2
			Adverse event	28	50	37
			Entry crit. not met	3	7	0
			Lost to follow-up	7	3	3
			Patient moved	6	1	3
			Personal conflict	28	25	23
			Protocol variance	3	5	1
5 12 Month	6933					
		278	Death	4	2	8
			Adverse event	35	41	31
			Entry crit. not met	5	1	0
			Lost to follow-up	4	2	2
			Patient moved	0	2	4
			Personal conflict	31	18	25
			Protocol completed	17	4	5
			Protocol variance	9	12	16
6 18 Month	6655					

		274	Death	3	1	3
			Adverse event	35	31	28
			Entry crit. not met	0	1	0
			Lost to follow-up	2	3	4
			Patient moved	3	5	4
			Personal conflict	21	18	16
			Protocol completed	57	13	11
			Protocol variance	4	5	6
7	6381					
24 Month						
		196	Death	6	1	2
			Adverse event	38	22	29
			Lost to follow-up	4	2	4
			Patient moved	2	2	0
			Personal conflict	22	22	8
			Protocol completed	16	8	2
			Protocol variance	1	0	5
8	6185					
30 Month						
		304	Death	3	2	2
			Adverse event	28	41	36
			Entry crit. not met	1	0	1
			Lost to follow-up	6	3	3
			Patient moved	5	3	8
			Personal conflict	41	38	42
			Protocol completed	9	4	4
			Protocol variance	7	12	8
9	5881					
36 Month						
		189	Death	6	4	6
			Adverse event	29	25	25
			Completed with A.E.	0	1	0
			Entry crit. not met	1	2	0
			Lost to follow-up	3	2	2
			Patient moved	2	3	1
			Personal conflict	19	17	18
			Protocol completed	9	5	1
			Protocol variance	4	4	0
10	5692					
42 Month						
		4957	Death	4	5	7
			Adverse event	25	16	17
			Completed with A.E.	13	6	12
			Entry crit. not met	1	0	0
			Lost to follow-up	6	5	4
			Patient moved	3	1	5
			Personal conflict	43	37	39
			Protocol completed	1513	1591	1598
			Protocol variance	1	3	2
11	735					
48 Month						
		735	Death	2	1	0
			Adverse event	1	1	1
			Completed with A.E.	3	1	0
			Personal conflict	7	3	6
			Protocol completed	224	231	251
			Protocol variance	1	0	2
12	0					
48 Month (Visit 11)						

SOURCE IS RMP.H3SP.SASMACRO(PTDSP) PS027 01C
DATA FROM RMP.SAS.H3SM.MCGGGKSC.FINAL

10.1.2. Significant Differences in Early Discontinuation by Sub-study

10.1.2.1. Substudy I

There was a statistically significant reduction in **early protocol completion** overall and in the pooled raloxifene group compared with the placebo group (Table GGGK.10.3).

- Both the raloxifene 60-mg group (0.7%) and the raloxifene 120-mg group (0.5%) had significantly fewer early completers than the placebo group (3.1%).

There were no statistically significant differences among the three treatment groups for **discontinuation for reasons other** than early protocol completion in Substudy I.

Table GGGK.10.3. Reasons for Study Discontinuation (Substudy I, H3S-MC-GGGK 48-Month Data)

Substudy: 1

Primary Reason for Discontinuation	Placebo (N= 1689)	Rlx060 (N= 1672)	Rlx120 (N= 1703)	Overall p-Value	Pooled Rlx p-Value
Total Discontinued	1689 (100.0%)	1672 (100.0%)	1703 (100.0%)		
Regular completed	1201 (71.1%)	1211 (72.4%)	1258 (73.9%)	.197	.124
Adverse Event	177 (10.5%)	206 (12.3%)	196 (11.5%)	.243	.131
Personal conflict or other patient decision	149 (8.8%)	144 (8.6%)	137 (8.0%)	.702	.551
Protocol variance	22 (1.3%)	36 (2.2%)	30 (1.8%)	.168	.094
Early completed	52 (3.1%)	11 (0.7%)c	8 (0.5%)c	<.001	<.001
Unable to contact patient (lost to follow-up)	22 (1.3%)	18 (1.1%)	19 (1.1%)	.808	.519
Protocol entry criteria not met	20 (1.2%)	16 (1.0%)	14 (0.8%)	.560	.316
Patient moved	19 (1.1%)	13 (0.8%)	15 (0.9%)	.558	.302
Death	15 (0.9%)	12 (0.7%)	16 (0.9%)	.764	.831
Patient completed protocol, but had an adverse event	12 (0.7%)	5 (0.3%)	10 (0.6%)	.244	.220
Total Continuing	0 (0.0%)	0 (0.0%)	0 (0.0%)		

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

Data: RMP.SAS.H3SM.MCGGGKSC.final
Source: RMP.H3S8K4YR.SASPGM(DCSUH@21) 95761 15NOV00
Output: RMP.H3SO.GGGK.FINAL(DCSUH21N)

10.1.2.2. Substudy II

There was a significant reduction in **early protocol completion** overall and in the pooled raloxifene group compared with the placebo group (Table GGGK.10.4).

- Both the raloxifene 60-mg group (2.6%) and the raloxifene 120-mg group (1.7%) had significantly fewer early completers than the placebo group (6.3%).

There was a significant increase in **normal end of study** ("regular completed") overall and in the pooled raloxifene group compared with the placebo group (Table GGGK.10.4).

- Both the raloxifene 60-mg group (69.0%) and the raloxifene 120-mg group (68.0%) had significantly more regular completers than the placebo group (60.4%).

There was a significant reduction in patients **lost to follow-up** overall and in the pooled raloxifene group compared with the placebo group (Table GGGK.10.4).

- The raloxifene 60-mg group (0.5%) had significantly fewer patients lost to follow-up than the placebo group (2.1%).

There were no statistically significant differences among the three treatment groups for **discontinuation for reasons other** than early protocol completion, regular completed, and lost to follow-up in Substudy II.

Table GGGK.10.4. Reasons for Study Discontinuation
Substudy II
H3S-MC-GGGK 48-Month Data

Substudy: 2

Primary Reason for Discontinuation	Placebo (N= 887)	Elx060 (N= 865)	Elx120 (N= 869)	Overall p-Value	Pooled Elx p-Value
Total Discontinued	887 (100.0%)	865 (100.0%)	869 (100.0%)		
Regular completed	536 (60.4%)	611 (69.0%)c	591 (68.0%)c	<.001	<.001
Adverse Event	108 (12.2%)	121 (13.7%)	102 (11.7%)	.438	.693
Personal conflict or other patient decision	104 (11.7%)	76 (8.6%)a	86 (9.9%)	.088	.045
Early completed	56 (6.3%)	23 (2.6%)c	15 (1.7%)c	<.001	<.001
Death	21 (2.4%)	11 (1.2%)	25 (2.9%) d	.054	.599
Protocol variance	13 (1.5%)	13 (1.5%)	20 (2.3%)	.306	.440
Protocol entry criteria not met	17 (1.9%)	15 (1.7%)	7 (0.8%)a	.125	.183
Unable to contact patient (lost to follow-up)	19 (2.1%)	4 (0.5%)b	10 (1.2%)	.006	.003
Patient moved	9 (1.0%)	8 (0.9%)	11 (1.3%)	.751	.871
Patient completed protocol, but had an adverse event	4 (0.5%)	3 (0.3%)	2 (0.2%)	.914	.495
Total Continuing	0 (0.0%)	0 (0.0%)	0 (0.0%)		

NOTE: Chi-square tests were used when total count >= 10, else Fisher's exact test was used.
a - pairwise comparison statistically significant (p < 0.05) different from placebo
b - pairwise comparison statistically significant (p < 0.01) different from placebo
c - pairwise comparison statistically significant (p < 0.001) different from placebo
d - pairwise comparison of ELX060 statistically significant (p < 0.05) different from ELX120

Data: RMP.SAS.H3SM.MCGGGKSC.Final
Source: RMP.H3SSK4YR.SASPGM(DCSUB022) 95741 15NOV00
Output: RMP.H3SO.GGGK.FINAL(DCSUB22N)

10.2. Protocol Violations