System Organ Class: Vascular disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=1725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	191 (14.9)	395 (14.5)	586 (14.6)	.774
PATIENTS WITH NO TESS	1095 (85.1)	1330 (85.5)	3425 (85.4)	.774
Vascular hypertensive disorders NEC	113 (8.8)	259 (9.5)	372 (9.3)	.484
Hypertension NOS	113 (8.8)	258 (9.5)	371 (9.2)	.521

Program: RMP.H3SSGGJY.SASPGM(SECT125) Input: RMP.SAS.H3SM.NCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART125)
* Frequencies are analyzed using a Fisher's Exact test.
SAS6.12 MVSXA VERSION: 6.0

12.2.2.2. Statistically Significant Treatment-Emergent Adverse Events During Study GGJY

Table GGJY.12.5 reports the incidence of statistically significant adverse events during Study GGJY among all patients. Terms in three system organ class categories were reported less frequently in raloxifene-treated patients than in placebo-treated patients (see discussion in Section 12.2.2.1). A statistically significant decrease in four breast tissue related events (high-level terms "reproductive organ" and "breast histopathology procedures" and "breast and nipple neoplasms malignant", and the preferred terms "breast cancer NOS" and "partial mastectomy") was observed in raloxifene-treated patients compared with placebo-treated patients. This is consistent with the breast cancer efficacy data obtained in this study (see Section 11.4.3) and in Study GGGK. Also, four bone-related events (high-level term "fracture treatments [excluding skull and spine]", and preferred terms "patella fracture", "femoral neck fracture", and "humerus fracture") were statistically significantly decreased in raloxifene-treated patients compared with placebo-treated patients.

12.2.2.2.1. High-Level and Preferred Terms Decreased in Raloxifene Patients

Statistically significant decreases in three skin cancer-related events (high-level terms "skin neoplasms malignant and unspecified (excluding melanoma)" and "skin lesion excisions"; and preferred term "basal cell carcinoma") were observed in raloxifene treated patients compared with placebo-treated patients. To date, there is no known mechanism of raloxifene to explain any protective effect for the skin; however, a beneficial effect of raloxifene on these events cannot be definitively dismissed.

Three eye-related terms (high-level term "partial vision loss", and preferred terms "vision blurred" and "eye irritation") were statistically significantly decreased in raloxifene treated patients compared with placebo-treated patients. While the incident rates for all of these terms were relatively low (24 patients, 12 patients, and 6 patients, respectively), these data continue to support that raloxifene has no adverse effect on the eyes or vision, as has been seen with tamoxifen (Gorin et al. 1998).

The high-level term "renal failure and impairment" as well as the preferred terms "hyperthyroidism" and "nerve compression" were all reported statistically significantly fewer times in raloxifene-treated patients compared with placebo-treated patients. These events were

rarely reported throughout the study (11 patients, 7 patients, and 7 patients, respectively), and there is no known causal mechanism between raloxifene and any of these events. Thus, any beneficial effect of raloxifene treatment on any of these three events is not likely. Similarly, although "pneumonia NOS" was reported more frequently than these other events (96 patients), the statistically significant decrease seen in raloxifene-treated patients compared with placebo-treated patients is likely not the result of a raloxifene treatment effect.

The preferred term "weight decreased" was reported in statistically significantly fewer patients in the raloxifene group (28 patients [1.0%]) than in the placebo group (23 patients [1.8%]) (p=0.050). Weight, which was collected as a vital sign, statistically significantly decreased from baseline through study termination in both the raloxifene and placebo groups, but the decrease was similar between the two groups. Only one report of "weight decreased", which was in the raloxifene group, was considered to be serious, and no patient discontinued the study due to this event.

In Study GGGK, there was a small, but statistically significant increase in weight from baseline through study termination in the pooled raloxifene groups (60 and 120 mg/day) compared with the placebo group after 3 and 4 years of study drug (Study H3S-MC-GGGK 3-Year and 4-Year Study Reports). The reduced reporting of "weight decreased" as an adverse event in raloxifene patients may be, in part, reflective of the vertebral fracture efficacy of raloxifene, as multiple vertebral fractures can result in loss of appetite and decreased body mass.

The high-level term "mood alterations with depressive symptoms" was statistically significantly decreased in raloxifene-treated patients. However, a similar event, "depression", was reported with increased frequency among raloxifene patients compared with placebo patients. This is further discussed in (Section 12.3.3.6).

12.2.2.2.2. High-Level and Preferred Terms Increased in Raloxifene Patients

"Allergies to foods, food additives, drugs and other chemicals" (high-level term) and "drug hypersensitivity" (preferred term) were statistically significantly increased among raloxifene patients compared with placebo patients. The actual terms reported in patients were primarily drug allergies. There was no apparent pattern of any specific drug or drug class that elicited the allergic response. Raloxifene has not been associated with increased sensitivity to pharmaceuticals in other clinical trials. Given the low occurrence of these events (14 patients [0.3%], and 12 patients [0.3%], respectively), it is unlikely that the increase is related to raloxifene therapy.

Reporting of the preferred term post-procedural pain was statistically significantly increased among raloxifene patients compared with placebo patients. The most commonly reported actual term for this event was postoperative pain. There was no emergent pattern of a specific site where the pain was more common or a specific event that elicited the pain. Because of the nonspecific nature of the term, it is difficult to definitively conclude whether it was related to study drug. However, the event rate was low (21 patients [0.5%]), no similar term was increased among raloxifene users during Study GGGK, and there is no known mechanism of action to

explain this finding. Thus, it is likely a result of multiple statistical comparisons and probably not related to raloxifene therapy.

Table GGJY.12.5. Statistically Significant Treatment Emergent Adverse Events during Study GGJY by System Organ Class, High-Level Term, and Preferred Term (All Patients Enrolled in Study GGJY)

System Organ Class	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	1029 (80.0)	2178 (79.9)	3207 (80.0)	.966
PATIENTS WITH NO TESS	257 (20.0)	547 (20.1)	804 (20.0)	.966
Surgical and medical procedures	243 (18.9)	416 (15.3)	659 (16.4)	.004
Investigations	144 (11.2)	240 (8.8)	384 (9.6)	.018
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	130 (10.1)	201 (7.4)	331 (8.3)	.004

Program: RMP.H3SSGGJY.SASPGM(SPC14118) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART14118)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0002 MEDDRA VERSION: 6.0 TESS calculations done at PT level

High Level Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	1029 (80.0)	2178 (79.9)	3207 (80.0)	.966
PATIENTS WITH NO TESS	257 (20.0)	547 (20.1)	804 (20.0)	.966
Reproductive organ and breast histopathology procedures	28 (2.2)	34 (1.2)	62 (1.5)	.029
Breast and nipple neoplasms malignant	23 (1.8)	24 (0.9)	47 (1.2)	.017
Skin neoplasms malignant and unspecified (excl melanoma)	24 (1.9)	22 (0.8)	46 (1.1)	.006
Fracture treatments (excl skull and spine)	23 (1.8)	21 (0.8)	44 (1.1)	.005
Skin lesion excisions	15 (1.2)	15 (0.6)	30 (0.7)	.048
Partial vision loss	14 (1.1)	10 (0.4)	24 (0.6)	.008
Allergies to foods, food additives, drugs and other chemicals	1 (0.1)	13 (0.5)	14 (0.3)	.047
Renal failure and impairment	8 (0.6)	3 (0.1)	11 (0.3)	.007
Mood alterations with depressive symptoms	5 (0.4)	2 (0.1)	7 (0.2)	.038

Program: RMP.H3SSGGJY.SASPGM(SPC14118) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART14118)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0002 MEDDRA VERSION: 6.0 TESS calculations done at PT level

Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	1029 (80.0)	2178 (79.9)	3207 (80.0)	.966
PATIENTS WITH NO TESS	257 (20.0)	547 (20.1)	804 (20.0)	.966
Depression	34 (2.6)	114 (4.2)	148 (3.7)	.015
Pneumonia NOS	40 (3.1)	56 (2.1)	96 (2.4)	.046
Weight decreased	23 (1.8)	28 (1.0)	51 (1.3)	.050
Basal cell carcinoma	19 (1.5)	17 (0.6)	36 (0.9)	.011
Humerus fracture	14 (1.1)	13 (0.5)	27 (0.7)	.037
Post procedural pain	2 (0.2)	19 (0.7)	21 (0.5)	.032
Drug hypersensitivity	0	12 (0.4)	12 (0.3)	.012
Vision blurred	9 (0.7)	3 (0.1)	12 (0.3)	.003
Breast cancer NOS	6 (0.5)	3 (0.1)	9 (0.2)	.035
Patella fracture	6 (0.5)	2 (0.1)	8 (0.2)	.016
Femoral neck fracture	5 (0.4)	2 (0.1)	7 (0.2)	.038
Hyperthyroidism	5 (0.4)	2 (0.1)	7 (0.2)	.038
Nerve compression	5 (0.4)	2 (0.1)	7 (0.2)	.038
Partial mastectomy	7 (0.5)	0	7 (0.2)	<.001
Eye irritation	5 (0.4)	1 (0.0)	6 (0.1)	.015

Program: RMP.H3SSGGJY.SASPGM(SPC14118) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART14118)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0002 MEDDRA VERSION: 6.0

12.2.2.3. Statistically Significant Treatment-Emergent Adverse Events from Study GGGK Baseline through Study GGJY Termination

All TEAEs from baseline in Study GGGK through the end of Study GGJY (that is, from Year 0 through Year 8) were analyzed. Table GGJY.14.22 summarizes these results by system organ class, high-level term, and preferred term in order of decreasing frequency.

Table GGJY.12.6 reports the incidence of those events that were statistically significant. The large patient population and long observation period resulted in many TEAEs, increasing the likelihood of statistical significance for some TEAEs by multiple comparisons. In general, the statistically significant events that are considered to be clinically relevant throughout this time period are consistent with data from the individual Studies GGGK and GGJY. Many of the events described in the following section were therefore observed during Study GGGK and were thoroughly discussed in the Study GGGK 3-Year Study Report.

12.2.2.3.1. Statistically Significant System Organ Class Terms

Statistically significant decreases were observed in the raloxifene group compared with the placebo group for two system organ class categories: "Surgical and medical procedures" and "Neoplasms benign, malignant and unspecified (including cysts and polyps)". One system organ class category, "Vascular disorders", was decreased among placebo-treated patients compared with raloxifene-treated patients.

The terms in the in the system organ class "Surgical and medical procedures" were reported less frequently in raloxifene patients compared with placebo patients (p=0.024).

The high-level terms included in this system organ class are so diverse that a beneficial effect of raloxifene is unlikely. The most commonly reported high-level terms in this system organ class were "therapeutic procedures NEC", "lens therapeutic procedures", "joint therapeutic procedures", "uterine therapeutic procedures", "fracture treatments (excluding skull and spine)", and "skin lesion excisions" (see Table GGJY.14.22). There were no statistically significant between-group differences in any of these high-level terms.

One high level term ("facial and bursal therapeutic procedures") and one preferred term ("endarterectomy") were statistically significantly decreased in raloxifene-treated patients compared with placebo-treated patients. No high-level terms and two preferred terms ("knee arthroplasty" and "tooth extraction NOS") were statistically significantly decreased in placebo-treated patients compared with raloxifene-treated patients. None of these individual high-level or preferred terms occurred frequently enough to account for the overall decrease in the system organ class.

The terms in the system organ class "Neoplasms benign, malignant and unspecified (including cysts and polyps)" were reported less frequently in the raloxifene group compared with the placebo group (p=0.006). Most of the events under this system organ class were reported under the high-level terms "skin neoplasms malignant and unspecified (excluding melanoma)",

"uterine neoplasms benign", and "breast and nipple neoplasms benign" (see Table GGJY.14.22). No statistically significant between-group differences were observed for any of these high-level terms.

Two high-level terms ("breast and nipple neoplasms malignant" and "neuromas") and three preferred terms ("Bowen's disease", "breast cancer NOS", and "breast cancer female") were statistically significantly decreased in raloxifene-treated patients compared with placebo-treated patients. The decrease in breast and nipple neoplasms and breast cancer is consistent with the breast cancer efficacy data previously presented (see Section 11.4.3). However, no between-group difference in the reporting of neuromas was identified in Study GGJY or previously in Study GGGK. Given the low incidence of this event (7 events [0.2%]) and the lack of any known explanatory mechanism for raloxifene to effect neuroma development, it is not likely that this decrease was actually due to raloxifene treatment.

Similarly, there is currently no known mechanism of raloxifene to explain the decreased incidence of Bowen's disease. However, this finding is consistent with the statistically significant decrease in skin neoplasms reported during Study GGJY, and an effect of raloxifene on the development of various skin malignancies may warrant further investigation.

The terms in the system organ class "Vascular disorders" were reported more frequently in the raloxifene group than in the placebo group (1591 patients total; p=0.006). The most commonly reported high-level terms under this system organ class were "vascular hypertensive disorders NEC", "peripheral vascular disorders NEC", and "varicose veins non site specific" (see Table GGJY.14.22). While vascular hypertensive disorders were very similar between groups (853 patients total; p=0.836), peripheral vascular disorders differed. Statistically significantly more patients in the raloxifene group reported a peripheral vascular disorder than in the placebo group (451 patients total; p<0.001). By far the most common preferred term under peripheral vascular disorders was "flushing", which was also statistically significantly higher in raloxifene-treated patients compared with placebo-treated patients (431 patients total; p<0.001). Flushing, or hot flushes, is a known adverse event associated with raloxifene, especially within the first 6 months of raloxifene therapy (see Section 12.3.3.4). Although "varicose veins non site specific" was not a statistically significant adverse event, proportionally more patients in the raloxifene group reported this event than in the placebo group (172 patients total; p=0.095). Thus, the difference between placebo and raloxifene in "peripheral vascular disorder" and in "varicose veins non site specific" largely account for the significant difference in this system organ class.

12.2.2.3.2. High-Level and Preferred Terms Related to Known Raloxifene Efficacy

The statistically significant decrease in the raloxifene group compared with the placebo group in the high-level term "breast and nipple neoplasms malignant" and in the preferred terms "breast mass NOS", "breast cancer NOS", "breast cancer female", and "partial mastectomy" are consistent with the breast cancer efficacy data (see Section 11.4.3). Likewise, the statistically significant reduction in the raloxifene group compared with the placebo group in the preferred

terms "hypercholesterolemia", and "blood cholesterol increased" can be explained by the known effects of raloxifene on lipids (see Study H3S-MC-GGGK 4-Year Study Report).

12.2.2.3.3. High-Level and Preferred Terms Consistent with Study GGGK Safety Data

12.2.2.3.3.1. Influenza-Like Illness

As in Study GGGK, the preferred term "influenza-like illness" was commonly reported and statistically significantly higher in the raloxifene group compared with the placebo group both in Study GGGK and in the Study GGJY cohort from Study GGGK baseline through Study GGJY termination. In Study GGGK, the increased reporting of "influenza-like illness" was most pronounced in the first 2 years, and raloxifene patients who continued in the study through Years 3 and 4 were no more likely to develop "influenza-like illness" de novo than placebo patients. Although there continued to be a statistically significant increase in "influenza-like illness" through the 8-year observation period, this is primarily due to the increased reporting in raloxifene users during the first 2 years of Study GGGK. Furthermore, reinitiating raloxifene therapy at the time of Study GGJY enrollment did not result in an increase in the reporting of this adverse event.

Because there is no plausible biological mechanism to explain the increased reporting of "influenza-like illness", this finding may be due to statistical chance associated with multiple analyses being performed. Thus, the increased reporting of "influenza-like illness" is not likely to be clinically relevant.

12.2.2.3.3.2. Muscle Cramp

As in Study GGGK, the preferred term "muscle cramp" was commonly reported and statistically significantly higher in the raloxifene group compared with the placebo group in the Study GGJY cohort from Study GGGK baseline through Study GGJY termination (see raloxifene Clinical Investigator's Brochure for MedDRA terms and Study H3S-MCGGGK 4-Year Study Report for CoSTART terms).

The differential reporting between treatment groups was most pronounced in the first 2 years of Study GGGK, and no statistically significant between-group difference was observed during the 3rd and 4th years of the study. Also, reporting of muscle cramp was not statistically significantly increased among raloxifene users during Study GGJY, nor was there an increase in reporting of this adverse event after re-initiation of raloxifene therapy in Study GGJY.

Nevertheless, "muscle cramps", in particular leg cramps, are still considered to be associated with raloxifene, especially early in the treatment regimen (see Section 12.3.3.5). "Night cramps" is a related adverse event that was statistically significantly increased among raloxifene patients compared with placebo patients, though it was a much rarer event.

12.2.2.3.3.3. Flushing

As in Study GGGK, the preferred term "flushing", or "hot flushes", were commonly reported and statistically significantly higher in the raloxifene group compared with the placebo group in the Study GGJY cohort from Study GGGK baseline through Study GGJY termination. Reporting of hot flushes was especially common within the first 6 months of raloxifene treatment during Study GGGK. "Flushing", or "hot flushes", is a known adverse event associated with raloxifene, especially within the first 6 months of raloxifene therapy. After the first 6 months of therapy in Study GGGK, the risk of flushing was similar between the pooled raloxifene group (60 and 120 mg/day) and placebo group (see Section 12.3.3.4).

12.2.2.3.3.4. Uterine Procedures and Benign Uterine Findings

The high-level terms "uterine neoplasms" and "reproductive tract disorders NEC (excluding neoplasms)", as well as the preferred terms "biopsy endometrium", "uterine polyp NOS", "uterine disorder NOS", and "ultrasound scan vagina" were all statistically significantly increased in the raloxifene group compared with the placebo group. Two of these terms, "biopsy endometrium" and "ultrasound scan vagina", are procedures not adverse events. Importantly, this increase in uterine investigations did not result in an increased reporting of any gynecological malignancies (see Section 12.3.3.3). The high level term "uterine neoplasms" contained only the preferred terms of "uterine polyp NOS" and "uterine cyst" and did not contain any malignancies (see Table GGJY.14.22).

Benign uterine findings (for example, endometrial fluid and polyps) were observed in Study GGGK, which included extensive uterine evaluations. There were no statistically significant between-group differences during Study GGJY for any uterus-related adverse event. Uterine findings are discussed further in (Section 12.3.3.3).

12.2.2.3.3.5. Diabetes Mellitus

The high-level term "diabetes mellitus (including subtypes)" was statistically significantly increased among raloxifene patients compared with placebo patients (103 patients total [2.6%]; p=0.018). In addition, the preferred term "diabetes mellitus NOS" was statistically significantly increased in the raloxifene group (p=0.043). In Study GGGK, women treated with raloxifene 60 mg/day were more likely than placebo treated women to report worsening Type 2 diabetes mellitus. Further review of the data showed baseline imbalances between raloxifene- and placebo-treated women with diabetes.
Specifically, baseline use of oral hypoglycemic agents, fasting plasma glucose levels, and hemoglobin A1C levels were all statistically significantly higher in raloxifene 60 mg/day patients with pre-existing diabetes compared with placebo patients with pre-existing diabetes. When the data were controlled for the baseline imbalance in fasting plasma glucose, raloxifene 60 mg/day-treated women had statistically significantly greater reductions in fasting glucose than placebo-treated women (Barrett- Connor et al. 2002). These results are consistent with the results of other smaller studies conducted specifically to evaluate the effects of raloxifene on glycemic control (Andersson et al. 2002, Cagnacci et al. 2002, Cucinelli et al. 2002). Importantly, no statistically significant increase in any diabetes-related term was observed in Study GGJY (for the high-level

term "diabetes mellitus [including subtypes]", 37 patients total; p=0.598) (Table GGJY.14.21). The increased reporting of diabetes mellitus seen in the raloxifene-treated patients in the Study GGJY cohort from Study GGGK baseline through Study GGJY is primarily the result of increased reporting during Study GGGK, which was due to the baseline imbalances described.

12.2.2.3.3.6. Edema

The preferred term "edema NOS" was reported more frequently in raloxifene-treated patients compared with placebo patients. In Study GGGK, a statistically significant increase in the reporting of peripheral edema was observed in the raloxifene HCl 120 mg/day group compared with the placebo group. Though there was no statistically significantly increased in the raloxifene HCl 60 mg/day group compared with placebo, the incidence of "peripheral edema" appeared dose-related.

In Study GGJY, "edema NEC" and "peripheral edema" were both reported similarly between treatment groups. Only 4 patients reported any kind of edema as an SAE (2 patients in each treatment group; see Section 12.3.2), and no patient discontinued the study due to edema during Study GGJY. Also, the cases of edema that were reported as serious were not related to a venous thromboembolism (VTE). It is concluded that the increase in edema among raloxifene patients seen in the Study GGJY cohort from Study GGGK baseline through Study GGJY is primarily the result of increased reporting during Study GGGK. Edema (in particular, "peripheral edema") may be a minor adverse event associated with raloxifene administration.

12.2.2.3.4. High-Level and Preferred Terms Not Consistent with Either Study GGGK or Study GGJY Safety Data

12.2.2.3.4.1. Memory Loss

In the Study GGJY cohort from Study GGGK baseline through Study GGJY termination, statistically significantly more patients reported the high-level term "memory loss (excluding dementia)" in the raloxifene group compared with the placebo group (166 patients total; p=0.041). Importantly, no other memory loss-related term, such as "dementia (excluding Alzheimer's type)" or "Alzheimer's disease (including subtypes)" was increased in raloxifene-treated patients during this observation period (Table GGJY.14.22).

In Study GGGK, cognitive function was prospectively evaluated after 3 years of raloxifene use. For all parameters measured, there were no statistically significant differences between the pooled raloxifene group (60 and 120 mg/day) and the placebo group. For memory loss specifically, raloxifene-treated women tended to have a lower risk of decline in cognitive function on the two tests of verbal memory (relative risk 0.77; 95% CI, 0.59 to 1.00; p=0.05) and attention (relative risk 0.87; 95% CI, 0.74 to 1.02; p=0.09) compared with women who received placebo (Study H3S-MCGGGK 3-Year Study Report; Yaffe et al. 2001). "Memory loss (excluding dementia)" was not increased in raloxifene users during either Study GGGK or Study GGJY (Table GGJY.14.21), and it is probably due to statistical chance rather than raloxifene treatment.

12.2.2.3.4.2. Pollakiuria

The preferred term "pollakiuria" was statistically significantly increased among raloxifene patients compared with placebo patients. Only one of these events (in the raloxifene group) was considered serious. Raloxifene did not increase the incidence of any other urinary disorder, such as urinary tract infection or incontinence. One related term, "cystitis chronic NOS", was actually decreased with raloxifene treatment compared with placebo, though the incidence rate was very low for this event (8 patients).

Raloxifene has not been associated with urinary tract dysfunction in other clinical trials.

Furthermore, in an analysis of 3-year safety data from two raloxifene studies (N=6926), raloxifene had an apparent protective effect on the incidence of surgical procedures for pelvic floor relaxation (odds ratio 0.50, 95% CI 0.31 to 0.81) (Goldstein et al. 2001).

These facts support that the finding of increased pollakiuria in the raloxifene group was not to be related to raloxifene therapy.

12.2.2.3.4.3. Knee arthroplasty

Reporting of the preferred term "knee arthroplasty" was statistically significantly greater in raloxifene-treated patients than in placebo-treated patients. There is no known mechanism of action of raloxifene to explain this finding, particularly why the knee might be more affected than other joints. "Hip arthroplasty" was a more commonly reported event and was reported less often in raloxifene-treated patients compared with placebo patients, though this reported event did not reach statistical significance. In fact, although the available clinical data are inconsistent (Nevitt et al. 1996; Vingard et al. 1997; Von Muhlen et al. 2002; Karlson et al. 2003), it is hypothesized that estrogen therapy and/or selective estrogen receptor modulators (SERMs) may actually protect against osteoarthritis and hence, joint replacement surgery, by increasing collagen production in postmenopausal women. Also, no increase in any similar event was observed during Study GGGK. This event is not likely related to raloxifene treatment.

12.2.2.3.4.4. Vaginosis Fungal NOS

Reporting of the preferred term "vaginosis fungal NOS" was statistically significantly greater in raloxifene-treated patients than in placebo-treated patients. Review of actual terms revealed that each of these events represented a vaginal yeast infection. No case of "vaginosis fungal NOS" was considered serious or led to study discontinuation.

Reporting of "vaginosis fungal NOS" was also statistically significantly increased in the pooled raloxifene group (60- and 120-mg/day treatment groups combined) after 4 years of therapy in Study GGGK. However, there did not appear to be a dose-response in Study GGGK (6 patients [0.2%] in the placebo group, 19 patients [0.7%] in the raloxifene HCl 60-mg/day group, and 11

patients [0.4%] in the raloxifene HCl 120-mg/day group), and it was not commonly reported in the Study GGJY cohort through approximately 8 years of follow-up (19 cases total).

Vaginal candidiasis is rare in postmenopausal women, presumably due to the low levels of endogenous estrogen. Although an increase in "thrush/candida" was noted in the tamoxifen International Breast Cancer Intervention Study (IBIS-1) among both premenopausal and postmenopausal patients (IBIS Investigators 2002), this adverse event has not been associated with tamoxifen in other clinical trials. There are few case reports in the literature of tamoxifen associated with vaginal yeast infection (Sobel et al. 1996).

In conclusion, although the event rate of "vaginosis fungal NOS" in Study GGJY was very low, a possible treatment effect of raloxifene cannot be dismissed.

12.2.2.3.4.5. Atrioventricular Block NOS

The preferred term "atrioventricular block NOS" was reported in 10 patients in the raloxifene group and in no patient in the placebo group. Two of these events were classified as "severe". Four events resulted in hospitalization, and a fifth event resulted in hospitalization and was also considered by the investigator to be life-threatening. Six of these events occurred during Study GGGK, 2 events during the time period between Study GGGK and Study GGJY while patients were not receiving study drug, and 2 events during Study GGJY. Based on only 10 events, it is not likely that long-term exposure to raloxifene results in atrioventricular block.

12.2.2.3.4.6. Axillary Pain

The preferred term "axillary pain" was reported in 10 patients in the raloxifene group and in no patient in the placebo group. All reports of axillary pain were mild, and no patient discontinued the study due to this event. In addition, none of the patients who experienced axillary pain had breast cancer or any kind of breast surgery during the observation period. Thus, axillary pain reported during the study appeared to be idiopathic and not related to breast events, and it was probably not related to raloxifene treatment.

12.2.2.3.4.7. Other

The preferred terms "tooth extraction", "muscle injury NOS", "eructation", and "gastrointestinal pain NOS" were all events that were reported statistically significantly more frequently in raloxifene patients than in placebo patients. None of these events was reported commonly (all occurred in $\leq$ 1% of patients) and none was increased in raloxifene users in Study GGJY. Only 1 event, "eructation", was increased among raloxifene users in Study GGGK; however, there is no plausible mechanism of action to explain this increase and only 32 (0.4%) events total were reported during the 4 years of the study (data not shown). Given these facts, none of these events is considered to be associated with raloxifene treatment.

Table GGJY.12.6. Statistically Significant Treatment-Emergent Adverse Events since Randomization in Study GGGK (All Patients Enrolled in Study GGJY)

By System Organ Class (SOC)

System Organ Class	PLACEBO (N=1286) n (%)	Ralox (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	1273 (99.0)	2688 (98.6)	3961 (98.8)	.446
PATIENTS WITH NO TESS	13 (1.0)	37 (1.4)	50 (1.2)	.446
Surgical and medical procedures	577 (44.9)	1119 (41.1)	1696 (42.3)	.024
Vascular disorders	477 (37.1)	1114 (40.9)	1591 (39.7)	.023
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	294 (22.9)	521 (19.1)	815 (20.3)	.006

Program: RMP.H3SSGGJY.SASPGM(SPCAET2S) Input: RMP.SAS.H3SM.L.MCGKJYSC.FINAL(EVENTS) Output: RMP.H3SO.GGJY.FINAL(AETE2S)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0002 MEDDRA VERSION: 6.0 TESS calculations done at PT level

By High Level Term

High Level Term	PLACEBO (N=1286) n (%)	Ralox (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	1273 (99.0)	2688 (98.6)	3961 (98.8)	.446
PATIENTS WITH NO TESS	13 (1.0)	37 (1.4)	50 (1.2)	.446
General signs and symptoms NEC	210 (16.3)	526 (19.3)	736 (18.3)	.023
Muscle related signs and symptoms NEC	167 (13.0)	438 (16.1)	605 (15.1)	.011
Peripheral vascular disorders NEC	99 (7.7)	352 (12.9)	451 (11.2)	<.001
Elevated cholesterol	167 (13.0)	280 (10.3)	447 (11.1)	.012
Memory loss (excl dementia)	41 (3.2)	125 (4.6)	166 (4.1)	.041
Infections NEC	60 (4.7)	89 (3.3)	149 (3.7)	.032
Diabetes mellitus (incl subtypes)	22 (1.7)	81 (3.0)	103 (2.6)	.018
Urinary abnormalities	45 (3.5)	58 (2.1)	103 (2.6)	.014
Cholesterol analyses	47 (3.7)	51 (1.9)	98 (2.4)	.001
Uterine neoplasms	19 (1.5)	78 (2.9)	97 (2.4)	.008
Nasal disorders NEC	36 (2.8)	36 (1.3)	72 (1.8)	.002
Breast and nipple neoplasms malignant	35 (2.7)	33 (1.2)	68 (1.7)	.001
Urinalysis NEC	17 (1.3)	18 (0.7)	35 (0.9)	.045
Total fluid volume increased	12 (0.9)	9 (0.3)	21 (0.5)	.018
Reproductive tract disorders NEC (excl neoplasms)	1 (0.1)	17 (0.6)	18 (0.4)	.019
Abdominal hernias, site unspecified	7 (0.5)	4 (0.1)	11 (0.3)	.045
Chest and lung injuries NEC	7 (0.5)	4 (0.1)	11 (0.3)	.045
Mood alterations with depressive symptoms	7 (0.5)	4 (0.1)	11 (0.3)	.045
Neuromas	7 (0.5)	4 (0.1)	11 (0.3)	.045
Fascial and bursal therapeutic procedures	7 (0.5)	2 (0.1)	9 (0.2)	.006
Neutropenias	6 (0.5)	3 (0.1)	9 (0.2)	.035
Hepatobiliary imaging procedures	5 (0.4)	1 (0.0)	6 (0.1)	.015

Program: RMP.H3SSGGJY.SASPGM(SPCAET2S) Input: RMP.SAS.H3SM.L.MCGKJYSC.FINAL(EVENTS) Output: RMP.H3SO.GGJY.FINAL(AETE2S)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0002 MEDDRA VERSION: 6.0 TESS calculations done at PT level

By Preferred Term

Preferred Term	PLACEBO (N=1286) n (%)	Ralox (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	1273 (99.0)	2688 (98.6)	3961 (98.8)	.446
PATIENTS WITH NO TESS	13 (1.0)	37 (1.4)	50 (1.2)	.446
Influenza like illness	188 (14.6)	466 (17.1)	654 (16.3)	.049
Muscle cramp	152 (11.8)	407 (14.9)	559 (13.9)	.006
Hypercholesterolaemia	167 (13.0)	279 (10.2)	446 (11.1)	.011
Flushing	89 (6.9)	342 (12.6)	431 (10.7)	<.001
Breast mass NOS	75 (5.8)	118 (4.3)	193 (4.8)	.040
Biopsy endometrium	40 (3.1)	148 (5.4)	188 (4.7)	.001
Excoriation	48 (3.7)	66 (2.4)	114 (2.8)	.025
Blood cholesterol increased	47 (3.7)	50 (1.8)	97 (2.4)	.001
Uterine polyp NOS	19 (1.5)	70 (2.6)	89 (2.2)	.029
Pollakiuria	15 (1.2)	57 (2.1)	72 (1.8)	.041
Diabetes mellitus NOS	13 (1.0)	51 (1.9)	64 (1.6)	.042
Uterine disorder NOS	12 (0.9)	48 (1.8)	60 (1.5)	.050
Ultrasound scan vagina	10 (0.8)	45 (1.7)	55 (1.4)	.028
Knee arthroplasty	9 (0.7)	43 (1.6)	52 (1.3)	.024
Periarthritis	22 (1.8)	27 (1.0)	50 (1.2)	.046
Epistaxis	23 (1.8)	23 (0.8)	46 (1.1)	.011
Tooth extraction NOS	7 (0.5)	35 (1.3)	42 (1.0)	.031
Rhinitis allergic NOS	19 (1.5)	20 (0.7)	39 (1.0)	.037
Sinus bradycardia	17 (1.3)	18 (0.7)	35 (0.9)	.045
Postnasal drip	17 (1.3)	16 (0.6)	33 (0.8)	.023
Flank pain	16 (1.2)	16 (0.6)	32 (0.8)	.036
Oedema NOS	4 (0.3)	27 (1.0)	31 (0.8)	.020
Muscle injury NOS	3 (0.2)	21 (0.8)	24 (0.6)	.047
Postoperative infection	13 (1.0)	8 (0.3)	21 (0.5)	.008
Vaginosis fungal NOS	2 (0.2)	17 (0.6)	19 (0.5)	.048
Breast cancer NOS	12 (0.9)	6 (0.2)	18 (0.4)	.006
Eructation	1 (0.1)	17 (0.6)	18 (0.4)	.019

Program: RMP.H78SGGJY.SASPGM(SPCART2S) Input: RMP.SAS.H1SM.L.MCGKJYSC.FINAL(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ARTE2S)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0002 MEDDRA VERSION: 6.0

Preferred Term	PLACEBO (N=1286) n (%)	Ralox (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Night cramps	1 (0.1)	15 (0.6)	16 (0.4)	.029
Proteinuria	9 (0.7)	5 (0.2)	14 (0.3)	.014
Venous insufficiency	8 (0.6)	5 (0.2)	13 (0.3)	.034
Breast cancer female	9 (0.7)	3 (0.1)	12 (0.3)	.003
Patella fracture	7 (0.5)	4 (0.1)	11 (0.3)	.045
Uterine cyst	0	11 (0.4)	11 (0.3)	.021
Atrioventricular block NOS	0	10 (0.4)	10 (0.2)	.036
Axillary pain	0	10 (0.4)	10 (0.2)	.036
Gastrointestinal pain NOS	0	10 (0.4)	10 (0.2)	.036
Partial mastectomy	8 (0.6)	2 (0.1)	10 (0.2)	.003
Depressed mood	6 (0.5)	3 (0.1)	9 (0.2)	.035
Genital rash	6 (0.5)	3 (0.1)	9 (0.2)	.035
Neutropenia	6 (0.5)	3 (0.1)	9 (0.2)	.035
Cystitis chronic NOS	6 (0.5)	2 (0.1)	8 (0.2)	.016
Bowen's disease	5 (0.4)	2 (0.1)	7 (0.2)	.038
Endarterectomy	5 (0.4)	2 (0.1)	7 (0.2)	.038

Program: RMP.H3SSGGJY.SASPGM(SPCART2S) Input: RMP.SAS.H1SM.L.MCGKJYSC.FINAL(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ARTE2S)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0002 MEDDRA VERSION: 6.0

12.2.2.4. Adverse Events from the End of Study GGGK through Study GGJY

Table GGJY.14.24 summarizes all common adverse events (those occurring in ≥ 2% of the patients) from the end of participation in Study GGGK to the end of participation in Study GGJY. In general, the adverse events reported during this time frame were similar to the TEAEs reported during Study GGJY. Two high-level terms ("gastrointestinal atonic and hypomotility disorders NEC" and "bladder and urethral symptoms") and two preferred terms ("constipation" and "urinary incontinence") that were not increased with raloxifene therapy during Study GGJY were statistically significantly increased among raloxifene patients ($p<0.05$ for all comparisons) when analyzed as adverse events from the end of Study GGGK through Study GGJY. However, there are no other data with raloxifene to indicate that these events are related to raloxifene.

Deaths, Other Serious Adverse Events, and Clinically Significant Adverse Events (12.3)

For CORE, an SAE was defined as any event that resulted in one of the following outcomes, or is significant for any other reason:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Severe or permanent disability
- Cancer
- Congenital anomaly

The analyses of SAEs presented in this report are based on the reporting database and include all enrolled patients who reported an adverse event that met any of the serious criteria whether or not the event was judged to be related to study drug.

Deaths and SAEs were also collected in a Pharmacovigilance database (Clintrace). The listing of SAEs from the Clintrace database may differ from the reporting database, as Clintrace contains SAEs that occurred after the patient discontinued from the trial and that were judged by the investigator to be potentially related to study drug. The reporting database contains only SAE information collected while the patient was participating in the study. At the time of database lock, there were no clinically significant differences between the reporting and Clintrace databases. Therefore, the analysis of the SAEs in the Clintrace database is not presented in this report.

Table GGJY.14.26 in Section 14.3.2 is a by-patient listing of all patients who died, experienced other SAEs, or discontinued due to adverse events. Section 14.3.3 presents these patient narratives. Appendix 16.3 includes case report forms for any patient who died, experienced other SAEs, or discontinued due to an adverse event.

Deaths (12.3.1)

At the time of datalock, 76 (1.9%) deaths were reported among the randomly assigned patients in the clinical trial database (29 [2.3%] in the placebo group, 46 [1.7%] in the raloxifene HCl 60-mg group) (see Table GGJY.12.7 and Table GGJY.12.8).

There was no statistically significant difference between the two treatment groups in the number of patients who died, nor in the number of patients who died of any individual event (preferred term). The most common causes of death were "death NOS" (3 deaths in the placebo group and 3 deaths in the raloxifene group), "myocardial infarction" (1 death in the placebo group and 3 deaths in the raloxifene group), "respiratory failure" (2 deaths in the placebo group and 2 deaths in the raloxifene group), and "sudden death" (1 death in the placebo group and 2 deaths in the raloxifene group).

Two deaths in raloxifene-treated patients were considered by the investigator to be possibly related to study drug (see Table GGJY.12.7). The cause of death for Patient 77-4246 was ovarian cancer. The patient received treatment with carboplatin, but did not undergo surgery or biopsy and died within 3 months of her diagnosis. Due to the undesirable effects of some SERMs on cancers of the female reproductive tract, the incidence of ovarian cancer has been closely monitored throughout the clinical development of raloxifene. No clinical trial data, including data from this study (see Section 12.3.3.2.2), have ever suggested any increase in the incidence of ovarian cancer in raloxifene-treated patients. This has been further confirmed by a retrospective study of
7 randomized, placebo-controlled raloxifene studies (N=9837), which found no increased risk of ovarian cancer among raloxifene patients compared with placebo patients (RR 0.50 95% CI, 0.19-1.35) (Neven et al. 2001). Thus, it is unlikely that raloxifene treatment contributed to the death of this patient.

Patient 243-17 became unwell at her home on [redacted] and was found dead in her home later that day. Upon examination by the coroner, the death was deemed accidental, and, therefore, no autopsy was conducted. Because a definitive cause of death for this patient was not identified, any conclusion regarding the relationship between raloxifene and this death is difficult. However, because the patient was receiving raloxifene at the time of her death, the investigator stated a causal relationship between raloxifene and the death cannot be ruled out. b(6)

Table GGJY.12.7. Patients Who Died During Study GGJY (All Patients Enrolled in Study GGJY)

Investigator	Patient Number	Treatment	Primary Cause of Death (MedDRA Preferred Term)	Investigator's Opinion of Possibl Relationship to Study Medication
38	5138	RLX060	Throat cancer NOS	No
42	4319	Placebo	Acute lymphocytic leukaemia	No
42	4326	Placebo	Lung squamous cell carcinoma stage IV	No
42	4408	RLX060	Respiratory arrest	No
44	5222	Placebo	Respiratory failure	Yes
44	5288	RLX060	Cardio-respiratory arrest	No
53	8772	RLX060	Death unexplained	No
53	8779	Placebo	Oesophageal adenocarcinoma NOS	No
56	2003	RLX060	Merkel cell carcinoma right leg	No
58	5366	RLX060	Lung cancer metastatic	No
67	8327	Placebo	Rectosigmoid cancer NOS	No
70	7746	Placebo	Metastatic obstruction small bowel carcinoma	No
73	3847	RLX060	Intracranial haemorrhage NOS	No
73	4346	Placebo	Pneumonia aspiration	No
75	8373	Placebo	Pancreatic carcinoma NOS	No
77	3107	RLX060	Respiratory arrest	No
77	3192	RLX060	Lou Gehrig's	No
77	4029	Placebo	Haemorrhagic stroke	No
77	4061	RLX060	Rectal cancer metastatic	No
77	4206	RLX060	Cerebrovascular accident	No
77	4230	RLX060	Haemorrhagic stroke	No
77	4246	RLX060	Ovarian cancer NOS	Yes
83	5341	RLX060	Cerebral infarction	No
85	6213	RLX060	Hepatic cancer metastatic	No
85	6288	RLX060	Anoxic encephalopathy	No
143	2955	RLX060	Subdural haematoma	No
145	3204	Placebo	Sudden death	No
145	3216	Placebo	Colon cancer NOS	No
145	3241	RLX060	Gastric cancer NOS	No
145	3266	Placebo	Cardiac failure NOS	No
147	3474	RLX060	Cerebral artery thrombosis	No
151	4122	RLX060	Myocardial infarction	No
200	3181	Placebo	Myocardial infarction	No
243	17	RLX060	Sudden death	Yes
243	70	Placebo	Metastases to lymph nodes	No
244	3042	Placebo	Pancreatitis NOS	No
245	4030	Placebo	Tumor of the left vertebrae	No
282	414	RLX060	Death unexplained	No
282	643	Placebo	Gastrointestinal tract cancer NOS	No

(continued)

Investigator	Patient Number	Treatment	Primary Cause of Death (MedDRA Preferred Term)	Investigator's Opinion of Possible Relationship to Study Medication
282	746	RLX060	Cardio-respiratory arrest	No
282	793	RLX060	Cardiac arrest	No
282	887	RLX060	Intestinal perforation NOS	No
282	975	RLX060	Sudden death	No
282	979	RLX060	Ruptured cerebral aneurysm	No
282	984	RLX060	Diabetic coma NOS	No
291	5274	RLX060	Lymphoma NOS	No
503	5221	RLX060	Respiratory failure	No
604	7250	Placebo	Cardiac failure NOS	No
604	7269	RLX060	Hepatic encephalopathy	No
700	7737	Placebo	Lip and/or oral cavity cancer NOS	No
700	7747	RLX060	Death NOS	No
700	7819	RLX060	Death NOS	No
700	7911	Placebo	Pancreatitis NOS	No
700	7917	Placebo	Death NOS	No
703	8312	RLX060	Pneumonia NOS	No
725	9639	Placebo	Lung cancer stage unspecified (excl metastatic tumours to lung)	No
742	345	Placebo	Angiosarcoma NOS	No
742	389	RLX060	Myocardial infarction	No
742	2610	RLX060	Death NOS	No
742	2773	RLX060	Metastatic neoplasm NOS, primary site unknown	No
742	3276	Placebo	Death NOS	No
742	3887	RLX060	Pulmonary embolism	No
742	3939	RLX060	Lung cancer metastatic	No
742	4290	RLX060	Hypothermia	No
743	4419	Placebo	Renal cancer metastatic	No
753	247	Placebo	Chronic myeloid leukaemia	No
753	277	RLX060	Sepsis NOS	No
802	6440	RLX060	Myocardial infarction	No
851	7352	RLX060	Electromechanical dissociation	No
855	8318	RLX060	Aortic aneurysm	No
867	9757	Placebo	Cardiac arrest	No
963	1464	Placebo	Respiratory failure	No
966	1923	RLX060	Intestinal infarction	No
968	2269	RLX060	Respiratory failure	No
993	6462	Placebo	Death NOS	No
993	6468	RLX060	Rectal cancer NOS	No

Abbreviations: CORE = Continuing Outcomes Relevant to Evista; NOS = not otherwise specified; PBO = placebo; RLX060 = raloxifene hydrochloride 60 mg.
Source: PS017 and AEL018

12.3.2. Other Serious Adverse Events

Table GGJY.12.8 summarizes SAEs that occurred during Study GGJY (CORE) by system organ class and preferred term in order of decreasing frequency (Visit 1 through end of participation). All serious TEAEs from baseline in Study GGGK (MORE) through the end of Study GGJY (that is, Year 0 through Year 8) are summarized in (Table GGJY.14.25).

SAEs overall were reported similarly between the two treatment groups. Only 3 SAEs were reported statistically significantly more often in raloxifene patients than placebo patients: "spinal fractures and dislocations", "osteoarthropathies", and "breathing abnormalities".

Spinal fractures and dislocations were reported more frequently as an SAE in raloxifene patients compared with placebo patients (3 patients [0.2%] in the placebo group and 21 patients [0.8%] in the raloxifene group; p=0.047). Each of these events referred to a fracture rather than a dislocation. Study GGJY was not designed to assess vertebral fractures, and no data to adjudicate the spinal fractures reported as an SAE was collected.

The number of reported events (24) is very small and does not reflect the number of vertebral fractures that would be expected in a population with osteoporosis of this size over 4 years of observation (Melton et al. 1989). Further, as described in Section 11, multiple confounders were present that influenced the fracture results. Given the known efficacy of raloxifene to prevent vertebral fractures in postmenopausal women with osteoporosis, this event is probably not a treatment effect.

Osteoarthropathies were reported in 5 patients in the placebo group (0.4%) and 30 patients (1.1%) in the raloxifene group (p=0.027). There is no known mechanism of action of raloxifene to explain this event. In fact, although the available clinical data are inconsistent (Nevitt et al. 1996; Vingard et al. 1997; Von Muhlen et al. 2002; Karlson et al. 2003) it is hypothesized that estrogen therapy and/or SERMs may actually protect against osteoarthritis by increasing collagen production in postmenopausal women. Also, no increase in any similar event was observed during Study GGGK (MORE).

Reviewer Comments: *is this a function of longer follow-up? Note that patients in CORE had continued on their originally assigned treatment in MORE. It is important to note the high rate of bisphosphonate and other active bone agent use in the trial.*

Breathing abnormalities were more common in raloxifene-treated patients compared with placebo-treated patients (1 patient [0.1%] in the placebo group and 13 patients [0.5%] in the raloxifene group; p=0.047). No similar event was observed among raloxifene patients in Study GGGK. The between-group difference for this event is probably a result of multiple statistical comparisons and not reflective of a true treatment effect.

Table GGJY.12.8. Summary of All Serious Adverse Events by System Organ Class, High-Level Term, and Preferred Term during CORE (All Patients Enrolled in CORE)

System Organ Class: Overall

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	317 (24.7)	622 (22.8)	939 (23.4)	.216
PATIENTS WITH NO EVENTS	969 (75.3)	2103 (77.2)	3072 (76.6)	.216

Program: EMP.H3SSGGJY.SASPGM(SPCT129) Input: EMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: EMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

System Organ Class: Blood and lymphatic system disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	9 (0.7)	17 (0.6)	26 (0.6)	.834
PATIENTS WITH NO EVENTS	1277 (99.3)	2708 (99.4)	3985 (99.4)	.834
Anaemia deficiencies	1 (0.1)	1 (0.0)	2 (0.0)	
Iron deficiency anaemia	1 (0.1)	1 (0.0)	2 (0.0)	
Anaemias NEC	5 (0.4)	13 (0.5)	18 (0.4)	.805
Anaemia NOS	5 (0.4)	11 (0.4)	16 (0.4)	1.00
Megaloblastic anaemia NOS	0	1 (0.0)	1 (0.0)	
Microcytic anaemia	0	1 (0.0)	1 (0.0)	
Leukocytoses NEC	0	1 (0.0)	1 (0.0)	
Eosinophilia	0	1 (0.0)	1 (0.0)	
Leukopenias NEC	0	1 (0.0)	1 (0.0)	
Leukopenia NOS	0	1 (0.0)	1 (0.0)	
Lymphatic system disorders NEC	1 (0.1)	0	1 (0.0)	
Lymphadenopathy	1 (0.1)	0	1 (0.0)	
Marrow depression and hypoplastic anaemias	2 (0.2)	1 (0.0)	3 (0.1)	
Pancytopenia	2 (0.2)	1 (0.0)	3 (0.1)	
Thrombocytopenias	0	1 (0.0)	1 (0.0)	
Idiopathic thrombocytopenic purpura	0	1 (0.0)	1 (0.0)	

Program: EMP.H3SSGGJY.SASPGM(SPCT129) Input: EMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: EMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

System Organ Class: Cardiac disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	38 (3.0)	109 (4.0)	147 (3.7)	.106
PATIENTS WITH NO EVENTS	1248 (97.0)	2616 (96.0)	3864 (96.3)	.106
Cardiac conduction disorders	1 (0.1)	2 (0.1)	3 (0.1)	
Atrioventricular block NOS	0	2 (0.1)	2 (0.0)	
Atrioventricular block second degree	1 (0.1)	0	1 (0.0)	
Aortic valvular disorders	0	3 (0.1)	3 (0.1)	
Aortic valve incompetence	0	2 (0.1)	2 (0.0)	
Aortic valve stenosis	0	1 (0.0)	1 (0.0)	
Cardiac signs and symptoms NEC	0	1 (0.0)	1 (0.0)	
Palpitations	0	1 (0.0)	1 (0.0)	
Cardiomyopathies	0	2 (0.1)	2 (0.0)	
Cardiomyopathy NOS	0	2 (0.1)	2 (0.0)	
Coronary artery disorders NEC	5 (0.4)	17 (0.6)	22 (0.5)	.492
Coronary artery disease NOS	4 (0.3)	9 (0.3)	13 (0.3)	1.00
Coronary artery atherosclerosis	0	5 (0.2)	5 (0.1)	
Coronary artery stenosis	0	3 (0.1)	3 (0.1)	
Coronary artery occlusion	1 (0.1)	0	1 (0.0)	
Ischaemic coronary artery disorders	15 (1.2)	44 (1.6)	59 (1.5)	.326
Myocardial infarction	5 (0.4)	18 (0.7)	23 (0.6)	.373
Angina pectoris	5 (0.4)	11 (0.4)	16 (0.4)	1.00
Acute myocardial infarction	3 (0.2)	6 (0.2)	9 (0.2)	1.00
Angina unstable	2 (0.2)	5 (0.2)	7 (0.2)	1.00
Acute coronary syndrome	0	3 (0.1)	3 (0.1)	
Myocardial ischaemia	1 (0.1)	1 (0.0)	2 (0.0)	
Heart failures NEC (excl ventricular failure)	5 (0.4)	15 (0.6)	20 (0.5)	.634
Cardiac failure congestive	2 (0.2)	7 (0.3)	9 (0.2)	.727
Cardiac failure NOS	2 (0.2)	6 (0.2)	8 (0.2)	1.00
Congestive cardiac failure aggravated	1 (0.1)	1 (0.0)	2 (0.0)	

Program: EMP.H3SSGGJY.SASPGM(SPCT129) Input: EMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: EMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

System Organ Class: Cardiac disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Cardiac failure acute	0	1 (0.0)	1 (0.0)	
Left ventricular failures	1 (0.1)	0	1 (0.0)	
Left ventricular failure	1 (0.1)	0	1 (0.0)	
Mitral valvular disorders	0	3 (0.1)	3 (0.1)	
Mitral valve incompetence	0	2 (0.1)	2 (0.0)	
Mitral valve disease NOS	0	1 (0.0)	1 (0.0)	
Pericardial disorders NEC	1 (0.1)	1 (0.0)	2 (0.0)	
Pericardial effusion	1 (0.1)	0	1 (0.0)	
Pericardial haemorrhage	0	1 (0.0)	1 (0.0)	
Rate and rhythm disorders NEC	3 (0.2)	7 (0.3)	10 (0.2)	1.00
Bradycardia NOS	3 (0.2)	1 (0.0)	4 (0.1)	
Tachycardia NOS	1 (0.1)	3 (0.1)	4 (0.1)	
Arrhythmia NOS	0	3 (0.1)	3 (0.1)	
Supraventricular arrhythmias	11 (0.9)	33 (1.2)	44 (1.1)	.417
Atrial fibrillation	8 (0.6)	29 (1.1)	37 (0.9)	.216
Sinus bradycardia	2 (0.2)	0	2 (0.0)	
Atrial flutter	0	1 (0.0)	1 (0.0)	
Sinus arrest	0	1 (0.0)	1 (0.0)	
Sinus arrhythmia	1 (0.1)	0	1 (0.0)	
Sinus tachycardia	0	1 (0.0)	1 (0.0)	
Supraventricular tachycardia	0	1 (0.0)	1 (0.0)	
Ventricular arrhythmias and cardiac arrest	2 (0.2)	7 (0.3)	9 (0.2)	.727
Cardiac arrest	2 (0.2)	1 (0.0)	3 (0.1)	
Cardio-respiratory arrest	0	2 (0.1)	2 (0.0)	
Ventricular tachycardia	0	2 (0.1)	2 (0.0)	
Electromechanical dissociation	0	1 (0.0)	1 (0.0)	
Ventricular fibrillation	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Congenital, familial and genetic disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	0	1 (0.0)	1 (0.0)	1.00
PATIENTS WITH NO EVENTS	1286 (100)	2724 (100)	4010 (100)	1.00
Renal and urinary tract disorders congenital NEC	0	1 (0.0)	1 (0.0)	
Urethral intrinsic sphincter deficiency	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Ear and labyrinth disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	3 (0.2)	1 (0.0)	4 (0.1)	.100
PATIENTS WITH NO EVENTS	1283 (99.8)	2724 (100)	4007 (99.9)	.100
Inner ear signs and symptoms	3 (0.2)	1 (0.0)	4 (0.1)	
Vertigo	3 (0.2)	1 (0.0)	4 (0.1)	

Program: RMP.H3SGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Endocrine disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	2 (0.2)	2 (0.1)	5 (0.1)	.336
PATIENTS WITH NO EVENTS	1283 (99.8)	2723 (99.9)	4006 (99.9)	.336
Hyperparathyroid disorders	1 (0.1)	0	1 (0.0)	
Hyperparathyroidism primary	1 (0.1)	0	1 (0.0)	
Posterior pituitary disorders	2 (0.2)	0	2 (0.0)	
Inappropriate antidiuretic hormone secretion	2 (0.2)	0	2 (0.0)	
Thyroid hyperfunction disorders	0	1 (0.0)	1 (0.0)	
Thyrotoxicosis	0	1 (0.0)	1 (0.0)	
Acute and chronic thyroiditis	0	1 (0.0)	1 (0.0)	
Thyroiditis NOS	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Eye disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	3 (0.2)	13 (0.5)	16 (0.4)	.297
PATIENTS WITH NO EVENTS	1283 (99.8)	2712 (99.5)	3995 (99.6)	.297
Blindness (excl colour blindness)	0	2 (0.1)	2 (0.0)	
Amaurosis fugax	0	1 (0.0)	1 (0.0)	
Blindness	0	1 (0.0)	1 (0.0)	
Cataracts (excl congenital)	1 (0.1)	3 (0.1)	4 (0.1)	
Cataract unilateral	1 (0.1)	2 (0.1)	3 (0.1)	
Cataract	0	1 (0.0)	1 (0.0)	
Corneal structural change, deposit and degeneration	0	1 (0.0)	1 (0.0)	
Corneal degeneration	0	1 (0.0)	1 (0.0)	
Glaucomas (excl congenital)	0	1 (0.0)	1 (0.0)	
Glaucoma NOS	0	1 (0.0)	1 (0.0)	
Ocular bleeding and vascular disorders NEC	0	1 (0.0)	1 (0.0)	
Ocular retrobulbar haemorrhage	0	1 (0.0)	1 (0.0)	
Ocular disorders NEC	1 (0.1)	0	1 (0.0)	
Retinal disorder	1 (0.1)	0	1 (0.0)	
Partial vision loss	1 (0.1)	0	1 (0.0)	
Visual acuity reduced	1 (0.1)	0	1 (0.0)	
Retinal bleeding and vascular disorders (excl retinopathy)	0	3 (0.1)	3 (0.1)	
Retinal vein thrombosis	0	2 (0.1)	2 (0.0)	
Retinal artery embolism	0	1 (0.0)	1 (0.0)	
Retinal structural change, deposit and degeneration	0	1 (0.0)	1 (0.0)	
Macular degeneration	0	1 (0.0)	1 (0.0)	
Retinopathies NEC	0	1 (0.0)	1 (0.0)	
Retinopathy hypertensive	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Gastrointestinal disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	31 (2.4)	69 (2.5)	100 (2.5)	.914
PATIENTS WITH NO EVENTS	1255 (97.6)	2656 (97.5)	3911 (97.5)	.914
Abdominal hernias, site unspecified	2 (0.2)	1 (0.0)	3 (0.1)	
Abdominal strangulated hernia	1 (0.1)	0	1 (0.0)	
Hernial eventration	1 (0.1)	0	1 (0.0)	
Ventral hernia	0	1 (0.0)	1 (0.0)	
Anal and rectal disorders NEC	0	2 (0.1)	2 (0.0)	
Rectal prolapse	0	2 (0.1)	2 (0.0)	
Colitis (excl infective)	0	1 (0.0)	1 (0.0)	
Colitis ulcerative	0	1 (0.0)	1 (0.0)	
Anal and colorectal neoplasms NEC	0	1 (0.0)	1 (0.0)	
Rectal polyp	0	1 (0.0)	1 (0.0)	
Diaphragmatic hernias	0	1 (0.0)	1 (0.0)	
Hiatus hernia	0	1 (0.0)	1 (0.0)	
Diarrhoea (excl infective)	2 (0.2)	3 (0.1)	5 (0.1)	
Diarrhoea NOS	2 (0.2)	3 (0.1)	5 (0.1)	
Diverticula	2 (0.2)	3 (0.1)	5 (0.1)	
Diverticulum NOS	2 (0.2)	2 (0.1)	4 (0.1)	
Diverticulum intestinal	0	1 (0.0)	1 (0.0)	
Diverticulum inflammations	1 (0.1)	4 (0.1)	5 (0.1)	
Diverticulitis NOS	1 (0.1)	4 (0.1)	5 (0.1)	
Duodenal and small intestinal stenosis and obstruction	0	1 (0.0)	1 (0.0)	
Small intestinal obstruction NOS	0	1 (0.0)	1 (0.0)	
Duodenal ulcers and perforation	0	2 (0.1)	2 (0.0)	
Duodenal ulcer	0	1 (0.0)	1 (0.0)	
Duodenal ulcer perforation	0	1 (0.0)	1 (0.0)	
Faeces abnormal	0	1 (0.0)	1 (0.0)	
Faecal abnormality NOS	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

System Organ Class: Gastrointestinal disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Femoral hernias	1 (0.1)	0	1 (0.0)	
Femoral hernia NOS	1 (0.1)	0	1 (0.0)	
Gastric and oesophageal haemorrhages	2 (0.2)	2 (0.1)	4 (0.1)	
Gastric haemorrhage	1 (0.1)	2 (0.1)	3 (0.1)	
Gastric antral vascular ectasia	1 (0.1)	0	1 (0.0)	
Gastric ulcers and perforation	1 (0.1)	5 (0.2)	6 (0.1)	.671
Gastric ulcer	0	5 (0.2)	5 (0.1)	
Gastric erosions	1 (0.1)	0	1 (0.0)	
Gastritis (excl infective)	0	3 (0.1)	3 (0.1)	
Gastritis NOS	0	3 (0.1)	3 (0.1)	
Gastrointestinal inflammatory disorders NEC	1 (0.1)	0	1 (0.0)	
Crohn's disease	1 (0.1)	0	1 (0.0)	
Gastrointestinal and abdominal pains (excl oral and throat)	4 (0.3)	8 (0.3)	12 (0.3)	1.00
Abdominal pain NOS	1 (0.1)	6 (0.2)	7 (0.2)	.441
Abdominal pain upper	1 (0.1)	2 (0.1)	3 (0.1)	
Abdominal pain lower	2 (0.2)	0	2 (0.0)	
Gastrointestinal atonic and hypomotility disorders NEC	1 (0.1)	3 (0.1)	4 (0.1)	
Constipation	1 (0.1)	1 (0.0)	2 (0.0)	
Gastrooesophageal reflux disease	0	2 (0.1)	2 (0.0)	
Gastrointestinal disorders NEC	1 (0.1)	1 (0.0)	2 (0.0)	
Gastrointestinal disorder NOS	1 (0.1)	1 (0.0)	2 (0.0)	
Non-site specific gastrointestinal haemorrhages	2 (0.2)	5 (0.2)	7 (0.2)	1.00
Gastrointestinal haemorrhage NOS	0	4 (0.1)	4 (0.1)	
Haematemesis	0	1 (0.0)	1 (0.0)	
Lower gastrointestinal haemorrhage	1 (0.1)	0	1 (0.0)	
Upper gastrointestinal haemorrhage	1 (0.1)	0	1 (0.0)	
Gastrointestinal necrosis and gangrene (excl gangrenous hernia)	1 (0.1)	0	1 (0.0)	
Intestinal gangrene NOS	1 (0.1)	0	1 (0.0)	

Program: RMP.H3SGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

System Organ Class: Gastrointestinal disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1186) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Gastrointestinal vascular occlusion and infarction	0	2 (0.1)	2 (0.0)	
Intestinal infarction	0	1 (0.0)	1 (0.0)	
Mesenteric artery embolism	0	1 (0.0)	1 (0.0)	
Gastrointestinal stenosis and obstruction NEC	2 (0.2)	4 (0.1)	6 (0.1)	1.00
Intestinal obstruction NOS	2 (0.2)	3 (0.1)	5 (0.1)	
Subileus	0	1 (0.0)	1 (0.0)	
Gastrointestinal ulcers and perforation, site unspecified	0	1 (0.0)	1 (0.0)	
Ruptured diverticulum NOS	0	1 (0.0)	1 (0.0)	
Haemorrhoids and gastrointestinal varices (excl oesophageal)	1 (0.1)	1 (0.0)	2 (0.0)	
Haemorrhoids	1 (0.1)	1 (0.0)	2 (0.0)	
Gastrointestinal vascular malformations	0	1 (0.0)	1 (0.0)	
Splenic artery aneurysm	0	1 (0.0)	1 (0.0)	
Intestinal haemorrhages	1 (0.1)	2 (0.1)	3 (0.1)	
Rectal haemorrhage	1 (0.1)	2 (0.1)	3 (0.1)	
Abdominal cavity hernias NEC	2 (0.2)	6 (0.2)	8 (0.2)	1.00
Rectocele	2 (0.2)	6 (0.2)	8 (0.2)	1.00
Gastrointestinal signs and symptoms NEC	1 (0.1)	1 (0.0)	2 (0.0)	
Dysphagia	1 (0.1)	1 (0.0)	2 (0.0)	
Nausea and vomiting symptoms	2 (0.2)	6 (0.2)	8 (0.2)	1.00
Vomiting NOS	1 (0.1)	5 (0.2)	6 (0.1)	.671
Nausea	2 (0.2)	3 (0.1)	5 (0.1)	
Oesophageal disorders NEC	1 (0.1)	0	1 (0.0)	
Oesophageal disorder NOS	1 (0.1)	0	1 (0.0)	
Oesophageal stenosis and obstruction	1 (0.1)	0	1 (0.0)	
Oesophageal stenosis acquired	1 (0.1)	0	1 (0.0)	
Oesophageal ulcers and perforation	1 (0.1)	0	1 (0.0)	
Oesophageal perforation	1 (0.1)	0	1 (0.0)	
Intestinal ulcers and perforation NEC	0	2 (0.1)	2 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ABT129)
* Frequencies are analyzed using a Fisher's Exact test.
XABS0021 MEDDRA VERSION: 6.0

System Organ Class: Gastrointestinal disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1186) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Diverticular perforation NOS	0	1 (0.0)	1 (0.0)	
Intestinal perforation NOS	0	1 (0.0)	1 (0.0)	
Acute and chronic pancreatitis	4 (0.3)	4 (0.1)	8 (0.2)	.278
Pancreatitis NOS	3 (0.2)	1 (0.0)	4 (0.1)	
Pancreatitis acute	1 (0.1)	2 (0.1)	3 (0.1)	
Pancreatitis chronic	0	1 (0.0)	1 (0.0)	
Peritoneal and retroperitoneal disorders	1 (0.1)	1 (0.0)	2 (0.0)	
Peritonitis	1 (0.1)	1 (0.0)	2 (0.0)	
Peritoneal and retroperitoneal fibrosis and adhesions	0	1 (0.0)	1 (0.0)	
Abdominal adhesions	0	1 (0.0)	1 (0.0)	
Peritoneal and retroperitoneal haemorrhages	1 (0.1)	0	1 (0.0)	
Peritoneal haemorrhage	1 (0.1)	0	1 (0.0)	
Rectal inflammations NEC	0	1 (0.0)	1 (0.0)	
Proctitis NOS	0	1 (0.0)	1 (0.0)	
Non-mechanical ileus	1 (0.1)	0	1 (0.0)	
Ileus paralytic	1 (0.1)	0	1 (0.0)	
Gastrointestinal mucosal dystrophies and secretion disorders	2 (0.2)	2 (0.1)	4 (0.1)	
Colonic polyp	2 (0.2)	2 (0.1)	4 (0.1)	
Oesophagitis (excl infective)	1 (0.1)	2 (0.1)	3 (0.1)	
Oesophagitis NOS	0	2 (0.1)	2 (0.0)	
Oesophagitis ulcerative	1 (0.1)	0	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ABT129)
* Frequencies are analyzed using a Fisher's Exact test.
XABS0021 MEDDRA VERSION: 6.0

System Organ Class: General disorders and administration site conditions

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	12 (0.9)	39 (1.4)	51 (1.3)	.227
PATIENTS WITH NO EVENTS	1274 (99.1)	2686 (98.6)	3960 (98.7)	.227
Asthenic conditions	2 (0.2)	3 (0.1)	5 (0.1)	
Asthenia	1 (0.1)	1 (0.0)	2 (0.0)	
Malaise	0	2 (0.1)	2 (0.0)	
Fatigue	1 (0.1)	0	1 (0.0)	
Death and sudden death	4 (0.3)	8 (0.3)	12 (0.3)	1.00
Death NOS	3 (0.2)	3 (0.1)	6 (0.1)	.393
Sudden death	1 (0.1)	2 (0.1)	3 (0.1)	
Death unexplained	0	2 (0.1)	2 (0.0)	
Brain death	0	1 (0.0)	1 (0.0)	
Febrile disorders	1 (0.1)	3 (0.1)	4 (0.1)	
Pyrexia	1 (0.1)	3 (0.1)	4 (0.1)	
General signs and symptoms NEC	0	4 (0.1)	4 (0.1)	
General physical health deterioration	0	1 (0.0)	1 (0.0)	
Mobility decreased	0	1 (0.0)	1 (0.0)	
Perforated ulcer NOS	0	1 (0.0)	1 (0.0)	
Ulcer haemorrhage NOS	0	1 (0.0)	1 (0.0)	
Healing abnormal NEC	0	1 (0.0)	1 (0.0)	
Impaired healing	0	1 (0.0)	1 (0.0)	
Interactions	1 (0.1)	0	1 (0.0)	
Drug interaction NOS	1 (0.1)	0	1 (0.0)	
Oedema NEC	0	1 (0.0)	1 (0.0)	
Gravitational oedema	0	1 (0.0)	1 (0.0)	
Pain and discomfort NEC	5 (0.4)	22 (0.8)	27 (0.7)	.151
Chest pain	5 (0.4)	21 (0.8)	26 (0.6)	.207
Chest discomfort	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

System Organ Class: Hepatobiliary disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	9 (0.7)	21 (0.8)	30 (0.7)	1.00
PATIENTS WITH NO EVENTS	1277 (99.3)	2704 (99.2)	3981 (99.3)	1.00
Bile duct infections and inflammations	0	1 (0.0)	1 (0.0)	
Cholangitis NOS	0	1 (0.0)	1 (0.0)	
Cholecystitis and cholelithiasis	9 (0.7)	16 (0.6)	25 (0.6)	.671
Cholelithiasis	5 (0.4)	12 (0.4)	17 (0.4)	1.00
Cholecystitis NOS	4 (0.3)	2 (0.1)	6 (0.1)	.088
Cholecystitis acute NOS	1 (0.1)	2 (0.1)	3 (0.1)	
Cholecystitis chronic NOS	0	3 (0.1)	3 (0.1)	
Hepatic failure and associated disorders	0	1 (0.0)	1 (0.0)	
Hepatic failure	0	1 (0.0)	1 (0.0)	
Hepatic fibrosis and cirrhosis	0	1 (0.0)	1 (0.0)	
Hepatic cirrhosis NOS	0	1 (0.0)	1 (0.0)	
Hepatobiliary neoplasms benign	0	1 (0.0)	1 (0.0)	
Biliary cyst	0	1 (0.0)	1 (0.0)	
Obstructive bile duct disorders (excl neoplasms)	0	1 (0.0)	1 (0.0)	
Bile duct stone	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

System Organ Class: Infections and infestations

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	42 (3.3)	68 (2.5)	110 (2.7)	.178
PATIENTS WITH NO EVENTS	1244 (96.7)	2657 (97.5)	3901 (97.3)	.178
Bacterial infections NEC	1 (0.1)	0	1 (0.0)	
Pneumonia bacterial NOS	1 (0.1)	0	1 (0.0)	
Bone and joint infections	0	1 (0.0)	1 (0.0)	
Osteomyelitis NOS	0	1 (0.0)	1 (0.0)	
Clostridia infections	1 (0.1)	0	1 (0.0)	
Clostridium colitis	1 (0.1)	0	1 (0.0)	
Ear infections	0	2 (0.1)	2 (0.0)	
Ear infection NOS	0	1 (0.0)	1 (0.0)	
Labyrinthitis NOS	0	1 (0.0)	1 (0.0)	
Abdominal and gastrointestinal infections	6 (0.5)	3 (0.1)	9 (0.2)	.035
Gastroenteritis NOS	4 (0.3)	3 (0.1)	7 (0.2)	.221
Appendicitis	2 (0.2)	0	2 (0.0)	
Herpes viral infections	0	2 (0.1)	2 (0.0)	
Herpes zoster ophthalmic	0	2 (0.1)	2 (0.0)	
Infections NEC	3 (0.2)	5 (0.2)	8 (0.2)	.717
Postoperative infection	1 (0.1)	2 (0.1)	3 (0.1)	
Localised infection	0	2 (0.1)	2 (0.0)	
Empyema NOS	1 (0.1)	0	1 (0.0)	
Injection site infection	0	1 (0.0)	1 (0.0)	
Respiratory tract infection NOS	1 (0.1)	0	1 (0.0)	
Influenza viral infections	0	2 (0.1)	2 (0.0)	
Influenza	0	2 (0.1)	2 (0.0)	
Lower respiratory tract and lung infections	18 (1.4)	25 (0.9)	43 (1.1)	.189
Pneumonia NOS	15 (1.2)	16 (0.6)	31 (0.8)	.055
Lobar pneumonia NOS	1 (0.1)	2 (0.1)	3 (0.1)	
Bronchitis acute NOS	0	2 (0.1)	2 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0011 MEDDRA VERSION: 6.0

System Organ Class: Infections and infestations

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Bronchitis chronic NOS	2 (0.2)	0	2 (0.0)	
Bronchopneumonia NOS	1 (0.1)	1 (0.0)	2 (0.0)	
Lung infection NOS	0	2 (0.1)	2 (0.0)	
Bronchiectasis NOS	0	1 (0.0)	1 (0.0)	
Lower respiratory tract infection NOS	0	1 (0.0)	1 (0.0)	
Mycoplasma infections	1 (0.1)	0	1 (0.0)	
Pneumonia primary atypical	1 (0.1)	0	1 (0.0)	
Female reproductive tract infections	2 (0.2)	0	2 (0.0)	
Pyometra	1 (0.1)	0	1 (0.0)	
Uterine infection NOS	1 (0.1)	0	1 (0.0)	
Sepsis, bacteraemia and viraemia	2 (0.2)	8 (0.3)	10 (0.2)	.517
Sepsis NOS	1 (0.1)	6 (0.2)	7 (0.2)	.441
Bacteraemia	1 (0.1)	1 (0.0)	2 (0.0)	
Urosepsis	0	1 (0.0)	1 (0.0)	
Skin structures and soft tissue infections	2 (0.2)	3 (0.1)	5 (0.1)	
Cellulitis	2 (0.2)	2 (0.1)	4 (0.1)	
Skin and subcutaneous tissue abscess NOS	0	1 (0.0)	1 (0.0)	
Streptococcal infections	3 (0.2)	6 (0.2)	9 (0.2)	1.00
Erysipelas	3 (0.2)	4 (0.1)	7 (0.2)	.687
Pneumonia streptococcal	0	2 (0.1)	2 (0.0)	
Upper respiratory tract infections - pathogen class unspecified	2 (0.2)	3 (0.1)	5 (0.1)	
Sinusitis NOS	1 (0.1)	1 (0.0)	2 (0.0)	
Epiglottitis	0	1 (0.0)	1 (0.0)	
Peritonsillar abscess	0	1 (0.0)	1 (0.0)	
Pharyngitis	1 (0.1)	0	1 (0.0)	
Urinary tract infections	3 (0.2)	9 (0.3)	12 (0.3)	.762
Pyelonephritis NOS	1 (0.1)	5 (0.2)	6 (0.1)	.671
Urinary tract infection NOS	2 (0.2)	4 (0.1)	6 (0.1)	1.00

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0011 MEDDRA VERSION: 6.0

System Organ Class: Infections and infestations

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Viral infections NEC	1 (0.1)	2 (0.1)	3 (0.1)	
Gastroenteritis viral NOS	1 (0.1)	2 (0.1)	3 (0.1)	
Campylobacter infections	0	1 (0.0)	1 (0.0)	
Campylobacter gastroenteritis	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(AET129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Injury, poisoning and procedural complications

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	64 (5.0)	124 (4.6)	188 (4.7)	.575
PATIENTS WITH NO EVENTS	1222 (95.0)	2601 (95.4)	3823 (95.3)	.575
Conditions caused by cold	1 (0.1)	1 (0.0)	2 (0.0)	
Hypothermia	1 (0.1)	1 (0.0)	2 (0.0)	
Device failure and malfunction	0	3 (0.1)	3 (0.1)	
Dislocation of joint prosthesis	0	3 (0.1)	3 (0.1)	
Lower limb fractures and dislocations	29 (2.3)	38 (1.4)	67 (1.7)	.064
Hip fracture	12 (0.9)	19 (0.7)	31 (0.8)	.442
Ankle fracture	4 (0.3)	7 (0.3)	11 (0.3)	.753
Femur fracture	3 (0.2)	7 (0.3)	10 (0.2)	1.00
Femoral neck fracture	5 (0.4)	2 (0.1)	7 (0.2)	.038
Patella fracture	3 (0.2)	0	3 (0.1)	
Lower limb fracture NOS	2 (0.2)	0	2 (0.0)	
Tibia fracture	0	2 (0.1)	2 (0.0)	
Fibula fracture	0	1 (0.0)	1 (0.0)	
Foot fracture	0	1 (0.0)	1 (0.0)	
Abdominal injuries NEC	1 (0.1)	0	1 (0.0)	
Gastrointestinal injury NOS	1 (0.1)	0	1 (0.0)	
Spinal cord injuries NEC	0	1 (0.0)	1 (0.0)	
Spinal cord injury	0	1 (0.0)	1 (0.0)	
Chest and lung injuries NEC	1 (0.1)	0	1 (0.0)	
Sternal injury	1 (0.1)	0	1 (0.0)	
Fractures and dislocations NEC	2 (0.2)	3 (0.1)	5 (0.1)	
Joint dislocation	0	2 (0.1)	2 (0.0)	
Fracture displacement	1 (0.1)	0	1 (0.0)	
Fracture NOS	1 (0.1)	0	1 (0.0)	
Open fracture	0	1 (0.0)	1 (0.0)	
Limb injuries NEC (incl traumatic amputation)	1 (0.1)	6 (0.2)	7 (0.2)	.441

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(AET129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Injury, poisoning and procedural complications

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Joint sprain	0	3 (0.1)	3 (0.1)	
Meniscus lesion	0	2 (0.1)	2 (0.0)	
Hip dislocation	1 (0.1)	0	1 (0.0)	
Limb injury NOS	0	1 (0.0)	1 (0.0)	
Skin injuries NEC	1 (0.1)	0	1 (0.0)	
Skin laceration	1 (0.1)	0	1 (0.0)	
Muscle, tendon and ligament injuries	1 (0.1)	1 (0.0)	2 (0.0)	
Tendon injury	1 (0.1)	0	1 (0.0)	
Tendon rupture	0	1 (0.0)	1 (0.0)	
Non-site specific injuries NEC	34 (2.6)	60 (2.2)	94 (2.3)	.434
Fall	30 (2.3)	54 (2.0)	84 (2.1)	.479
Road traffic accident	3 (0.2)	5 (0.2)	8 (0.2)	.717
Arthropod bite	0	1 (0.0)	1 (0.0)	
Polytraumatism	1 (0.1)	0	1 (0.0)	
Non-site specific procedural complications	2 (0.2)	4 (0.1)	6 (0.1)	1.00
Post procedural haemorrhage	1 (0.1)	2 (0.1)	3 (0.1)	
Post procedural complication	0	1 (0.0)	1 (0.0)	
Post procedural pain	0	1 (0.0)	1 (0.0)	
Procedural complication	1 (0.1)	0	1 (0.0)	
Pelvic fractures and dislocations	3 (0.2)	10 (0.4)	13 (0.3)	.569
Fractured pelvis NOS	3 (0.2)	4 (0.1)	7 (0.2)	.687
Pubic rami fracture	0	5 (0.2)	5 (0.1)	
Acetabulum fracture	0	1 (0.0)	1 (0.0)	
Poisoning and toxicity	0	1 (0.0)	1 (0.0)	
Therapeutic agent poisoning	0	1 (0.0)	1 (0.0)	
Radiation injuries	0	1 (0.0)	1 (0.0)	
Radiation injury NOS	0	1 (0.0)	1 (0.0)	
Site specific injuries NEC	4 (0.3)	2 (0.1)	6 (0.1)	.088

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Injury, poisoning and procedural complications

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Head injury	1 (0.1)	2 (0.1)	3 (0.1)	
Back injury NOS	2 (0.2)	0	2 (0.0)	
Face injury	1 (0.1)	0	1 (0.0)	
Skull fractures, facial bone fractures and dislocations	2 (0.2)	3 (0.1)	5 (0.1)	
Facial bones fracture	1 (0.1)	2 (0.1)	3 (0.1)	
Skull fracture NOS	0	1 (0.0)	1 (0.0)	
Skull fractured base	1 (0.1)	0	1 (0.0)	
Spinal fractures and dislocations	3 (0.2)	21 (0.8)	24 (0.6)	.047
Spinal compression fracture	2 (0.2)	8 (0.3)	10 (0.2)	.517
Fractured sacrum	1 (0.1)	3 (0.1)	4 (0.1)	
Lumbar vertebral fracture	1 (0.1)	3 (0.1)	4 (0.1)	
Spinal fracture NOS	0	4 (0.1)	4 (0.1)	
Thoracic vertebral fracture	0	3 (0.1)	3 (0.1)	
Cervical vertebral fracture	0	1 (0.0)	1 (0.0)	
Thermal burns	0	1 (0.0)	1 (0.0)	
Thermal burn	0	1 (0.0)	1 (0.0)	
Thoracic cage fractures and dislocations	3 (0.2)	3 (0.1)	6 (0.1)	.393
Sternal fracture	2 (0.2)	2 (0.1)	4 (0.1)	
Rib fracture	2 (0.2)	1 (0.0)	3 (0.1)	
Upper limb fractures and dislocations	18 (1.4)	22 (0.8)	40 (1.0)	.089
Wrist fracture	7 (0.5)	7 (0.3)	14 (0.3)	.159
Humerus fracture	6 (0.5)	7 (0.3)	13 (0.3)	.371
Radius fracture	2 (0.2)	3 (0.1)	5 (0.1)	
Upper limb fracture NOS	1 (0.1)	3 (0.1)	4 (0.1)	
Ulna fracture	2 (0.2)	1 (0.0)	3 (0.1)	
Forearm fracture	1 (0.1)	1 (0.0)	2 (0.0)	
Hand fracture	1 (0.1)	0	1 (0.0)	
Scapula fracture	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
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XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Injury, poisoning and procedural complications

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1296) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Cerebral injuries NEC	3 (0.2)	8 (0.3)	11 (0.3)	1.00
Subdural haematoma	2 (0.2)	6 (0.2)	8 (0.2)	1.00
Concussion	1 (0.1)	2 (0.1)	3 (0.1)	
Intracranial injury NOS	1 (0.1)	1 (0.0)	2 (0.0)	
Brain contusion	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Investigations

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1296) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	13 (1.0)	22 (0.8)	35 (0.9)	.586
PATIENTS WITH NO EVENTS	1273 (99.0)	2703 (99.2)	3976 (99.1)	.586
Respiratory tract and thoracic imaging procedures	0	1 (0.0)	1 (0.0)	
Bronchoscopy	0	1 (0.0)	1 (0.0)	
Cardiac imaging procedures	2 (0.2)	4 (0.1)	6 (0.1)	1.00
Catheterisation cardiac	1 (0.1)	3 (0.1)	4 (0.1)	
Arteriogram coronary	1 (0.1)	1 (0.0)	2 (0.0)	
Gastrointestinal and abdominal imaging procedures	1 (0.1)	5 (0.2)	6 (0.1)	.671
Colonoscopy	1 (0.1)	2 (0.1)	3 (0.1)	
Endoscopy small intestine	0	1 (0.0)	1 (0.0)	
Endoscopy upper gastrointestinal tract	0	1 (0.0)	1 (0.0)	
Laparoscopy	0	1 (0.0)	1 (0.0)	
Hepatobiliary histopathology procedures	0	1 (0.0)	1 (0.0)	
Biopsy liver	0	1 (0.0)	1 (0.0)	
Histopathology procedures NEC	4 (0.3)	3 (0.1)	7 (0.1)	.221
Biopsy NOS	2 (0.2)	3 (0.1)	5 (0.1)	
Aspiration biopsy	2 (0.2)	0	2 (0.0)	
Imaging procedures NEC	0	1 (0.0)	1 (0.0)	
Endoscopy NOS	0	1 (0.0)	1 (0.0)	
Musculoskeletal and soft tissue histopathology procedures	1 (0.1)	0	1 (0.0)	
Biopsy bone	1 (0.1)	0	1 (0.0)	
Musculoskeletal and soft tissue imaging procedures	0	1 (0.0)	1 (0.0)	
Arthroscopy	0	1 (0.0)	1 (0.0)	
Physical examination procedures	0	1 (0.0)	1 (0.0)	
Weight decreased	0	1 (0.0)	1 (0.0)	
Reproductive organ and breast histopathology procedures	3 (0.2)	2 (0.1)	5 (0.1)	
Biopsy breast	3 (0.2)	2 (0.1)	5 (0.1)	
Reproductive organ and breast imaging procedures	0	1 (0.0)	1 (0.0)	

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XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Investigations

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1296) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Hysteroscopy	0	1 (0.0)	1 (0.0)	
Urinary tract imaging procedures	1 (0.1)	1 (0.0)	2 (0.0)	
Cystoscopy	1 (0.1)	1 (0.0)	2 (0.0)	
Vascular imaging procedures NEC	1 (0.1)	1 (0.0)	2 (0.0)	
Angiogram NOS	1 (0.1)	1 (0.0)	2 (0.0)	
Virus identification and serology	0	1 (0.0)	1 (0.0)	
Hepatitis B virus	0	1 (0.0)	1 (0.0)	
Heart rate and pulse investigations	0	1 (0.0)	1 (0.0)	
Heart rate irregular	0	1 (0.0)	1 (0.0)	
ECG investigations	1 (0.1)	0	1 (0.0)	
Electrocardiogram change NOS	1 (0.1)	0	1 (0.0)	

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XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Metabolism and nutrition disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	11 (0.9)	11 (0.4)	22 (0.5)	.106
PATIENTS WITH NO EVENTS	1275 (99.1)	2714 (99.6)	3989 (99.5)	.106
Appetite disorders	1 (0.1)	0	1 (0.0)	
Anorexia	1 (0.1)	0	1 (0.0)	
Calcium increased disorders	1 (0.1)	0	1 (0.0)	
Hypercalcaemia	1 (0.1)	0	1 (0.0)	
Diabetes mellitus (incl subtypes)	0	2 (0.1)	2 (0.0)	
Diabetes mellitus inadequate control	0	1 (0.0)	1 (0.0)	
Diabetes mellitus NOS	0	1 (0.0)	1 (0.0)	
Diabetic complications NEC	0	1 (0.0)	1 (0.0)	
Diabetic ketoacidosis	0	1 (0.0)	1 (0.0)	
General nutritional disorders NEC	1 (0.1)	1 (0.0)	2 (0.0)	
Cachexia	0	1 (0.0)	1 (0.0)	
Malnutrition NOS	1 (0.1)	0	1 (0.0)	
Hyperglycaemic conditions NEC	1 (0.1)	2 (0.1)	3 (0.1)	
Hyperglycaemia NOS	1 (0.1)	2 (0.1)	3 (0.1)	
Hypoglycaemic conditions NEC	0	1 (0.0)	1 (0.0)	
Hypoglycaemia NOS	0	1 (0.0)	1 (0.0)	
Iron deficiencies	1 (0.1)	0	1 (0.0)	
Iron deficiency	1 (0.1)	0	1 (0.0)	
Potassium imbalance	1 (0.1)	2 (0.1)	3 (0.1)	
Hypokalaemia	1 (0.1)	2 (0.1)	3 (0.1)	
Sodium imbalance	3 (0.2)	1 (0.0)	4 (0.1)	
Hyponatraemia	3 (0.2)	1 (0.0)	4 (0.1)	
Total fluid volume decreased	2 (0.2)	6 (0.2)	8 (0.2)	1.00
Dehydration	2 (0.2)	6 (0.2)	8 (0.2)	1.00

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Musculoskeletal and connective tissue disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	27 (2.1)	85 (3.1)	112 (2.8)	.080
PATIENTS WITH NO EVENTS	1259 (97.9)	2640 (96.9)	3899 (97.2)	.080
Arthropathies NEC	1 (0.1)	7 (0.3)	8 (0.2)	.449
Arthritis NOS	1 (0.1)	5 (0.2)	6 (0.1)	.671
Monoarthritis	0	2 (0.1)	2 (0.0)	
Bone related signs and symptoms	0	1 (0.0)	1 (0.0)	
Pain in jaw	0	1 (0.0)	1 (0.0)	
Cartilage disorders	0	1 (0.0)	1 (0.0)	
Costochondritis	0	1 (0.0)	1 (0.0)	
Connective tissue disorders (excl LE)	0	1 (0.0)	1 (0.0)	
Polymyalgia rheumatica	0	1 (0.0)	1 (0.0)	
Crystal arthropathic disorders	0	2 (0.1)	2 (0.0)	
Chondrocalcinosis pyrophosphate	0	1 (0.0)	1 (0.0)	
Gouty arthritis	0	1 (0.0)	1 (0.0)	
Spine and neck deformities	0	1 (0.0)	1 (0.0)	
Spondylolisthesis acquired	0	1 (0.0)	1 (0.0)	
Bursal disorders	0	1 (0.0)	1 (0.0)	
Bursitis	0	1 (0.0)	1 (0.0)	
Intervertebral disc disorders NEC	2 (0.2)	2 (0.1)	4 (0.1)	
Intervertebral disc herniation	2 (0.2)	2 (0.1)	4 (0.1)	
Joint related signs and symptoms	6 (0.5)	8 (0.3)	14 (0.3)	.398
Arthralgia	5 (0.4)	8 (0.3)	13 (0.3)	.767
Joint swelling	1 (0.1)	0	1 (0.0)	
Metabolic bone disorders	0	1 (0.0)	1 (0.0)	
Osteoporosis NOS	0	1 (0.0)	1 (0.0)	
Bone disorders NEC	1 (0.1)	7 (0.3)	8 (0.2)	.449
Aseptic necrosis bone	0	3 (0.1)	3 (0.1)	
Pseudarthrosis	0	2 (0.1)	2 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
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XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Musculoskeletal and connective tissue disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Osteitis deformans	0	1 (0.0)	1 (0.0)	
Osteonecrosis	0	1 (0.0)	1 (0.0)	
Spinal disorder NOS	1 (0.1)	0	1 (0.0)	
Joint related disorders NEC	0	7 (0.3)	7 (0.2)	.105
Rotator cuff syndrome	0	7 (0.3)	7 (0.2)	.105
Musculoskeletal and connective tissue signs and symptoms NEC	10 (0.8)	10 (0.4)	20 (0.5)	.095
Back pain	8 (0.6)	7 (0.3)	15 (0.4)	.096
Pain in extremity	1 (0.1)	3 (0.1)	4 (0.1)	
Dupuytren's contracture	1 (0.1)	0	1 (0.0)	
Muscle related signs and symptoms NEC	0	1 (0.0)	1 (0.0)	
Muscle cramp	0	1 (0.0)	1 (0.0)	
Myopathies	0	1 (0.0)	1 (0.0)	
Muscle necrosis	0	1 (0.0)	1 (0.0)	
Pathological fractures and complications	1 (0.1)	2 (0.1)	3 (0.1)	
Osteoporotic fracture	1 (0.1)	1 (0.0)	2 (0.0)	
Fracture nonunion	0	1 (0.0)	1 (0.0)	
Rheumatoid arthropathies	0	3 (0.1)	3 (0.1)	
Rheumatoid arthritis	0	3 (0.1)	3 (0.1)	
Soft tissue disorders NEC	0	2 (0.1)	2 (0.0)	
Fistula NOS	0	1 (0.0)	1 (0.0)	
Groin pain	0	1 (0.0)	1 (0.0)	
Tendon disorders	0	2 (0.1)	2 (0.0)	
Ganglion	0	1 (0.0)	1 (0.0)	
Tendonitis	0	1 (0.0)	1 (0.0)	
Spondyloarthropathies	1 (0.1)	1 (0.0)	2 (0.0)	
Spinal fusion acquired	1 (0.1)	1 (0.0)	2 (0.0)	
Osteoarthropathies	5 (0.4)	30 (1.1)	35 (0.9)	.027
Localised osteoarthritis	4 (0.3)	22 (0.8)	26 (0.6)	.090

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Musculoskeletal and connective tissue disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Osteoarthritis NOS	2 (0.2)	8 (0.3)	10 (0.2)	.517

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
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XARS0021 MEDDRA VERSION: 6.0

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

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	88 (6.8)	120 (4.4)	208 (5.2)	.002
PATIENTS WITH NO EVENTS	1198 (93.2)	2605 (95.6)	3803 (94.8)	.002
B-cell lymphomas NEC	0	2 (0.1)	2 (0.0)	
B-cell lymphoma stage I	0	1 (0.0)	1 (0.0)	
B-cell lymphoma NOS	0	1 (0.0)	1 (0.0)	
Bladder neoplasms malignant	1 (0.1)	0	1 (0.0)	
Bladder cancer recurrent	1 (0.1)	0	1 (0.0)	
Bone neoplasms unspecified malignancy	1 (0.1)	0	1 (0.0)	
Bone neoplasm NOS	1 (0.1)	0	1 (0.0)	
Breast and nipple neoplasms malignant	23 (1.8)	24 (0.9)	47 (1.2)	.017
Breast cancer invasive NOS	11 (0.9)	12 (0.4)	23 (0.6)	.118
Breast cancer NOS	6 (0.5)	3 (0.1)	9 (0.2)	.035
Breast cancer in situ	2 (0.2)	5 (0.2)	7 (0.2)	1.00
Breast cancer stage I	3 (0.2)	2 (0.1)	5 (0.1)	
Breast cancer stage II	1 (0.1)	2 (0.1)	3 (0.1)	
Breast cancer stage III	1 (0.1)	0	1 (0.0)	
Cardiovascular neoplasms malignant and unspecified	1 (0.1)	0	1 (0.0)	
Angiosarcoma NOS	1 (0.1)	0	1 (0.0)	
Cervix neoplasms malignant	1 (0.1)	1 (0.0)	2 (0.0)	
Cervical carcinoma stage 0	1 (0.1)	1 (0.0)	2 (0.0)	
Colonic neoplasms malignant	3 (0.2)	13 (0.5)	16 (0.4)	.297
Colon cancer NOS	3 (0.2)	7 (0.3)	10 (0.2)	1.00
Colon cancer stage III	0	3 (0.1)	3 (0.1)	
Colon cancer metastatic	0	2 (0.1)	2 (0.0)	
Colon cancer stage II	0	1 (0.0)	1 (0.0)	
Colorectal and anal neoplasms malignancy unspecified	1 (0.1)	0	1 (0.0)	
Colon neoplasm NOS	1 (0.1)	0	1 (0.0)	
Diffuse large B-cell lymphomas	1 (0.1)	0	1 (0.0)	

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XARS0021 MEDDRA VERSION: 6.0

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

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n	(%)	RLX060 (N=2725) n	(%)	Total (N=4011) n	(%)	p-Value*
Diffuse large B-cell lymphoma NOS	1	(0.1)	0		1	(0.0)	
Endocrine neoplasms malignant and unspecified NEC	0		1	(0.0)	1	(0.0)	
Neuroendocrine carcinoma	0		1	(0.0)	1	(0.0)	
Endometrial neoplasms malignant	2	(0.2)	4	(0.1)	6	(0.1)	1.00
Endometrial cancer stage I	1	(0.1)	3	(0.1)	4	(0.1)	
Endometrial cancer NOS	1	(0.1)	1	(0.0)	2	(0.0)	
Female reproductive neoplasms unspecified malignancy	1	(0.1)	0		1	(0.0)	
Ovarian neoplasm NOS	1	(0.1)	0		1	(0.0)	
Gastric neoplasms malignant	0		5	(0.2)	5	(0.1)	
Gastric cancer NOS	0		4	(0.1)	4	(0.1)	
Gastric cancer stage II	0		1	(0.0)	1	(0.0)	
Gastrointestinal neoplasms benign NEC	0		2	(0.1)	2	(0.0)	
Benign small intestinal neoplasm NOS	0		1	(0.0)	1	(0.0)	
Salivary gland neoplasm benign NOS	0		1	(0.0)	1	(0.0)	
Gastrointestinal neoplasms malignant NEC	2	(0.2)	2	(0.1)	4	(0.1)	
Gastrointestinal tract cancer NOS	2	(0.2)	1	(0.0)	3	(0.1)	
Gastrointestinal cancer metastatic	0		1	(0.0)	1	(0.0)	
Gastrointestinal neoplasms malignancy unspecified NEC	2	(0.2)	0		2	(0.0)	
Gastrointestinal stromal tumour	2	(0.2)	0		2	(0.0)	
Glial tumours malignant	0		1	(0.0)	1	(0.0)	
Glioblastoma	0		1	(0.0)	1	(0.0)	
Hepatic neoplasms malignant	1	(0.1)	2	(0.1)	3	(0.1)	
Hepatic neoplasm malignant NOS	1	(0.1)	1	(0.0)	2	(0.0)	
Hepatic cancer metastatic	0		1	(0.0)	1	(0.0)	
Hepatobiliary neoplasms malignancy unspecified	0		1	(0.0)	1	(0.0)	
Hepatic neoplasm NOS	0		1	(0.0)	1	(0.0)	
Laryngeal neoplasms malignant	1	(0.1)	0		1	(0.0)	
Laryngeal cancer NOS	1	(0.1)	0		1	(0.0)	

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XARS0021 MEDDRA VERSION: 6.0

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

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n	(%)	RLX060 (N=2725) n	(%)	Total (N=4011) n	(%)	p-Value*
Leiomyosarcomas	0		1	(0.0)	1	(0.0)	
Leiomyosarcoma NOS	0		1	(0.0)	1	(0.0)	
Leukaemias acute lymphocytic	1	(0.1)	0		1	(0.0)	
Acute lymphocytic leukaemia	1	(0.1)	0		1	(0.0)	
Leukaemias chronic lymphocytic	0		1	(0.0)	1	(0.0)	
Chronic lymphocytic leukaemia NOS	0		1	(0.0)	1	(0.0)	
Leukaemias chronic myeloid	1	(0.1)	0		1	(0.0)	
Chronic myeloid leukaemia	1	(0.1)	0		1	(0.0)	
Lip and oral cavity neoplasms malignant	1	(0.1)	0		1	(0.0)	
Lip and/or oral cavity cancer NOS	1	(0.1)	0		1	(0.0)	
Lip and oral cavity neoplasms benign	0		1	(0.0)	1	(0.0)	
Salivary gland adenoma	0		1	(0.0)	1	(0.0)	
Lower gastrointestinal neoplasms benign	0		1	(0.0)	1	(0.0)	
Colon adenoma	0		1	(0.0)	1	(0.0)	
Lymphomas unspecified NEC	0		2	(0.1)	2	(0.0)	
Lymphoma NOS	0		2	(0.1)	2	(0.0)	
Skin melanomas (excl ocular)	1	(0.1)	4	(0.1)	5	(0.1)	
Malignant melanoma	1	(0.1)	3	(0.1)	4	(0.1)	
Malignant melanoma stage IV	0		1	(0.0)	1	(0.0)	
Metastases to specified sites	3	(0.2)	3	(0.1)	6	(0.1)	.393
Metastases to bone	1	(0.1)	1	(0.0)	2	(0.0)	
Metastases to central nervous system	1	(0.1)	1	(0.0)	2	(0.0)	
Metastases to lung	0		2	(0.1)	2	(0.0)	
Metastases to liver	0		1	(0.0)	1	(0.0)	
Metastases to lymph nodes	1	(0.1)	0		1	(0.0)	
Metastases to unknown and unspecified sites	0		1	(0.0)	1	(0.0)	
Metastases NOS	0		1	(0.0)	1	(0.0)	
Myeloproliferative disorders (excl leukaemias)	1	(0.1)	0		1	(0.0)	

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XARS0021 MEDDRA VERSION: 6.0

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

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Myeloproliferative disorder NOS	1 (0.1)	0	1 (0.0)	
Neoplasms malignant site unspecified NEC	5 (0.4)	12 (0.4)	17 (0.4)	1.00
Squamous cell carcinoma	4 (0.3)	8 (0.3)	12 (0.3)	1.00
Adenocarcinoma NOS	0	3 (0.1)	3 (0.1)	
Metastatic neoplasm NOS, primary site unknown	1 (0.1)	1 (0.0)	2 (0.0)	
Carcinoma NOS	0	1 (0.0)	1 (0.0)	
Metastatic carcinoma	0	1 (0.0)	1 (0.0)	
Neoplasms benign site unspecified NEC	1 (0.1)	1 (0.0)	2 (0.0)	
Adenoma benign NOS	0	1 (0.0)	1 (0.0)	
Fibroma NOS	1 (0.1)	0	1 (0.0)	
Nervous system neoplasms unspecified malignancy NEC	1 (0.1)	2 (0.1)	3 (0.1)	
Meningioma	1 (0.1)	1 (0.0)	2 (0.0)	
Brain neoplasm NOS	0	1 (0.0)	1 (0.0)	
Non-small cell neoplasms malignant of the respiratory tract cell typ	1 (0.1)	1 (0.0)	2 (0.0)	
Lung squamous cell carcinoma stage IV	1 (0.1)	0	1 (0.0)	
Non-small cell lung cancer stage IIIB	0	1 (0.0)	1 (0.0)	
Oesophageal neoplasms malignant	1 (0.1)	1 (0.0)	2 (0.0)	
Oesophageal adenocarcinoma NOS	1 (0.1)	0	1 (0.0)	
Oesophageal carcinoma NOS	0	1 (0.0)	1 (0.0)	
Ovarian neoplasms malignant (excl germ cell)	2 (0.2)	2 (0.1)	4 (0.1)	
Ovarian cancer NOS	1 (0.1)	1 (0.0)	2 (0.0)	
Ovarian adenocarcinoma	1 (0.1)	0	1 (0.0)	
Ovarian cancer metastatic	0	1 (0.0)	1 (0.0)	
Ovarian epithelial cancer recurrent	0	1 (0.0)	1 (0.0)	
Pancreatic neoplasms malignant (excl islet cell and carcinoid)	2 (0.2)	3 (0.1)	5 (0.1)	
Pancreatic carcinoma NOS	2 (0.2)	2 (0.1)	4 (0.1)	
Adenocarcinoma pancreas	0	1 (0.0)	1 (0.0)	
Rectal neoplasms malignant	3 (0.2)	2 (0.1)	5 (0.1)	

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XARS0021 MEDDRA VERSION: 6.0

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

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Rectal cancer metastatic	1 (0.1)	1 (0.0)	2 (0.0)	
Rectal cancer stage III	1 (0.1)	0	1 (0.0)	
Rectal cancer NOS	0	1 (0.0)	1 (0.0)	
Rectosigmoid cancer NOS	1 (0.1)	0	1 (0.0)	
Renal cell carcinomas	2 (0.2)	4 (0.1)	6 (0.1)	1.00
Clear cell carcinoma of the kidney	0	2 (0.1)	2 (0.0)	
Renal cell carcinoma stage unspecified	1 (0.1)	1 (0.0)	2 (0.0)	
Renal cancer metastatic	1 (0.1)	0	1 (0.0)	
Renal cell carcinoma stage II	0	1 (0.0)	1 (0.0)	
Respiratory tract and pleural neoplasms malignant cell type unspecif	4 (0.3)	6 (0.2)	10 (0.2)	.735
Lung cancer stage unspecified (excl metastatic tumours to lung)	2 (0.2)	2 (0.1)	4 (0.1)	
Lung cancer metastatic	0	3 (0.1)	3 (0.1)	
Bronchial carcinoma	1 (0.1)	0	1 (0.0)	
Lung carcinoma cell type unspecified recurrent	1 (0.1)	0	1 (0.0)	
Throat cancer NOS	0	1 (0.0)	1 (0.0)	
Skin neoplasms benign	1 (0.1)	1 (0.0)	2 (0.0)	
Benign skin neoplasm NOS	0	1 (0.0)	1 (0.0)	
Pyogenic granuloma	1 (0.1)	0	1 (0.0)	
Skin neoplasms malignant and unspecified (excl melanoma)	21 (1.6)	20 (0.7)	41 (1.0)	.011
Basal cell carcinoma	18 (1.4)	17 (0.6)	35 (0.9)	.018
Squamous cell carcinoma of skin	2 (0.2)	3 (0.1)	5 (0.1)	
Bowen's disease	2 (0.2)	1 (0.0)	3 (0.1)	
Skin carcinoma NOS	1 (0.1)	1 (0.0)	2 (0.0)	
Respiratory tract small cell carcinomas	0	1 (0.0)	1 (0.0)	
Small cell lung cancer metastatic	0	1 (0.0)	1 (0.0)	
Small intestinal neoplasms malignant	2 (0.2)	0	2 (0.0)	
Malignant neoplasm of appendix vermiformis	1 (0.1)	0	1 (0.0)	
Small intestine carcinoma metastatic	1 (0.1)	0	1 (0.0)	

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XARS0021 MEDDRA VERSION: 6.0

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

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)*	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Thyroid neoplasms benign	1 (0.1)	0	1 (0.0)	
Thyroid adenoma NOS	1 (0.1)	0	1 (0.0)	
Thyroid neoplasms malignant	0	2 (0.1)	2 (0.0)	
Medullary thyroid cancer	0	1 (0.0)	1 (0.0)	
Papillary thyroid cancer	0	1 (0.0)	1 (0.0)	
Uterine neoplasms benign	1 (0.1)	1 (0.0)	2 (0.0)	
Uterine fibroids	1 (0.1)	1 (0.0)	2 (0.0)	
Uterine neoplasms malignant NEC	1 (0.1)	0	1 (0.0)	
Uterine cancer NOS	1 (0.1)	0	1 (0.0)	

Program: EMP.H3SSGGJY.SASPGM(SECT129) Input: EMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: EMP.H3SO.GGJY.FINAL(AET129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Nervous system disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	34 (2.6)	101 (3.7)	135 (3.4)	.091
PATIENTS WITH NO EVENTS	1252 (97.4)	2624 (96.3)	3876 (96.6)	.091
Alzheimer's disease (incl subtypes)	0	1 (0.0)	1 (0.0)	
Dementia of the Alzheimer's type NOS	0	1 (0.0)	1 (0.0)	
Central nervous system aneurysms	0	1 (0.0)	1 (0.0)	
Cerebral arterial aneurysm	0	1 (0.0)	1 (0.0)	
Central nervous system haemorrhages and cerebrovascular accidents	13 (1.0)	40 (1.5)	53 (1.3)	.300
Cerebrovascular accident	4 (0.3)	20 (0.7)	24 (0.6)	.126
Cerebral infarction	3 (0.2)	7 (0.3)	10 (0.2)	1.00
Ischaemic stroke NOS	3 (0.2)	6 (0.2)	9 (0.2)	1.00
Cerebral haemorrhage	1 (0.1)	3 (0.1)	4 (0.1)	
Cerebral thrombosis NOS	0	2 (0.1)	2 (0.0)	
Haemorrhagic stroke	1 (0.1)	1 (0.0)	2 (0.0)	
Intracranial haemorrhage NOS	1 (0.1)	1 (0.0)	2 (0.0)	
Brain stem haemorrhage	0	1 (0.0)	1 (0.0)	
Cerebral artery thrombosis	0	1 (0.0)	1 (0.0)	
Ruptured cerebral aneurysm	0	1 (0.0)	1 (0.0)	
Central nervous system vascular disorders NEC	1 (0.1)	6 (0.2)	7 (0.2)	.441
Carotid artery stenosis	1 (0.1)	4 (0.1)	5 (0.1)	
Cerebral haematoma	0	1 (0.0)	1 (0.0)	
Lacunar infarction	0	1 (0.0)	1 (0.0)	
Cerebellar coordination and balance disturbances	0	1 (0.0)	1 (0.0)	
Ataxia	0	1 (0.0)	1 (0.0)	
Cortical dysfunction NEC	1 (0.1)	0	1 (0.0)	
Aphasia	1 (0.1)	0	1 (0.0)	
Dementia (excl Alzheimer's type)	1 (0.1)	1 (0.0)	2 (0.0)	
Dementia NOS	1 (0.1)	1 (0.0)	2 (0.0)	
Disturbances in consciousness NEC	6 (0.5)	18 (0.7)	24 (0.6)	.519

Program: EMP.H3SSGGJY.SASPGM(SECT129) Input: EMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: EMP.H3SO.GGJY.FINAL(AET129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Nervous system disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Syncope	4 (0.3)	14 (0.5)	18 (0.4)	.456
Loss of consciousness	1 (0.1)	2 (0.1)	3 (0.1)	
Syncope vasovagal	1 (0.1)	2 (0.1)	3 (0.1)	
Dyskinesias and movement disorders NEC	1 (0.1)	0	1 (0.0)	
Movement disorder NOS	1 (0.1)	0	1 (0.0)	
Encephalopathies toxic and metabolic	0	1 (0.0)	1 (0.0)	
Hepatic encephalopathy	0	1 (0.0)	1 (0.0)	
Encephalopathies NEC	0	2 (0.1)	2 (0.0)	
Anoxic encephalopathy	0	2 (0.1)	2 (0.0)	
Hypoxic encephalopathy	0	1 (0.0)	1 (0.0)	
Headaches NEC	0	3 (0.1)	3 (0.1)	
Headache	0	2 (0.1)	2 (0.0)	
Cluster headache	0	1 (0.0)	1 (0.0)	
Hydrocephalic conditions	0	1 (0.0)	1 (0.0)	
Normal pressure hydrocephalus	0	1 (0.0)	1 (0.0)	
Memory loss (excl dementia)	0	1 (0.0)	1 (0.0)	
Global amnesia	0	1 (0.0)	1 (0.0)	
Mental impairment (excl dementia and memory loss)	0	1 (0.0)	1 (0.0)	
Cognitive disorder	0	1 (0.0)	1 (0.0)	
Migraine headaches	0	1 (0.0)	1 (0.0)	
Migraine NOS	0	1 (0.0)	1 (0.0)	
Mononeuropathies	3 (0.2)	3 (0.1)	6 (0.1)	.393
Sciatica	2 (0.2)	3 (0.1)	5 (0.1)	
Radial nerve palsy	1 (0.1)	0	1 (0.0)	
Motor neurone diseases	0	2 (0.1)	2 (0.0)	
Amyotrophic lateral sclerosis	0	2 (0.1)	2 (0.0)	
Neurologic visual problems NEC	0	1 (0.0)	1 (0.0)	
Hemianopia NOS	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SFCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Nervous system disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Neurological signs and symptoms NEC	1 (0.1)	4 (0.1)	5 (0.1)	
Dizziness	1 (0.1)	4 (0.1)	5 (0.1)	
Paraesthesias and dysaesthesias	1 (0.1)	5 (0.2)	6 (0.1)	.671
Hypoaesthesia	0	4 (0.1)	4 (0.1)	
Paraesthesia	1 (0.1)	1 (0.0)	2 (0.0)	
Paralysis and paresis (excl congenital and cranial nerve)	2 (0.2)	3 (0.1)	5 (0.1)	
Hemiparesis	2 (0.2)	2 (0.1)	4 (0.1)	
Hemiplegia	0	1 (0.0)	1 (0.0)	
Seizures and seizure disorders NEC	0	4 (0.1)	4 (0.1)	
Convulsions NOS	0	3 (0.1)	3 (0.1)	
Epilepsy NOS	0	1 (0.0)	1 (0.0)	
Speech and language abnormalities	0	1 (0.0)	1 (0.0)	
Dysphonia	0	1 (0.0)	1 (0.0)	
Spinal cord and nerve root disorders NEC	3 (0.2)	2 (0.1)	5 (0.1)	
Spinal stenosis NOS	3 (0.2)	1 (0.0)	4 (0.1)	
Nerve root compression NOS	0	1 (0.0)	1 (0.0)	
Radiculopathy NOS	0	1 (0.0)	1 (0.0)	
Structural brain disorders NEC	0	1 (0.0)	1 (0.0)	
Cerebral atrophy	0	1 (0.0)	1 (0.0)	
Transient cerebrovascular events	8 (0.6)	12 (0.4)	20 (0.5)	.474
Transient ischaemic attack	8 (0.6)	12 (0.4)	20 (0.5)	.474
Vagus nerve disorders	0	1 (0.0)	1 (0.0)	
Vocal cord paralysis	0	1 (0.0)	1 (0.0)	
Coma states	0	3 (0.1)	3 (0.1)	
Coma	0	1 (0.0)	1 (0.0)	
Diabetic coma NOS	0	1 (0.0)	1 (0.0)	
Diabetic hyperglycaemic coma	0	1 (0.0)	1 (0.0)	
Cervical spinal cord and nerve root disorders	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SFCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Nervous system disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Cervical spinal stenosis	0	1 (0.0)	1 (0.0)	
Lumbar spinal cord and nerve root disorders	1 (0.1)	3 (0.1)	4 (0.1)	
Lumbar spinal stenosis	1 (0.1)	3 (0.1)	4 (0.1)	
Nervous system disorders NEC	0	2 (0.1)	2 (0.0)	
Cerebral disorder	0	1 (0.0)	1 (0.0)	
Neurological disorder NOS	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Psychiatric disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	5 (0.4)	7 (0.3)	12 (0.3)	.536
PATIENTS WITH NO EVENTS	1281 (99.6)	2718 (99.7)	3999 (99.7)	.536
Anxiety symptoms	0	1 (0.0)	1 (0.0)	
Agitation	0	1 (0.0)	1 (0.0)	
Confusion and disorientation	0	2 (0.1)	2 (0.0)	
Confusional state	0	2 (0.1)	2 (0.0)	
Depressive disorders	4 (0.3)	2 (0.1)	6 (0.1)	.088
Depression	1 (0.1)	2 (0.1)	3 (0.1)	
Major depressive disorder NOS	3 (0.2)	0	3 (0.1)	
Mental disorders NEC	0	1 (0.0)	1 (0.0)	
Mental status changes	0	1 (0.0)	1 (0.0)	
Schizophrenia NEC	1 (0.1)	1 (0.0)	2 (0.0)	
Schizophrenia NOS	0	1 (0.0)	1 (0.0)	
Schizophrenia, paranoid type	1 (0.1)	0	1 (0.0)	
Suicidal and self-injurious behaviour	0	1 (0.0)	1 (0.0)	
Suicidal ideation	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Renal and urinary disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	11 (0.9)	20 (0.7)	31 (0.8)	.701
PATIENTS WITH NO EVENTS	1275 (99.1)	2705 (99.3)	3980 (99.2)	.701
Urinary abnormalities	1 (0.1)	0	1 (0.0)	
Proteinuria	1 (0.1)	0	1 (0.0)	
Bladder and urethral symptoms	4 (0.3)	7 (0.3)	11 (0.3)	.753
Urinary incontinence	1 (0.1)	3 (0.1)	4 (0.1)	
Stress incontinence	1 (0.1)	2 (0.1)	3 (0.1)	
Dysuria	1 (0.1)	0	1 (0.0)	
Pollakiuria	0	1 (0.0)	1 (0.0)	
Urge incontinence	1 (0.1)	0	1 (0.0)	
Urinary retention	0	1 (0.0)	1 (0.0)	
Bladder disorders NEC	3 (0.2)	8 (0.3)	11 (0.3)	1.00
Cystocele	3 (0.2)	4 (0.1)	7 (0.2)	.487
Bladder prolapse	0	4 (0.1)	4 (0.1)	
Bladder infections and inflammations	0	3 (0.1)	3 (0.1)	
Cystitis NOS	0	2 (0.1)	2 (0.0)	
Cystitis interstitial	0	1 (0.0)	1 (0.0)	
Bladder neoplasms	0	1 (0.0)	1 (0.0)	
Urinary bladder polyp	0	1 (0.0)	1 (0.0)	
Renal failure and impairment	4 (0.3)	0	4 (0.1)	
Renal failure acute	3 (0.2)	0	3 (0.1)	
Oliguria	1 (0.1)	0	1 (0.0)	
Renal failure NOS	1 (0.1)	0	1 (0.0)	
Renal lithiasis	0	1 (0.0)	1 (0.0)	
Nephrolithiasis	0	1 (0.0)	1 (0.0)	
Renal obstructive disorders	0	1 (0.0)	1 (0.0)	
Hydronephrosis	0	1 (0.0)	1 (0.0)	
Renal vascular and ischaemic conditions	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Renal and urinary disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Renal artery stenosis	0	1 (0.0)	1 (0.0)	
Urinary tract lithiasis (excl renal)	0	1 (0.0)	1 (0.0)	
Calculus ureteric	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Reproductive system and breast disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	10 (0.8)	20 (0.7)	30 (0.7)	.847
PATIENTS WITH NO EVENTS	1276 (99.2)	2705 (99.3)	3981 (99.3)	.847
Pelvis and broad ligament disorders NEC	0	1 (0.0)	1 (0.0)	
Pelvic peritoneal adhesions	0	1 (0.0)	1 (0.0)	
Uterine disorders NEC	1 (0.1)	2 (0.1)	3 (0.1)	
Endometrial hyperplasia	1 (0.1)	1 (0.0)	2 (0.0)	
Endometriosis	0	1 (0.0)	1 (0.0)	
Menopausal effects on the genitourinary tract	0	3 (0.1)	3 (0.1)	
Postmenopausal haemorrhage	0	2 (0.1)	2 (0.0)	
Vaginitis atrophic	0	1 (0.0)	1 (0.0)	
Ovarian and fallopian tube cysts and neoplasms	1 (0.1)	6 (0.2)	7 (0.2)	.441
Ovarian cyst	1 (0.1)	6 (0.2)	7 (0.2)	.441
Pelvic prolapse	6 (0.5)	6 (0.2)	12 (0.3)	.217
Uterine prolapse	3 (0.2)	2 (0.1)	5 (0.1)	
Vaginal prolapse	1 (0.1)	2 (0.1)	3 (0.1)	
Uterovaginal prolapse	2 (0.2)	0	2 (0.0)	
Genital prolapse NOS	0	1 (0.0)	1 (0.0)	
Pelvic muscles inadequate	0	1 (0.0)	1 (0.0)	
Reproductive tract signs and symptoms NEC	0	1 (0.0)	1 (0.0)	
Pelvic pain NOS	0	1 (0.0)	1 (0.0)	
Breast disorders NEC	2 (0.2)	1 (0.0)	3 (0.1)	
Breast mass NOS	2 (0.2)	1 (0.0)	3 (0.1)	
Uterine neoplasms	0	1 (0.0)	1 (0.0)	
Uterine polyp NOS	0	1 (0.0)	1 (0.0)	
Vulvovaginal disorders NEC	0	1 (0.0)	1 (0.0)	
Vaginal haemorrhage	0	1 (0.0)	1 (0.0)	
Breast signs and symptoms	0	1 (0.0)	1 (0.0)	
Breast pain	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Respiratory, thoracic and mediastinal disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	19 (1.5)	44 (1.6)	63 (1.6)	.787
PATIENTS WITH NO EVENTS	1267 (98.5)	2681 (98.4)	3948 (98.4)	.787
Breathing abnormalities	1 (0.1)	13 (0.5)	14 (0.3)	.047
Dyspnoea	1 (0.1)	11 (0.4)	12 (0.3)	.118
Respiratory arrest	0	2 (0.1)	2 (0.0)	
Dyspnoea exacerbated	0	1 (0.0)	1 (0.0)	
Bronchial conditions NEC	0	4 (0.1)	4 (0.1)	
Bronchitis NOS	0	4 (0.1)	4 (0.1)	
Bronchospasm and obstruction	8 (0.6)	7 (0.3)	15 (0.4)	.096
Asthma NOS	2 (0.2)	4 (0.1)	6 (0.1)	1.00
Chronic obstructive airways disease	4 (0.3)	1 (0.0)	5 (0.1)	
Chronic obstructive airways disease exacerbated	3 (0.2)	2 (0.1)	5 (0.1)	
Coughing and associated symptoms	1 (0.1)	4 (0.1)	5 (0.1)	
Haemoptysis	1 (0.1)	2 (0.1)	3 (0.1)	
Cough	0	2 (0.1)	2 (0.0)	
Diaphragmatic disorders (excl congenital)	0	2 (0.1)	2 (0.0)	
Diaphragmatic hernia NOS	0	2 (0.1)	2 (0.0)	
Laryngeal and adjacent sites disorders NEC (excl infections and neop	0	2 (0.1)	2 (0.0)	
Laryngitis NOS	0	1 (0.0)	1 (0.0)	
Vocal cord polyp	0	1 (0.0)	1 (0.0)	
Lower respiratory tract inflammatory and immunologic conditions	2 (0.2)	1 (0.0)	3 (0.1)	
Pneumonia aspiration	2 (0.2)	1 (0.0)	3 (0.1)	
Lower respiratory tract signs and symptoms	2 (0.2)	1 (0.0)	3 (0.1)	
Pleuritic pain	2 (0.2)	1 (0.0)	3 (0.1)	
Nasal disorders NEC	1 (0.1)	0	1 (0.0)	
Epistaxis	1 (0.1)	0	1 (0.0)	
Pharyngeal disorders (excl infections and neoplasms)	0	1 (0.0)	1 (0.0)	
Pharyngeal pouch	0	1 (0.0)	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

System Organ Class: Respiratory, thoracic and mediastinal disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Pneumothorax and pleural effusions NEC	2 (0.2)	6 (0.2)	8 (0.2)	1.00
Pleural effusion	1 (0.1)	5 (0.2)	6 (0.1)	.671
Pneumothorax NOS	1 (0.1)	1 (0.0)	2 (0.0)	
Pulmonary oedemas	1 (0.1)	1 (0.0)	2 (0.0)	
Acute pulmonary oedema	1 (0.1)	0	1 (0.0)	
Pulmonary oedema NOS	0	1 (0.0)	1 (0.0)	
Pulmonary thrombotic and embolic conditions	0	9 (0.3)	9 (0.2)	.066
Pulmonary embolism	0	9 (0.3)	9 (0.2)	.066
Respiratory failures (excl neonatal)	3 (0.2)	2 (0.1)	5 (0.1)	
Respiratory failure	3 (0.2)	2 (0.1)	5 (0.1)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

System Organ Class: Skin and subcutaneous tissue disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	1 (0.1)	4 (0.1)	5 (0.1)	1.00
PATIENTS WITH NO EVENTS	1285 (99.9)	2721 (99.9)	4006 (99.9)	1.00
Dermal and epidermal conditions NEC	0	1 (0.0)	1 (0.0)	
Skin lesion NOS	0	1 (0.0)	1 (0.0)	
Dermatitis ascribed to specific agent	0	1 (0.0)	1 (0.0)	
Dermatitis medicamentosa	0	1 (0.0)	1 (0.0)	
Panniculitides	0	1 (0.0)	1 (0.0)	
Panniculitis	0	1 (0.0)	1 (0.0)	
Skin injuries and mechanical dermatoses	0	1 (0.0)	1 (0.0)	
Contusion	0	1 (0.0)	1 (0.0)	
Skin and subcutaneous conditions NEC	1 (0.1)	0	1 (0.0)	
Skin nodule	1 (0.1)	0	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

System Organ Class: Surgical and medical procedures

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n	(%)	RLX060 (N=2725) n	(%)	Total (N=4011) n	(%)	p-Value*
PATIENTS WITH >= 1 EVENT	88	(6.8)	166	(6.1)	254	(6.3)	.367
PATIENTS WITH NO EVENTS	1198	(93.2)	2559	(93.9)	3757	(93.7)	.367
Anorectal therapeutic procedures	1	(0.1)	2	(0.1)	3	(0.1)	
Haemorrhoid operation	0		1	(0.0)	1	(0.0)	
Rectal prolapse repair	0		1	(0.0)	1	(0.0)	
Resection of rectum	1	(0.1)	0		1	(0.0)	
Arterial therapeutic procedures (excl aortic)	6	(0.5)	13	(0.5)	19	(0.5)	1.00
Coronary artery surgery	1	(0.1)	8	(0.3)	9	(0.2)	.287
Arterial bypass operation	1	(0.1)	1	(0.0)	2	(0.0)	
Arterial stent insertion NOS	1	(0.1)	1	(0.0)	2	(0.0)	
Coronary angioplasty	2	(0.2)	0		2	(0.0)	
Endarterectomy	1	(0.1)	1	(0.0)	2	(0.0)	
Coronary arterial stent insertion	0		1	(0.0)	1	(0.0)	
Triple vessel bypass graft	0		1	(0.0)	1	(0.0)	
Biliary tract and gallbladder therapeutic procedures	5	(0.4)	5	(0.2)	10	(0.2)	.307
Cholecystectomy	5	(0.4)	5	(0.2)	10	(0.2)	.307
Bladder therapeutic procedures	0		5	(0.2)	5	(0.1)	
Bladder operation NOS	0		3	(0.1)	3	(0.1)	
Bladder repair	0		2	(0.1)	2	(0.0)	
Bone therapeutic procedures NEC	1	(0.1)	6	(0.2)	7	(0.2)	.441
Osteosynthesis	0		3	(0.1)	3	(0.1)	
Bone operation NOS	0		2	(0.1)	2	(0.0)	
Bone graft	0		1	(0.0)	1	(0.0)	
Osteotomy	1	(0.1)	0		1	(0.0)	
Cardiac pacemaker therapeutic procedures	3	(0.2)	3	(0.1)	6	(0.1)	.393
Cardiac pacemaker insertion	3	(0.2)	3	(0.1)	6	(0.1)	.393
Cardiac valve therapeutic procedures	0		3	(0.1)	3	(0.1)	
Aortic valve replacement	0		2	(0.1)	2	(0.0)	

Program: RMP.H3SSGGJY.SASPGM(SRCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

System Organ Class: Surgical and medical procedures

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n	(%)	RLX060 (N=2725) n	(%)	Total (N=4011) n	(%)	p-Value*
Mitral valve repair NOS	0		1	(0.0)	1	(0.0)	
Facial therapeutic procedures	0		1	(0.0)	1	(0.0)	
Plastic surgery to the face	0		1	(0.0)	1	(0.0)	
Fallopian tube therapeutic procedures	0		1	(0.0)	1	(0.0)	
Salpingo-oophorectomy bilateral	0		1	(0.0)	1	(0.0)	
Fascial and bursal therapeutic procedures	1	(0.1)	0		1	(0.0)	
Dupuytren's contracture operation	1	(0.1)	0		1	(0.0)	
Gastric therapeutic procedures	0		2	(0.1)	2	(0.0)	
Gastrectomy NOS	0		2	(0.1)	2	(0.0)	
Gastric operation NOS	0		1	(0.0)	1	(0.0)	
Gastrointestinal therapeutic procedures NEC	0		3	(0.1)	3	(0.1)	
Intestinal operation NOS	0		2	(0.1)	2	(0.0)	
Intestinal stoma	0		1	(0.0)	1	(0.0)	
Hernia repairs	2	(0.2)	0		2	(0.0)	
Femoral hernia repair	1	(0.1)	0		1	(0.0)	
Inguinal hernia repair	1	(0.1)	0		1	(0.0)	
Joint therapeutic procedures	16	(1.2)	39	(1.4)	55	(1.4)	.771
Hip arthroplasty	12	(0.9)	23	(0.8)	35	(0.9)	.856
Hip operation NOS	3	(0.2)	4	(0.1)	7	(0.2)	.687
Knee arthroplasty	0		6	(0.2)	6	(0.1)	.186
Joint arthroplasty	0		4	(0.1)	4	(0.1)	
Ankle operation	0		1	(0.0)	1	(0.0)	
Joint operation NOS	1	(0.1)	0		1	(0.0)	
Knee meniscectomy	0		1	(0.0)	1	(0.0)	
Knee operation	0		1	(0.0)	1	(0.0)	
Rotator cuff repair	0		1	(0.0)	1	(0.0)	
Renal therapeutic procedures	0		1	(0.0)	1	(0.0)	
Nephrectomy	0		1	(0.0)	1	(0.0)	

Program: RMP.H3SSGGJY.SASPGM(SRCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

System Organ Class: Surgical and medical procedures

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Large intestine therapeutic procedures	2 (0.2)	12 (0.4)	14 (0.3)	.250
Colectomy partial	1 (0.1)	4 (0.1)	5 (0.1)	
Colostomy	0	2 (0.1)	2 (0.0)	
Sigmoidectomy	0	2 (0.1)	2 (0.0)	
Appendicectomy	1 (0.1)	0	1 (0.0)	
Colectomy NOS	0	1 (0.0)	1 (0.0)	
Colon operation NOS	0	1 (0.0)	1 (0.0)	
Colon polypectomy	0	1 (0.0)	1 (0.0)	
Large intestine anastomosis	0	1 (0.0)	1 (0.0)	
Laryngeal therapeutic procedures	1 (0.1)	1 (0.0)	2 (0.0)	
Laryngeal operation NOS	1 (0.1)	0	1 (0.0)	
Laryngeal polypectomy	0	1 (0.0)	1 (0.0)	
Lens therapeutic procedures	1 (0.1)	3 (0.1)	4 (0.1)	
Cataract extraction	1 (0.1)	2 (0.1)	3 (0.1)	
Lens implant	0	1 (0.0)	1 (0.0)	
Limb therapeutic procedures	1 (0.1)	3 (0.1)	4 (0.1)	
Limb operation NOS	1 (0.1)	3 (0.1)	4 (0.1)	
Lymphoid tissue therapeutic procedures	0	1 (0.0)	1 (0.0)	
Lymphadenectomy	0	1 (0.0)	1 (0.0)	
Mastectomies	4 (0.3)	11 (0.4)	15 (0.4)	.786
Mastectomy NOS	2 (0.2)	9 (0.3)	11 (0.3)	.520
Partial mastectomy	3 (0.2)	0	3 (0.1)	
Radical mastectomy	0	2 (0.1)	2 (0.0)	
Abdominal therapeutic procedures NEC	1 (0.1)	2 (0.1)	3 (0.1)	
Abdominal operation NOS	0	1 (0.0)	1 (0.0)	
Abdominal sinus repair	0	1 (0.0)	1 (0.0)	
Block dissection groin	1 (0.1)	0	1 (0.0)	
Breast therapeutic procedures NEC	2 (0.2)	4 (0.1)	6 (0.1)	1.000

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(AET129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

System Organ Class: Surgical and medical procedures

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Breast lump removal NOS	2 (0.2)	2 (0.1)	4 (0.1)	
Breast operation NOS	0	1 (0.0)	1 (0.0)	
Breast reconstruction	0	1 (0.0)	1 (0.0)	
Cardiac therapeutic procedures NEC	0	1 (0.0)	1 (0.0)	
Implantable defibrillator insertion	0	1 (0.0)	1 (0.0)	
Eye therapeutic procedures NEC	1 (0.1)	0	1 (0.0)	
Vitrectomy	1 (0.1)	0	1 (0.0)	
Therapeutic procedures NEC	19 (1.5)	22 (0.8)	41 (1.0)	.063
Operation NOS	10 (0.8)	15 (0.6)	25 (0.6)	.396
Lump excision	3 (0.2)	2 (0.1)	5 (0.1)	
Malignant tumour excision NOS	2 (0.2)	1 (0.0)	3 (0.1)	
Tumour excision NOS	1 (0.1)	2 (0.1)	3 (0.1)	
Drug delivery device implantation	0	1 (0.0)	1 (0.0)	
Medical device removal	1 (0.1)	0	1 (0.0)	
Plastic surgery NOS	1 (0.1)	0	1 (0.0)	
Polypectomy	0	1 (0.0)	1 (0.0)	
Prolapse repair NOS	1 (0.1)	0	1 (0.0)	
Stent insertion NOS	0	1 (0.0)	1 (0.0)	
Wound closure	0	1 (0.0)	1 (0.0)	
Nasal therapeutic procedures	0	1 (0.0)	1 (0.0)	
Septoplasty	0	1 (0.0)	1 (0.0)	
Ovarian therapeutic procedures	0	3 (0.1)	3 (0.1)	
Oophorectomy bilateral	0	1 (0.0)	1 (0.0)	
Oophorectomy NOS	0	1 (0.0)	1 (0.0)	
Ovarian cystectomy	0	1 (0.0)	1 (0.0)	
Parathyroid gland therapeutic procedures	1 (0.1)	1 (0.0)	2 (0.0)	
Parathyroid gland operation	0	1 (0.0)	1 (0.0)	
Parathyroidectomy	1 (0.1)	0	1 (0.0)	

Program: RMP.H3SSGGJY.SASPGM(SPCT129) Input: RMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: RMP.H3SO.GGJY.FINAL(AET129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

System Organ Class: Surgical and medical procedures

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Peripheral nerve therapeutic procedures	1 (0.1)	0	1 (0.0)	
Carpal tunnel decompression	1 (0.1)	0	1 (0.0)	
Retinal therapeutic procedures	2 (0.2)	1 (0.0)	3 (0.1)	
Retinal operation NOS	2 (0.2)	1 (0.0)	3 (0.1)	
Salivary gland therapeutic procedures	0	1 (0.0)	1 (0.0)	
Parotidectomy	0	1 (0.0)	1 (0.0)	
Skin grafts	0	1 (0.0)	1 (0.0)	
Skin graft NOS	0	1 (0.0)	1 (0.0)	
Skin lesion excisions	1 (0.1)	5 (0.2)	6 (0.1)	.671
Skin neoplasm excision	1 (0.1)	4 (0.1)	5 (0.1)	
Skin lesion excision NOS	0	1 (0.0)	1 (0.0)	
Small intestine therapeutic procedures	1 (0.1)	0	1 (0.0)	
Ileal operation NOS	1 (0.1)	0	1 (0.0)	
Ileostomy	1 (0.1)	0	1 (0.0)	
Spine and spinal cord therapeutic procedures	1 (0.1)	7 (0.3)	8 (0.2)	.449
Spinal laminectomy	0	5 (0.2)	5 (0.1)	
Spinal operation NOS	1 (0.1)	2 (0.1)	3 (0.1)	
Spinal decompression	0	1 (0.0)	1 (0.0)	
Tendon therapeutic procedures	1 (0.1)	1 (0.0)	2 (0.0)	
Tendon sheath lesion excision	1 (0.1)	1 (0.0)	2 (0.0)	
Thyroid therapeutic procedures	1 (0.1)	0	1 (0.0)	
Thyroidectomy NOS	1 (0.1)	0	1 (0.0)	
Tonsillar therapeutic procedures	1 (0.1)	1 (0.0)	2 (0.0)	
Tonsillectomy	1 (0.1)	1 (0.0)	2 (0.0)	
Fracture treatments (excl skull and spine)	13 (1.0)	10 (0.4)	23 (0.6)	.022
Fracture treatment NOS	5 (0.4)	5 (0.2)	10 (0.2)	.307
Open reduction of fracture	3 (0.2)	3 (0.1)	6 (0.1)	.393
Internal fixation of fracture	3 (0.2)	1 (0.0)	4 (0.1)	

Program: EMP.H3SSGGJY.SASPGM(SPCT129) Input: EMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: EMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Surgical and medical procedures

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Closed fracture manipulation	1 (0.1)	0	1 (0.0)	
Fracture debridement	0	1 (0.0)	1 (0.0)	
Removal of internal fixation	1 (0.1)	0	1 (0.0)	
Uterine therapeutic procedures	8 (0.6)	7 (0.3)	15 (0.4)	.096
Hysterectomy	6 (0.5)	5 (0.2)	11 (0.3)	.118
Hysterosalpingo-oophorectomy	2 (0.2)	1 (0.0)	3 (0.1)	
Uterine dilation and curettage	1 (0.1)	1 (0.0)	2 (0.0)	
Vaginal hysterectomy	0	1 (0.0)	1 (0.0)	
Vaginal therapeutic procedures	1 (0.1)	1 (0.0)	2 (0.0)	
Pelvic floor repair	0	1 (0.0)	1 (0.0)	
Vaginal operation NOS	1 (0.1)	0	1 (0.0)	
Vascular therapeutic procedures NEC	1 (0.1)	3 (0.1)	4 (0.1)	
Angioplasty	1 (0.1)	1 (0.0)	2 (0.0)	
Vascular operation	0	2 (0.1)	2 (0.0)	
Venous therapeutic procedures	1 (0.1)	1 (0.0)	2 (0.0)	
Varicose vein operation NOS	1 (0.1)	0	1 (0.0)	
Vena cava filter insertion	0	1 (0.0)	1 (0.0)	

Program: EMP.H3SSGGJY.SASPGM(SPCT129) Input: EMP.SAS.H3SM.MCGGJYSC(EVENTS) Output: EMP.H3SO.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XARS0021 MEDDRA VERSION: 6.0

System Organ Class: Vascular disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	23 (1.8)	37 (1.4)	60 (1.5)	.329
PATIENTS WITH NO EVENTS	1263 (98.2)	2688 (98.6)	3951 (98.5)	.329
Accelerated and malignant hypertension	1 (0.1)	0	1 (0.0)	
Hypertensive crisis	1 (0.1)	0	1 (0.0)	
Aneurysms and dissections non-site specific	0	1 (0.0)	1 (0.0)	
Aneurysm	0	1 (0.0)	1 (0.0)	
Aortic aneurysms and dissections	0	3 (0.1)	3 (0.1)	
Aortic aneurysm	0	3 (0.1)	3 (0.1)	
Aortic necrosis and vascular insufficiency	1 (0.1)	3 (0.1)	4 (0.1)	
Aortic stenosis	1 (0.1)	2 (0.1)	3 (0.1)	
Aortic occlusion	0	1 (0.0)	1 (0.0)	
Circulatory collapse and shock	2 (0.2)	0	2 (0.0)	
Circulatory collapse	1 (0.1)	0	1 (0.0)	
Shock	1 (0.1)	0	1 (0.0)	
Haemorrhages NEC	2 (0.2)	1 (0.0)	3 (0.1)	
Haematoma NOS	2 (0.2)	1 (0.0)	3 (0.1)	
Vascular hypertensive disorders NEC	1 (0.1)	3 (0.1)	4 (0.1)	
Hypertension NOS	1 (0.1)	3 (0.1)	4 (0.1)	
Lymphangiopathies	1 (0.1)	0	1 (0.0)	
Lymphangitis	1 (0.1)	0	1 (0.0)	
Non-site specific necrosis and vascular insufficiency NEC	1 (0.1)	2 (0.1)	3 (0.1)	
Atherosclerosis	1 (0.1)	1 (0.0)	2 (0.0)	
Arterial occlusion	0	1 (0.0)	1 (0.0)	
Arterial stenosis NOS	0	1 (0.0)	1 (0.0)	
Peripheral embolism and thrombosis	7 (0.5)	17 (0.6)	24 (0.6)	.830
Deep vein thrombosis	5 (0.4)	14 (0.5)	19 (0.5)	.806
Venous thrombosis NOS limb	0	2 (0.1)	2 (0.0)	
Iliac artery thrombosis	1 (0.1)	0	1 (0.0)	

Program: RMP.H38SGGJY.SASPGM(SPCT129) Input: RMP.SAS.H38M.MCGGJYSC(EVENTS) Output: RMP.H38O.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

System Organ Class: Vascular disorders

HLT: High Level Term PT: Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Subclavian vein thrombosis	0	1 (0.0)	1 (0.0)	
Thrombophlebitis	1 (0.1)	0	1 (0.0)	
Peripheral vascular disorders NEC	3 (0.2)	2 (0.1)	4 (0.1)	
Peripheral vascular disorder NOS	2 (0.2)	2 (0.1)	4 (0.1)	
Peripheral vasoconstriction, necrosis and vascular insufficiency	3 (0.2)	2 (0.1)	5 (0.1)	
Intermittent claudication	2 (0.2)	1 (0.0)	3 (0.1)	
Peripheral ischaemia	1 (0.1)	1 (0.0)	2 (0.0)	
Varicose veins non-site specific	1 (0.1)	0	1 (0.0)	
Varicose veins NOS	1 (0.1)	0	1 (0.0)	
Non-site specific vascular disorders NEC	1 (0.1)	1 (0.0)	2 (0.0)	
Vascular disorder NOS	1 (0.1)	0	1 (0.0)	
Vascular pseudoaneurysm	0	1 (0.0)	1 (0.0)	
Vasculitides NEC	0	1 (0.0)	1 (0.0)	
Vasculitis NOS	0	1 (0.0)	1 (0.0)	
Phlebitis NEC	2 (0.2)	0	2 (0.0)	
Phlebitis superficial	2 (0.2)	0	2 (0.0)	
Site specific necrosis and vascular insufficiency NEC	1 (0.1)	1 (0.0)	2 (0.0)	
Aorto-iliac arterial stenosis	0	1 (0.0)	1 (0.0)	
Iliac artery stenosis	1 (0.1)	0	1 (0.0)	
Lymphoedemas	1 (0.1)	0	1 (0.0)	
Lymphoedema NOS	1 (0.1)	0	1 (0.0)	
Vascular hypotensive disorders	0	2 (0.1)	2 (0.0)	
Orthostatic hypotension	0	2 (0.1)	2 (0.0)	

Program: RMP.H38SGGJY.SASPGM(SPCT129) Input: RMP.SAS.H38M.MCGGJYSC(EVENTS) Output: RMP.H38O.GGJY.FINAL(ART129)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0021 MEDDRA VERSION: 6.0

Clinically Significant Adverse Events (12.3.3)

12.3.3.1. Adverse Events Leading to Discontinuation

Table GGJY.12.9 is divided into three parts to summarize: 1) patients who completed the protocol but had an adverse event, 2) patients who discontinued due to an adverse event, and 3) deaths, in the order of decreasing frequency. Section 12.3.1 provides further information regarding deaths during Study GGJY.

Discontinuations due to an adverse event were similar between the two treatment groups (31 patients [2.4%] in the placebo group and 53 patients [1.9%] in the raloxifene group; p=0 .336). Also, there were no statistically significant between-group differences for any adverse event leading to discontinuation. The most common adverse events that lead to discontinuation for both groups were "dementia of the Alzheimer's type NOS" (6 patients), "death NOS" (6 patients), "dementia NOS" (5 patients), "memory impairment" (4 patients), "myocardial infarction" (4 patients), and "respiratory failure" (4 patients).

Table GGJY.12.9. Summary of Adverse Events Leading to Discontinuation by Preferred Term during Study GGJY (All Patients Enrolled in Study GGJY)

Reason for Discont.: Patient completed the protocol, but had an adverse event

Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS DISCONTINUED				
Breast cancer invasive NOS	2 (0.2)	5 (0.2)	7 (0.2)	.843
Deep vein thrombosis	1 (0.1)	1 (0.0)	2 (0.0)	
Breast cancer NOS	0	2 (0.1)	2 (0.0)	
Dementia NOS	0	1 (0.0)	1 (0.0)	
Flushing	0	1 (0.0)	1 (0.0)	
	1 (0.1)	0	1 (0.0)	

SOURCE IS RMP.H3SP.SASMACRO(ARS3A) AP001 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
* Frequencies are analyzed using a Chi-Square test.
XARS0003 MEDDRA VERSION: 6.0

Reason for Discont.: Adverse event

Preferred Term	PLACEBO (N=1286) n	(%)	RLX060 (N=2725) n	(%)	Total (N=4011) n	(%)	p-Value*
PATIENTS DISCONTINUED	31	(2.4)	53	(1.9)	84	(2.1)	.336
Dementia of the Alzheimer's type NOS	2	(0.2)	4	(0.1)	6	(0.1)	.947
Dementia NOS	2	(0.2)	3	(0.1)	5	(0.1)	.704
Memory impairment	1	(0.1)	3	(0.1)	4	(0.1)	
Cerebrovascular accident	0		3	(0.1)	3	(0.1)	
Muscle cramp	2	(0.2)	1	(0.0)	3	(0.1)	
Breast cancer invasive NOS	1	(0.1)	1	(0.0)	2	(0.0)	
Breast cancer stage II	0		2	(0.1)	2	(0.0)	
Ischaemic stroke NOS	1	(0.1)	1	(0.0)	2	(0.0)	
Localised osteoarthritis	0		2	(0.1)	2	(0.0)	
Lung cancer stage unspecified (excl metastatic tumours to lung)	1	(0.1)	1	(0.0)	2	(0.0)	
Macular degeneration	0		2	(0.1)	2	(0.0)	
Major depressive disorder NOS	2	(0.2)	0		2	(0.0)	
Pancreatic carcinoma NOS	1	(0.1)	1	(0.0)	2	(0.0)	
Senile dementia NOS	0		2	(0.1)	2	(0.0)	
Spinal fracture NOS	0		2	(0.1)	2	(0.0)	
Transient ischaemic attack	1	(0.1)	1	(0.0)	2	(0.0)	
Acute myocardial infarction	1	(0.1)	0		1	(0.0)	
Amyotrophic lateral sclerosis	0		1	(0.0)	1	(0.0)	
Angina pectoris	0		1	(0.0)	1	(0.0)	
Arrhythmia NOS	0		1	(0.0)	1	(0.0)	
Arthralgia	0		1	(0.0)	1	(0.0)	
Asthenia	1	(0.1)	0		1	(0.0)	
Asthma NOS	0		1	(0.0)	1	(0.0)	
Back pain	0		1	(0.0)	1	(0.0)	
Brain neoplasm NOS	0		1	(0.0)	1	(0.0)	

SOURCE IS RMP.H3SP.SASMACRO(AES1A) AP001 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
* Frequencies are analyzed using a Chi-Square test.
XAES0003 MEDDRA VERSION: 6.0

Reason for Discont.: Adverse event

Preferred Term	PLACEBO (N=1286) n	(%)	RLX060 (N=2725) n	(%)	Total (N=4011) n	(%)	p-Value*
Breast cancer in situ	0		1	(0.0)	1	(0.0)	
Breast cancer NOS	1	(0.1)	0		1	(0.0)	
Bronchial carcinoma	1	(0.1)	0		1	(0.0)	
Cerebral disorder	0		1	(0.0)	1	(0.0)	
Cerebral haemorrhage	1	(0.1)	0		1	(0.0)	
Cerebral infarction	1	(0.1)	0		1	(0.0)	
Cerebral thrombosis NOS	0		1	(0.0)	1	(0.0)	
Chronic obstructive airways disease	1	(0.1)	0		1	(0.0)	
Colon cancer stage III	0		1	(0.0)	1	(0.0)	
Cough	0		1	(0.0)	1	(0.0)	
Diffuse large B-cell lymphoma NOS	1	(0.1)	0		1	(0.0)	
Dyspepsia	1	(0.1)	0		1	(0.0)	
Emphysema	1	(0.1)	0		1	(0.0)	
Facial palsy	1	(0.1)	0		1	(0.0)	
Femur fracture	0		1	(0.0)	1	(0.0)	
Leiomyosarcoma NOS	0		1	(0.0)	1	(0.0)	
Lung carcinoma cell type unspecified recurrent	1	(0.1)	0		1	(0.0)	
Mastectomy NOS	0		1	(0.0)	1	(0.0)	
Mental status changes	1	(0.1)	0		1	(0.0)	
Mesenteric artery embolism	0		1	(0.0)	1	(0.0)	
Metastases to bone	1	(0.1)	0		1	(0.0)	
Metastatic neoplasm NOS, primary site unknown	1	(0.1)	0		1	(0.0)	
Musculoskeletal pain	0		1	(0.0)	1	(0.0)	
Oesophageal carcinoma NOS	0		1	(0.0)	1	(0.0)	
Parkinson's disease NOS	1	(0.1)	0		1	(0.0)	
Parkinsonism	0		1	(0.0)	1	(0.0)	

SOURCE IS RMP.H3SP.SASMACRO(AES1A) AP001 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
* Frequencies are analyzed using a Chi-Square test.
XAES0003 MEDDRA VERSION: 6.0

Reason for Discont.: Adverse event

Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Renal cell carcinoma stage unspecified	1 (0.1)	0	1 (0.0)	
Retinal artery embolism	0	1 (0.0)	1 (0.0)	
Retinal vein thrombosis	0	1 (0.0)	1 (0.0)	
Retinitis pigmentosa	0	1 (0.0)	1 (0.0)	
Spinal compression fracture	0	1 (0.0)	1 (0.0)	
Tibia fracture	0	1 (0.0)	1 (0.0)	

SOURCE IS RMP.H3SP.SASMACRO(AR83A) AP001 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
* Frequencies are analyzed using a Chi-Square test.
KARS0003 MEDDRA VERSION: 6.0

Reason for Discont.: Death

Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
PATIENTS DISCONTINUED	29 (2.3)	47 (1.7)	76 (1.9)	.250
Death NOS	3 (0.2)	3 (0.1)	6 (0.1)	.346
Myocardial infarction	1 (0.1)	3 (0.1)	4 (0.1)	
Respiratory failure	2 (0.2)	2 (0.1)	4 (0.1)	
Sudden death	1 (0.1)	2 (0.1)	3 (0.1)	
Cardiac arrest	1 (0.1)	1 (0.0)	2 (0.0)	
Cardiac failure NOS	2 (0.2)	0	2 (0.0)	
Cardio-respiratory arrest	0	2 (0.1)	2 (0.0)	
Death unexplained	0	2 (0.1)	2 (0.0)	
Haemorrhagic stroke	1 (0.1)	1 (0.0)	2 (0.0)	
Lung cancer metastatic	0	2 (0.1)	2 (0.0)	
Pancreatitis NOS	2 (0.2)	0	2 (0.0)	
Respiratory arrest	0	2 (0.1)	2 (0.0)	
Acute lymphocytic leukaemia	1 (0.1)	0	1 (0.0)	
Amyotrophic lateral sclerosis	0	1 (0.0)	1 (0.0)	
Angiosarcoma NOS	1 (0.1)	0	1 (0.0)	
Anoxic encephalopathy	0	1 (0.0)	1 (0.0)	
Aortic aneurysm	0	1 (0.0)	1 (0.0)	
Bone neoplasm NOS	1 (0.1)	0	1 (0.0)	
Cerebral artery thrombosis	0	1 (0.0)	1 (0.0)	
Cerebral infarction	0	1 (0.0)	1 (0.0)	
Cerebrovascular accident	0	1 (0.0)	1 (0.0)	
Chronic myeloid leukaemia	1 (0.1)	0	1 (0.0)	
Colon cancer NOS	1 (0.1)	0	1 (0.0)	
Diabetic coma NOS	0	1 (0.0)	1 (0.0)	
Electromechanical dissociation	0	1 (0.0)	1 (0.0)	

SOURCE IS RMP.H3SP.SASMACRO(AR83A) AP001 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
* Frequencies are analyzed using a Chi-Square test.
KARS0003 MEDDRA VERSION: 6.0

Reason for Discont.: Death

Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Gastric cancer NOS	0	1 (0.0)	1 (0.0)	
Gastrointestinal tract cancer NOS	1 (0.1)	0	1 (0.0)	
Hepatic cancer metastatic	0	1 (0.0)	1 (0.0)	
Hepatic encephalopathy	0	1 (0.0)	1 (0.0)	
Hypothermia	0	1 (0.0)	1 (0.0)	
Intestinal infarction	0	1 (0.0)	1 (0.0)	
Intestinal perforation NOS	0	1 (0.0)	1 (0.0)	
Intracranial haemorrhage NOS	0	1 (0.0)	1 (0.0)	
Lip and/or oral cavity cancer NOS	1 (0.1)	0	1 (0.0)	
Lung cancer stage unspecified (excl metastatic tumours to lung)	1 (0.1)	0	1 (0.0)	
Lung squamous cell carcinoma stage IV	1 (0.1)	0	1 (0.0)	
Lymphoma NOS	0	1 (0.0)	1 (0.0)	
Metastases to lymph nodes	1 (0.1)	0	1 (0.0)	
Metastatic neoplasm NOS, primary site unknown	0	1 (0.0)	1 (0.0)	
Neuroendocrine carcinoma	0	1 (0.0)	1 (0.0)	
Oesophageal adenocarcinoma NOS	1 (0.1)	0	1 (0.0)	
Ovarian cancer NOS	0	1 (0.0)	1 (0.0)	
Pancreatic carcinoma NOS	1 (0.1)	0	1 (0.0)	
Pneumonia aspiration	1 (0.1)	0	1 (0.0)	
Pneumonia NOS	0	1 (0.0)	1 (0.0)	
Pulmonary embolism	0	1 (0.0)	1 (0.0)	
Rectal cancer metastatic	0	1 (0.0)	1 (0.0)	
Rectal cancer NOS	0	1 (0.0)	1 (0.0)	
Rectosigmoid cancer NOS	1 (0.1)	0	1 (0.0)	
Renal cancer metastatic	1 (0.1)	0	1 (0.0)	
Ruptured cerebral aneurysm	0	1 (0.0)	1 (0.0)	

SOURCE IS RMP.H3SP.SASMACRO(AES3A) AP001 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
* Frequencies are analyzed using a Chi-Square test.
XAES0003 MEDDRA VERSION: 6.0

Reason for Discont.: Death

Preferred Term	PLACEBO (N=1286) n (%)	RLX060 (N=2725) n (%)	Total (N=4011) n (%)	p-Value*
Sepsis NOS	0	1 (0.0)	1 (0.0)	
Small intestine carcinoma metastatic	1 (0.1)	0	1 (0.0)	
Subdural haematoma	0	1 (0.0)	1 (0.0)	
Throat cancer NOS	0	1 (0.0)	1 (0.0)	

SOURCE IS RMP.H3SP.SASMACRO(AES3A) AP001 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
* Frequencies are analyzed using a Chi-Square test.
XAES0003 MEDDRA VERSION: 6.0

12.3.3.2. Adverse Events of Interest from Prior Experience

Several adverse events were identified as adverse events of interest from prior data obtained in Study GGGK. These include endometrial cancer, ovarian cancer, and VTE.

Endometrial cancer and VTEs were both solicited during Study GGJY. The incidence of these events in the Study GGJY cohort is reported for two periods of observations:
1) During Study GGJY (see Table GGJY.12.10), and
2) From Study GGGK baseline through Study GGJY termination (see Table GGJY.12.11).

Table GGJY.14.27 is a listing of endometrial and ovarian cancers and Table GGJY14.28 is a listing of VTEs for all Study GGJY patients who reported one of these events at any time from the end of their participation in Study GGGK through the end of Study GGJY.
Section 14.3.3 presents these patient narratives.

12.3.3.2.1. Endometrial Cancer

Endometrial cancer was assessed only in patients with an intact uterus at baseline (3146 patients at Study GGJY baseline and 3193 patients at Study GGGK baseline).

Seven cases (0.3% of placebo-treated patients and 0.2% of raloxifene-treated patients) of endometrial cancer were reported during Study GGJY. When the Study GGJY cohort is observed from Study GGGK baseline through Study GGJY termination, 11 cases (0.4% of placebo-treated patients and 0.3% of raloxifene-treated patients) were reported. For both observation periods, there was a non statistically significant reduction in the relative risk of endometrial cancer among raloxifene patients compared with placebo patients.

These data are consistent with the findings in Study GGGK (relative risk = 0.81; 95% CI [0.27, 2.47]; see Study H3S-MC-GGGK 4-Year Study Report) and support the safety of raloxifene in the endometrium during long-term administration.

12.3.3.2.2. Ovarian Cancer

Ovarian cancer was reported in 4 patients during Study GGJY. When the Study GGJY cohort was observed from Study GGGK baseline through Study GGJY termination, 5 cases of ovarian cancer were reported. For both observation periods, there was a non-statistically significant reduction in the relative risk of ovarian cancer among raloxifene patients compared with placebo patients. These data are consistent with the findings in Study GGGK, during which there were 6 reported cases of ovarian cancer in the placebo group and 6 cases in the pooled raloxifene group (p=0.223; see Study H3SMC- GGGK 4-Year Study Report).

12.3.3.2.3. Venous Thromboembolism Events

Venous thromboembolism (VTE) was defined as follows:

1) Any acute venous thrombosis (clot) involving a deep peripheral vein (commonly known as deep vein thrombosis [DVT])
2) Acute pulmonary embolism (PE)
3) Other acute serious vein thromboses, including mesenteric and intracerebral vein thromboses (of these "other" thromboses, only retinal vein thrombosis [RVT] was actually reported).

All reported cases of DVT, PE, and other serious vein thromboses were included in the primary analyses without regard to likelihood of diagnostic accuracy, presence of known risk factor(s) preceding the event (that is, non idiopathic included), or likelihood of causal relationship to study drug. Excluded from this analysis are superficial vein thromboses and arterial thromboses. Table GGJY.14.28 lists all patients who experienced a VTE after Study GGGK termination.

Venous thrombotic events (VTE), including deep vein thromboses, pulmonary embolism, and retinal vein thrombosis, were solicited events in Study GGJY. Any probable VTE was coded as an event, regardless of documentation to support a diagnosis or whether an investigator deemed

the event related to study drug. All VTEs were considered serious adverse events (SAEs) by the sponsor, regardless of the investigator's designation.

Although additional clinical information was not collected as part of Study GGJY, through the sponsor's safety surveillance process, the investigative site was asked to provide documentation to support the diagnosis of VTE (for example, Doppler studies or pulmonary angiogram). In addition, in most cases, additional information on the clinical history was provided. The clinical information on each event is described in the one page patient summaries (see Section 14.3.3). Each of these cases was reviewed internally by an unblinded physician; the findings are summarized in the following text.

A VTE event was reported in 28 patients during Study GGJY (Table GGJY.12.10).

When the Study GGJY cohort was observed from Study GGGK baseline through Study GGJY termination, 62 patients had a VTE event (Table GGJY.12.11); 10 of these patients (12 events) occurred during the time interval between Study GGGK termination and Study GGJY enrollment when patients were not receiving study drug. There were no statistically significant between-group differences for VTEs overall or for any specific category of VTE (DVT, PE, or RVT) during either observation period. However, numerical increases in the raloxifene group compared with the placebo group were seen for VTEs overall and for each category during both observation periods.

To determine whether resuming raloxifene therapy in Study GGJY resulted in an increased VTE risk similar to that seen during the first 4 months of Study GGGK, VTE events were categorized by visit (corresponding approximately to yearly intervals; see Table GGJY.12.12). Note that events that occurred during Visits 2 and 3 are combined due to the short duration of time between Visits 1 and 2 and the fact that approximately half of Study GGJY patients did not have a Visit 2 (see Section 9.1); the combined Visit 2/3 period represents approximately the first 12 to 18 months of exposure in Study GGJY.

The event rates for each time interval were too small, especially in the placebo group, to allow meaningful risk ratios to be calculated.

Figure GGJY.12.1 depicts VTE event rates as the number of women experiencing a VTE in the visit per 1000 women on study (with Visits 2 and 3 combined), with reference lines designating ± 2 standard deviations for each therapy group.

From the graph, the average event rate per visit is 3.0 events per 1000 women for raloxifene-treated patients and 1.6 events per 1000 women for placebo-treated patients. For both placebo- and raloxifene-treated patients, all observations are within 2 standard deviations of their respective mean and are consistent with each other across all visits.

Additionally, the day of each VTE event that occurred in Study GGJY relative to enrollment in Study GGJY (using the Visit 1 date as the enrollment date) were calculated, and no VTE was reported during the first 4 months of study drug (see Table GGJY.14.29).

(In [Table GGJY.14.29], a negative number for the relative date of therapy onset represents a VTE that occurred before Study GGJY baseline, when patients were not receiving study drug.)

Thus, the available data from Study GGJY do not indicate that the highest risk for VTE occurs during the first 4 months after resuming therapy, such as was seen upon therapy initiation in Study GGGK.

In conclusion, raloxifene therapy confers a small but clinically important excess risk of VTE. VTE data from Study GGJY do not alter the previously known effects of raloxifene on the incidence rate of these events. Also, while somewhat limited, Study GGJY data do not indicate a peak in VTE risk during the first 4 months of re-challenging a patient with raloxifene therapy.

12.3.3.2.3.1. Description of VTE Cases

Twenty-eight patients experienced 34 VTE events after study drug was resumed in Study GGJY. An additional 10 patients experienced a VTE prior to study drug resumption in Study GGJY; that is, during the interval between Study GGGK termination and Study GGJY baseline. Six patients who received study drug in Study GGJY experienced more than one VTE event (for example, a DVT and PE). The following information provides a brief summary of the cases by visit.

Visit 1: In total, 10 patients (3 placebo-treated patients and 7 raloxifene-treated patients) experienced a VTE during the interval between Study GGGK termination and Study GGJY baseline. Due to the timing of these events, none of the patients was receiving study drug at this time. Two patients experienced a combined DVT and PE event. Of these 10 patients, 2 were already accounted for and included in the Study GGGK VTE analyses (Patient 850-7091 and Patient 058 5384; see Study H3SMC-GGGK 4-Year Study Report).

Visit 2: No VTE events were reported.

Visit 3: In total, 11 patients (0 placebo-treated patients and 11 raloxifene-treated patients) experienced a VTE. Study drug had not been dispensed to 3 of these patients for at least 58 days prior to their event; of these 3 patients, 1 patient was immobilized at the time of her reported event (ankle fracture) and 1 patient had a past medical history of VTE. An additional 2 patients were immobilized at the time of the event (1 patient was bedridden and 1 patient was in the post-operative recovery phase from a laminectomy).

For the remaining 6 patients, no precipitating conditions were noted at the time of the VTE report.

Visit 4: In total, 9 patients (4 placebo-treated patients and 5 raloxifene-treated patients) experienced a VTE. One of these patients (in the placebo group) had never resumed study drug in Study GGJY due to the use of open-label hormone replacement therapy.

Two patients (1 in each treatment group) had experienced a VTE earlier in the study (at Visits 1 or 3) and had not received study drug since the prior VTE. One patient (in the placebo group)

experienced her event following immobilization (hemiparesis following prolonged hospitalization for bilateral carotid endarterectomy) and had been off study drug for 48 days. For the remaining 5 patients (1 placebo-treated patient and 4 raloxifene-treated patients), no precipitating conditions were noted at the time of the VTE report.

Visit 5: In total, 9 patients (1 placebo-treated patient and 8 raloxifene-treated patients) experienced a VTE. Three of these patients (all in the raloxifene group) had been off study drug > 58 days prior to their event, with 2 patients receiving chemotherapy for metastatic cancer and the 3rd patient being immobilized due to ankle fracture. Additional 2 patients (1 patient in each treatment group) had experienced immobilization at the time of the report due to hip fracture or femoral-popliteal bypass surgery. For the remaining 4 patients (all in the raloxifene group), no precipitating conditions were noted at the time of the VTE report. One of these patients died of a massive pulmonary embolism (raloxifene Patient 742-3887).

In summary, while it is clear that raloxifene is associated with an increased risk of VTE, review of individual cases reveals several important features. Notably, several of the VTE cases occurred in patients who were either not on study drug in Study GGJY, or who had discontinued several months prior to the event. Many of the cases had secondary conditions or risk factors, such as prolonged immobilization, hospitalization, surgery, or fracture. This finding reinforces the importance of discontinuing raloxifene therapy when these conditions arise. In conclusion, the increased risk of VTE associated with raloxifene does not appear to differ from that previously reported in Study GGGK (Study H3S-MC-GGGK 4-Year Study Report).

Table GGJY.12.10. Adverse Events of Interest during Study GGJY (All Patients Enrolled in Study GGJY)

	PLACEBO n/N (%)	Ralox n/N (%)	Relative Risk(95% CI)	P-VALUE#
Endometrial cancer*	3/1008 (0.30)	4/2128 (0.19)	0.63(0.14, 2.80)	0.667
Ovarian cancer**	2/1286 (0.16)	2/2725 (0.07)	0.47(0.07, 3.35)	0.597
Venous thromboembolism	5/1286 (0.39)	23/2725 (0.84)	2.17(0.83, 5.70)	0.153
Deep vein thrombophlebitis	5/1286 (0.39)	17/2725 (0.62)	1.60(0.59, 4.34)	0.492
Pulmonary embolism	0/1286 (0.00)	9/2725 (0.33)	N/A	0.065
Retinal vein thrombosis	0/1286 (0.00)	2/2725 (0.07)	N/A	1.000
All events of interest	10/1286 (0.78)	28/2725 (1.03)	1.32(0.64, 2.71)	0.490

* Excludes hysterectomized patients at baseline.
** Ovarian cancer was not a solicited adverse event. All others were solicited at each visit.
# P-value from Fisher exact test
Abbreviations: CORE-Continuing Outcomes Relevant to Evista; Ralox-raloxifene; CI-confidence interval.

Program: RMP.H3SSGGJY.SASPGM(SFCT1211) OUTPUT: RMP.H3SO.GGJY.FINAL(ART1211)

	PLACEBO n/N (%)	Ralox n/N (%)	Relative Risk(95% CI)	P-VALUE#
Endometrial cancer*	4/1026 (0.39)	7/2167 (0.32)	0.83(0.24, 2.82)	0.753
Ovarian cancer	2/1286 (0.16)	3/2725 (0.11)	0.71(0.12, 4.23)	0.658
Venous thromboembolism	15/1286 (1.17)	47/2725 (1.72)	1.48(0.83, 2.62)	0.217
Deep vein thrombophlebitis	11/1286 (0.86)	31/2725 (1.14)	1.33(0.67, 2.64)	0.507
Pulmonary embolism	3/1286 (0.23)	17/2725 (0.62)	2.67(0.79, 9.11)	0.147
Retinal vein thrombosis	2/1286 (0.16)	6/2725 (0.22)	1.42(0.29, 7.00)	1.000
All events of interest	21/1286 (1.63)	55/2725 (2.02)	1.24(0.75, 2.03)	0.457

* Excludes hysterectomized patients at baseline.
# P-value from Fisher exact test

Abbreviations: CI-confidence interval; CORE-Continuing Outcoms Relevant to Evista; MORE-Multiple Outcomes of Raloxifene Evaluation; Ralox-raloxifene.

Program: RMP.H1SSGGJY.SASPGM(SFCT1212) OUTPUT: RMP.H3SO.GGJY.FINAL(ART1212)

Table GGJY.12.12. By-Visit Summary of Patients with VTE Events during Study GGJY (All 4011 Study GGJY Patients)

Event[a]	Visit 1[b]		Visit 2[c]		Visit 3		Visit 4		Visit 5	
	Pbo n=1286	Rlx n=2725	Pbo n=648	Rlx n=1363	Pbo n=1281	Rlx n=2688	Pbo n=1225	Rlx n=2572	Pbo n=1160	Rlx n=2413
VTE	3	7	0	0	0	11	4	5	1	8
DVT	3	2	0	0	0	8	4	3	1	6
PE	1	4	0	0	0	2	0	3	0	4
RVT	0	2	0	0	0	2	0	0	0	0

Abbreviations: DVT = deep vein thrombosis; n = number; Pbo = placebo; PE = pulmonary embolism; Rlx = raloxifene hydrochloride 60 mg/day; RVT = retinal vein thrombosis; VTE = venous thromboembolism.

[a] A patient may be counted at more than one Visit.

[b] Visit 1 events occurred during the time interval after Study GGGK termination and prior to Study GGJY enrollment, when patients were not receiving study drug.

[c] Visit 2 was timed to correspond to the 5-year anniversary of enrollment in Study GGGK, respectively. If the date a patient enrolled in Study GGJY (Visit 1) was sufficiently near the 5-year anniversary of their enrollment in Study GGGK, the patient would not have a Visit 2 in Study GGJY. Approximately half of the Study GGJY patients did not have a Visit 2.

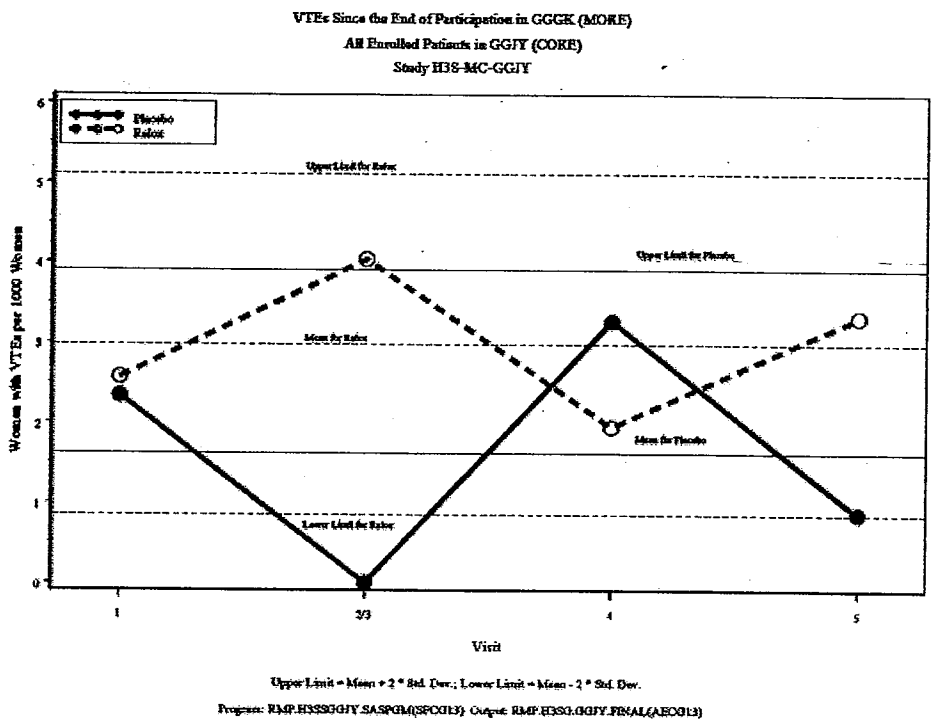

Figure GGJY.12.1. VTEs since the end of participation in Study GGGK.

12.3.3.3. Uterine Safety

In the Study GGJY cohort from Study GGGK baseline through Study GGJY termination, "uterine neoplasms", "reproductive tract disorders NEC (excluding neoplasms)", and "uterine polyp NOS", were all statistically significantly increased in the raloxifene group compared with the placebo group. Similar results were observed during Study GGGK, in which a prospective uterine surveillance plan was in place. These events were not prospectively surveyed in Study GGJY, and no increase in raloxifene-treated patients was detected. To summarize, there was no statistically significant increase in the raloxifene group in benign uterine findings during Study GGJY, and the increased reporting of these events seen in the Study GGJY cohort from Study GGGK baseline through Study GGJY termination is probably reflective of findings in Study GGGK during uterine surveillance.

Importantly, no increase in any malignancy of the female reproductive tract was increased in either Study GGGK or Study GGJY (see also Section 12.3.3.2.1 and Section 12.3.3.2.2).

12.3.3.3.1. Uterine Disorder and Endometrial Fluid

During Study GGGK, statistically significantly more patients in the raloxifene group reported "endometrial disorder" compared with the placebo group. Further investigation of this term revealed that the most commonly reported actual term comprising endometrial disorder was endometrial fluid diagnosed during the prospectively-defined transvaginal ultrasounds in Study GGGK. No endometrial carcinomas were reported among the cases of endometrial fluid, and there were no clinical symptoms related to the presence of endometrial fluid (specifically, there was no evidence that patients with reported endometrial fluid experienced vaginal discharge or urinary loss more frequently than the rest of the patient population in any of the three treatment groups). For the Study GGJY cohort observed from Study GGGK baseline through Study GGJY termination, no increase in endometrial disorder was observed; however, the incidence of the related term "uterine disorder NOS" was statistically significantly increased among raloxifene patients compared with placebo patients. Both "endometrial disorder" and "uterine disorder NOS" are preferred terms that are categorized under the same high-level term, "uterine disorders NEC".

The incidence of "uterine disorder" was significantly increased at both the 36-month and 48-month visits of Study GGGK for both raloxifene doses (60 and 120 mg/day).

However, the most common actual term for uterine disorder was "endometrial fluid", which was detected during routine uterine monitoring during the study and is considered a minor adverse effect of raloxifene therapy. The increase in endometrial fluid was not associated with discharge as observed with tamoxifen (Fisher et al. 1998). Given that there is no MedDRA term for endometrial fluid, an extensive search of actual terms was conducted to identify these cases in Study GGJY. Only three cases of endometrial fluid (1 patient in the placebo group and 2 patients in the raloxifene group) were identified.

Study GGJY more accurately reflects the true clinical setting in which uterine investigation is the result of a gynecologic event such as vaginal bleeding and is not done as routine monitoring. Thus, the endometrial fluid findings of Study GGGK probably detected as a result of intensive uterine surveillance during the study.

12.3.3.4. Flushing

Although flushing, or hot flushes, was not increased among raloxifene users during Study GGJY, it is still considered to be one of the few adverse events associated with raloxifene therapy. In Study GGGK, flushing was a common (315 patients [11.6%] of 7705 patients) and statistically significantly increased event among raloxifene patients; however, it was neither common (41 patients [1.0%] of 4011 patients) nor statistically significantly increased in raloxifene patients during Study GGJY. When the Study GGJY cohort was analyzed from Study GGGK baseline through Study GGJY termination, the event was again common (431 patients [10.7%] of 4011 patients) and statistically significantly greater in the raloxifene group compared with the placebo group. Thus, data from both Study GGGK and Study GGJY support that the increased risk of flushing due to raloxifene therapy occurs early in the treatment regimen (typically within the first 6 months of therapy).

12.3.3.5. Muscle Cramps

Although reporting of muscle cramps was not statistically significantly increased during Study GGJY, it is still considered to be one of the few adverse events associated with raloxifene therapy. The increased reporting of muscle cramps in raloxifene patients during Study GGGK was most pronounced during the first 2 years of therapy and diminished thereafter. Compared with placebo, patients on raloxifene continuing into the 3rd and 4th years of Study GGGK did not have a statistically significantly increased incidence of leg cramps de novo. The increase in muscle cramps was also observed in the Study GGJY cohort from Study GGGK baseline through Study GGJY termination.

Compared with placebo, patients on raloxifene continuing into the 3rd and 4th years of the study did not have a statistically significantly increased incidence of leg cramps de novo. A mechanism for raloxifene-associated muscle cramps is not known (that is, they appear to be of the idiopathic variety and do not appear to be caused by muscle damage, hypocalcemia, or vascular insufficiency). However, data from both Study GGGK and Study GGJY support that they are only relevant relatively early during the raloxifene treatment regimen.

12.3.3.6. Depression

The preferred term "depression" was reported more frequently in raloxifene patients than in placebo patients during Study GGJY (p=0.015) (see Section 12.2.2.1 and Table GGJY.12.4). Depression was not a solicited adverse event during this study, and no supporting documentation was obtained by the sites to allow for validation of depression events.
Several preferred terms can be used to indicate a diagnosis of depression, including "major depressive disorder NOS", "dysthymic disorder", and "depressed mood". One of these events,

"depressed mood", was statistically significantly lower among raloxifene treated patients. In addition, there are several clinical manifestations that may have been reported as an adverse event due to an underlying depression (for example, idiopathic pain, sleep disorders, difficulty concentrating, etcetera). Because many adverse events could have been, but were not necessarily, used to describe depression, it is not possible to accurately analyze the effect of raloxifene on depression using the unsolicited adverse event data.

A lack of a raloxifene effect on depression is further emphasized by other Study GGJY data. One high-level term, "mood alterations with depressive symptoms", was statistically significantly lower among raloxifene patients in Study GGJY (p=0.038; Table GGJY.12.5) and for the period from Study GGGK baseline through Study GGJY termination (p=0.045; Table GGJY.14.22). Also, a preferred term under the high-level term "depressed mood" was statistically significantly decreased in raloxifene-treated patients compared with placebo-treated patients in the Study GGJY cohort observed from Study GGGK baseline through Study GGJY termination (p=0.035) (see Table GGJY.12.6). Neither of these events was common and is probably not indicative of a treatment effect of raloxifene on depression.

The finding of increased depression among raloxifene users in Study GGJY is inconsistent with prospectively collected data from Study GGGK and other smaller raloxifene studies. As assessed by the Affective Rating Scale in Study GGGK, patients who received either raloxifene 60 or 120 mg/day were similar to placebo patients with regard to depressive symptoms after 3 years of treatment (Study H3S-MC-GGJY 3-Year Study Report). A small study (N=36) of non-depressed postmenopausal women also showed no difference between raloxifene and placebo after 3 and 12 months of treatment using the Hamilton Depression Rating Scale (Jarkova et al. 2002). Similarly, a Phase 2 study of postmenopausal women with osteoporosis (N=143) evaluated mood endpoints using the Geriatric Depression Scale and found no difference between raloxifene 60- or 120-mg/day and placebo at any timepoint tested (1, 6, and 12 months) (Nickelsen et al. 1998).

In conclusion, depression was not prospectively assessed in Study GGJY, and the reporting of depression as a single preferred term is not a reliable indicator of a treatment effect of raloxifene. Likewise, the presence of other depression-related terms that favored raloxifene is not sufficient to conclude a protective effect. Previous studies have investigated the effects of raloxifene on mood and all have concluded a neutral effect of raloxifene with respect to depressive symptoms.

12.3.3.7. Cardiovascular (Coronary and Cerebrovascular) Events

Coronary heart disease and cerebrovascular events, in particular myocardial infarction (MI) and stroke, have been associated with the use of hormone therapy in clinical trials such as the Heart and Estrogen/Progestin Replacement Study (HERS; Hulley et al. 1998) and the Women's Health Initiative (WHI; Rossouw et al. 2002).

Cerebrovascular events were also increased with tamoxifen treatment in the Breast Cancer Prevention Trial, although this increase did not reach statistical significance (Fisher et al. 1998). Because of the results from these studies, the unsolicited cardiovascular events during Study GGJY were further evaluated, despite the lack of statistical significance.

There were no statistically significant increases between treatment groups for either MI or cerebrovascular accident (stroke) during Study GGJY. However, the numeric increases in the raloxifene group compared with the placebo group for these events, in concert with the known effects of estrogen on risk of cardiovascular events, warrant further investigation.

12.3.3.7.1. Assessment of Cardiovascular Events

There are several important limitations to the cardiovascular (CV) safety data collected in Study GGJY. Unlike Study GGGK, CV events were not solicited in Study GGJY and no additional clinical information was specifically collected to properly ascertain that an event had occurred.

Another limitation concerns the investigator's assessment of a CV event as serious. Investigators were asked to evaluate each TEAE as serious according to the following criteria: death, disability, hospitalization, cancer, or other reason for serious. Many of the CV events in Studies GGGK and GGJY, for example, 42% of the MI events and 27% of the stroke events, did not meet the criteria for being serious, and as such, no additional data were received by Lilly pharmacovigilance on these cases. In addition, lipid-lowering medication use was higher in the placebo group than the raloxifene group at Study GGJY baseline.

The cardiovascular data are further complicated due to significant differences in baseline CV risk factors between the patients who enrolled in Study GGJY and those who chose not to enroll. Tables GGJY.14.13 and GGJY.14.14 compare multiple baseline characteristics that are relevant to CV risk between the two populations. To summarize the demographic differences, the patients who did not enter Study GGJY were more often diabetic and were more likely to take CV medications (including lipid-lowering agents, anti-hypertensives, β blocking agents, diuretics, and aspirin). This point is further illustrated in Figures GGJY.12.2 and GGJY.12.3, which show the incidence rates of MI and stroke in the two populations. The rates of MI and stroke are significantly higher (1.9-fold, $p<0.001$ for MI and 2.7-fold, $p<0.001$ for stroke) among patients who chose not to enter Study GGJY compared with patients who did enroll.

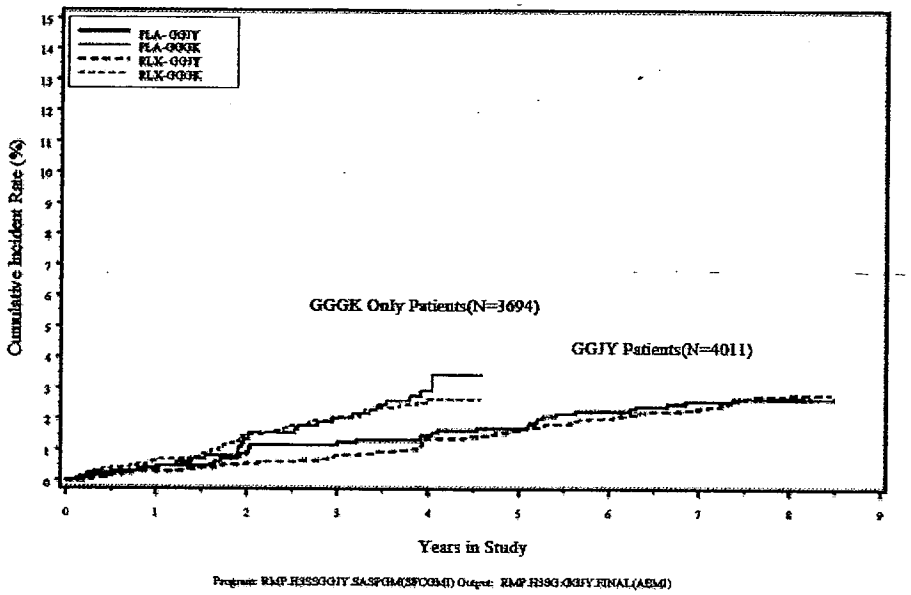

Figure GGJY.12.2. Incidence of myocardial infarction in the Study GGJY cohort from Study GGGK baseline through Study GGJY termination.

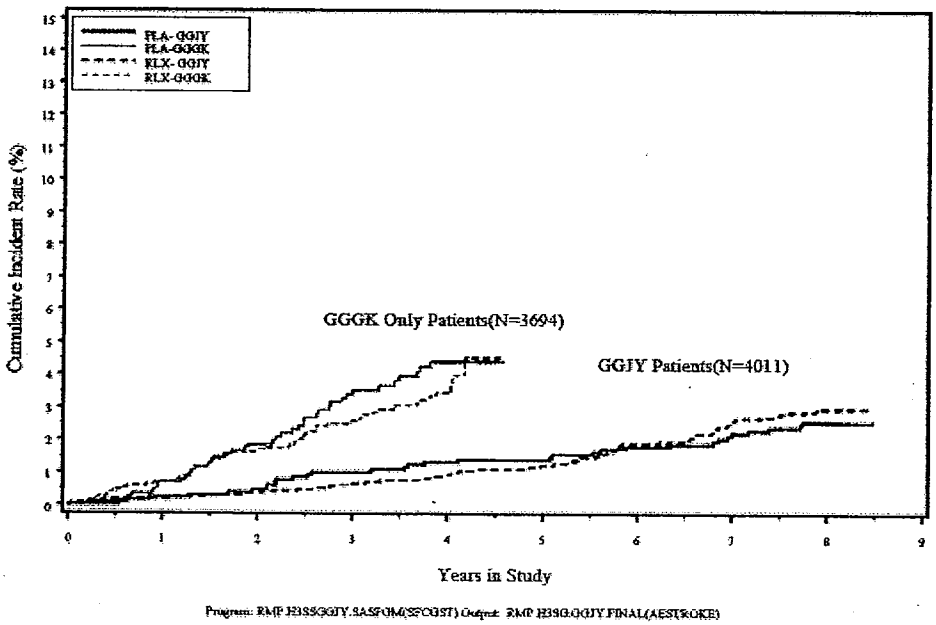

Figure GGJY.12.3. Incidence of stroke in the Study GGJY cohort from Study GGGK baseline through Study GGJY termination.

12.3.3.7.2. Serious and Non-serious Myocardial Infarction Events

In Study GGJY, the MedDRA preferred term "myocardial infarction" was reported as a TEAE in 5 patients (0.4%) in the placebo group compared with 20 patients (0.7%) in the raloxifene group (p=0.282; see Table GGJY.14.21). Myocardial infarction falls under the high-level term "ischemic coronary artery disorders", which was a common (2.8%) TEAE in Study GGJY (30 patients [2.3%] in the placebo group and 81 patients [3.0%] in the raloxifene group; p=0.302; see Table GGJY.14.21 or Table GGJY.12.5).

Although "myocardial infarction" is a specific term in the MedDRA dictionary, various other terms are available and may have been used by investigators to indicate myocardial infarction in a patient. Other preferred terms that likely indicate an MI diagnosis include "acute MI", "myocardial ischemia", "age indeterminate MI", "coronary artery occlusion", and "coronary artery thrombosis". (These terms, combined with myocardial infarction, are hereafter referred to as the myocardial infarction search category.)

Considering all events in the myocardial infarction search category, 13 patients (1.01%) in the placebo group and 34 patients (1.25%) in the raloxifene group experienced an MI during the 4 years of Study GGJY (RR 1.23, 95% CI [0.65, 2.33]) (see Table GGJY.12.13). When the myocardial infarction search category is analyzed for the Study GGJY cohort (N=4011) from baseline of Study GGGK through Study GGJY termination, 34 patients (2.64%) in the placebo group and 74 patients (2.72%) in the raloxifene group experienced an MI (RR 1.03, CI [0.69,1.53]).

Table GGJY.12.13. Myocardial Infarction (Treatment-Emergent Adverse Events, All 4011 GGJY (CORE) Patients)

Time Period	Placebo (N = 1286) % (n)	Raloxifene (N =2725) % (n)	Relative Risk (95% Conf. Int.)[a]	p-Value[b]
Study GGJY	1.01 (13)	1.25 (34)	1.23 (0.65, 2.33)	0.638
Study GGGK baseline through Study GGJY termination	2.64 (34)	2.72 (74)	1.03 (0.69, 1.53)	1.000

Note: Myocardial Infarction determined using the MI search category.
[a] 95% confidence interval based on Mantel-Haenszel method.
[b] Fisher's exact test.

12.3.3.7.2.1. Serious Myocardial Infarction Events

In Study GGJY, 35 events in the MI search category were identified as serious (10 patients [0.78%] in the placebo group and 25 patients [0.92%] in the raloxifene group (RR 1.18, 95% CI [0.57, 2.45]; see Table GGJY.12.14). Considering the Study GGJY cohort (N=4011) from Study GGGK baseline through Study GGJY termination, 63 serious TEAEs were reported in the MI

search category (18 patients [1.40%] in the placebo group and 45 patients [1.65%] in the raloxifene group; RR 1.18, 95% CI [0.69, 2.03]) (see Table GGJY.12.13).

Table GGJY.12.14. Serious Myocardial Infarction (Treatment-Emergent Adverse Events, All 4011 GGJY (CORE) Patients)

Time Period	Placebo (N = 1286) % (n)	Raloxifene (N =2725) % (n)	Relative Risk (95% Conf. Int.)[a]	p-Value[b]
Study GGJY	0.78 (10)	0.92 (25)	1.18 (0.57, 2.45)	0.720
Study GGGK baseline through Study GGJY termination	1.40 (18)	1.65 (45)	1.18 (0.69, 2.03)	0.589

Note: Myocardial Infarction determined using the MI search category.
[a] 95% confidence interval based on Mantel-Haenszel method.
[b] Fisher's exact test.

12.3.3.7.2.2. Myocardial Infarction in Patients Who Received at Least One Dose of Study Drug

As described in Section 11.3, approximately 20% of the patients enrolled in Study GGJY never resumed study drug; that is, they did not take a single dose of study drug during Study GGJY. Assuming a true drug effect, exclusion of these non-treated patients from the analysis would be expected to increase any observed treatment effect. Using the myocardial infarction search category and including only Study GGJY patients who received at least one dose of study drug (n=3200), 39 MI events were identified during Study GGJY (12 patients [1.18%] in the placebo group and 27 patients [1.24%] in the raloxifene group; RR 1.05, 95% CI [0.53, 2.06]) (see Table GGJY.12.15). Thus, although there is not a statistically significant increase in MI in the entire Study GGJY cohort, the numeric increase that is observed in raloxifene-treated patients is not present when only drug-treated patients are included in the analysis.

Table GGJY.12.15. Myocardial Infarction (Treatment-Emergent Adverse Events All 3200 GGJY (CORE) Patients who resumed Study Drug in GGJY)

Time Period	Placebo (N = 1018) % (n)	Raloxifene (N = 2182) % (n)	Relative Risk (95% Conf. Int.)[a]	p-Value[b]
Study GGJY	1.18 (12)	1.24 (27)	1.05 (0.53, 2.06)	1.000

Note: Myocardial Infarction determined using the MI search category.
[a] 95% confidence interval based on Mantel-Haenszel method.
[b] Fisher's exact test.

12.3.3.7.2.3. Discontinuations and Deaths Due to MI

Discontinuations and deaths due to MI were investigated using the myocardial infarction search category applied to Table GGJY.12.9. In Study GGJY, there was 1 patient (0.1%) in the placebo group who discontinued due to the adverse event of MI, compared with 0 patients in the raloxifene group. There were 4 patients (0.1%) who discontinued Study GGJY due to death from

MI (1 patient [0.1%] in the placebo group versus 3 patients [0.1%] in the raloxifene group). Thus, discontinuations due to the adverse event of MI and deaths from MI were rare events in Study GGJY and did not differ between the two groups.

12.3.3.7.3. Serious and Non-serious Stroke (Cerebrovascular Accident) Events

In Study GGJY, the preferred term "cerebrovascular accident" was reported as a TEAE in 5 patients (0.4%) in the placebo group and 26 patients (1.0%) in the raloxifene group (p=0.080) from Study GGJY baseline to termination (Table GGJY.14.21). Other preferred terms that are consistent with a diagnosis of stroke are all preferred terms under the high-level term "central nervous system haemorrhages and cerebrovascular accidents", in addition to the preferred terms "lacunar infarction" and "cerebral haematoma" (hereafter referred to as the stroke search category). In Study GGJY, events in the stroke search category were reported in 14 patients [1.09%] in the placebo group and 49 patients [1.80%] in the raloxifene group (RR 1.65, 95% CI [0.92, 2.98]) (see Table GGJY.12.16). When the stroke search category is analyzed for TEAEs for the Study GGJY cohort (N=4011) from baseline of Study GGGK through Study GGJY termination, 32 patients (2.49%) in the placebo group and 78 patients (2.86%) in the raloxifene group reported a stroke event (RR 1.15, 95% CI [0.77, 1.73]) (see Table GGJY.12.15).

Table GGJY.12.16. Stroke (Treatment-Emergent Adverse Events, All 4011 GGJY (CORE) Patients)

Time Period	Placebo (N = 1286) % (n)	Raloxifene (N =2725) % (n)	Relative Risk (95% Conf. Int.)[a]	p-Value[b]
Study GGJY	1.09 (14)	1.80 (49)	1.65 (0.92, 2.98)	0.103
Study GGGK baseline through Study GGJY termination	2.49 (32)	2.86 (78)	1.15 (0.77, 1.73)	0.536

Note: Stroke determined using the stroke search category.
[a] 95% confidence interval based on Mantel-Haenszel method.
[b] Fisher's exact test.

12.3.3.7.3.1. Serious Stroke Events

In Study GGJY, 53 events in the stroke search category were identified as serious (13 patients [1.01%] in the placebo group and 40 patients [1.47%] in the raloxifene group (RR 1.45, 95% CI [0.78, 2.71]) (see Table GGJY.12.17). Considering the Study GGJY cohort (N=4011) from Study GGGK baseline through Study GGJY termination, 80 serious TEAEs were reported in the stroke search category (23 patients [1.79%] in the placebo group and 57 patients [2.09%] in the raloxifene group (RR 1.17, 95% CI [0.72, 1.89], Table GGJY.12.16).

Table GGJY.12.17. Serious Stroke (Treatment-Emergent Adverse Events, All 4011 GGJY (CORE) Patients)

Time Period	Placebo (N = 1286) % (n)	Raloxifene (N =2725) % (n)	Relative Risk (95% Conf. Int.)[a]	p-Value[b]
Study GGJY	1.01 (13)	1.47 (40)	1.45 (0.78, 2.71)	0.300
Study GGGK baseline through Study GGJY termination	1.79 (23)	2.09 (57)	1.17 (0.72, 1.89)	0.629

Note: Stroke determined using the stroke search category.
[a] 95% confidence interval based on Mantel-Haenszel method.
[b] Fisher's exact test.

12.3.3.7.3.2. Stroke in Patients Who Received at Least One Dose of Study Drug

As described in Section 11.3, approximately 20% of the patients enrolled in Study GGJY never resumed study drug; that is, they did not take a single dose of raloxifene during Study GGJY. Assuming a true drug effect, exclusion of these non-treated patients from the analysis might be expected to increase the observed treatment effect. Using the stroke search category, and including only Study GGJY patients who received at least one dose of study drug (n=3200), 50 stroke events were identified during Study GGJY (11 patients [1.08%] in the placebo group and 39 patients [1.79%] in the raloxifene group) (RR 1.65, 95% CI [0.85, 3.22]) (see Table GGJY.12.18).

Table GGJY.12.18. Stroke (Treatment-Emergent Adverse Events, All 3200 GGJY (CORE) Patients who Resumed Study Drug in GGJY)

Time Period	Placebo (N = 1018) % (n)	Raloxifene (N = 2182) % (n)	Relative Risk (95% Conf. Int.)[a]	p-Value[b]
Study GGJY	1.08 (11)	1.79 (39)	1.65 (0.85, 3.22)	0.168

Note: Stroke determined using the stroke search category.
[a] 95% confidence interval based on Mantel-Haenszel method.
[b] Fisher's exact test.

12.3.3.7.3.3. Discontinuations and Deaths Due to Stroke

In Study GGJY, there were 3 patients (0.2%) in the placebo group who discontinued due to the adverse event of stroke, compared with 5 patients (0.2%) in the raloxifene group (p=0.717, Fisher's exact test). There were 6 patients (0.2%) who discontinued Study GGJY due to death from stroke (1 patient [0.1%] in the placebo group versus 5 patients [0.2%] in the raloxifene group [p=0.671, Fisher's exact test]). Thus, discontinuations due to the adverse event of stroke and deaths from stroke were rare events in Study GGJY and did not differ between the two groups.

12.3.3.7.3.4. Atrial Fibrillation and Stroke

Given the known association of atrial fibrillation and stroke and the numerical increase in these adverse events in raloxifene-treated patients during Study GGJY, an analysis was undertaken to evaluate a possible association with raloxifene. Table GGJY.12.19 shows the number of patients in the Study GGJY cohort who did or did not have atrial fibrillation versus those who did or did not experience a stroke from Study GGGK baseline through Study GGJY termination. Eight percent of the patients in Study GGJY with atrial fibrillation also experienced a stroke. With respect to treatment, 10% of patients in the placebo arm versus 7% in the raloxifene arm experienced both atrial fibrillation and stroke. While these data support an increased risk of stroke in patients with atrial fibrillation, there is no evidence of a treatment effect.

Table GGJY.12.19. Relation between Treatment Emergent Atrial Fibrillation and Stroke [GGGK (MORE) Baseline through GGJY (CORE) Termination, All 4011 Patients Enrolled in GGJY (CORE)]

	Atrial Fibrillation		
Stroke	Yes	No	Total
Yes	9	101	110
No	109	3792	3901
Total	118	3893	4011

Note: Ten percent of the placebo patients with atrial fibrillation and 7% of the raloxifene patients had a stroke. Overall, 8% of the patients with atrial fibrillation had a stroke.

12.3.3.7.4. Atrial Fibrillation

In Study GGGK, there was an increased incidence of "arrhythmia" deemed serious by the investigators in the raloxifene arms (7 patients [0.3%] in the raloxifene 60-mg/day group and 5 patients [0.2%] in the raloxifene 120-mg/day group) compared with placebo (1 patient [<0.1%]) (overall p=0.113, pooled raloxifene group versus placebo, p=0.049).

A TEAE related to arrhythmia, "atrial fibrillation" was numerically increased in Study GGGK in the combined raloxifene arms compared with the placebo arm (33 patients [1.3%] in the placebo group, 35 patients [1.4%] in the raloxifene 60-mg/day group, and 52 patients [2.0%] in the raloxifene 120-mg/day group; p=0.064). At the interim analysis of Study GGJY, conducted 3 December 2001, serious cases of atrial fibrillation were statistically significantly increased in the raloxifene group, though this finding was not considered clinically important by the members of the Data and Safety Monitoring Board, and no comments were made to the Sponsor. Given the heterogeneous nature of the term "arrhythmia" and the lack of biological plausibility, this result was not felt to be clinically significant.

In Study GGJY, 59 cases of atrial fibrillation were reported with no statistically significant between-group difference, though a larger proportion of raloxifene patients did report this event compared with placebo patients (15 patients [1.2%] in the placebo group versus 44 patients [1.6%] in the raloxifene group; p=0.326) (see Table GGJY.14.21). Analyzing the Study GGJY cohort from Study GGGK baseline through Study GGJY, 118 patients reported atrial fibrillation

(29 patients [2.3%] in the placebo group versus 89 patients [3.3%] in the raloxifene group; p=0.088) (see Table GGJY.14.22). Importantly, there was no between-group difference in the high level term "supraventricular arrhythmias" in the Study GGJY cohort over 8 years of observation (p=0.597), in part reflecting reductions in the incidence of other atrial arrhythmias in the raloxifene arm, such as "sinus bradycardia" (p=0.045) and "atrial flutter" (p=0.088) (see Table GGJY.14.22).

12.3.3.7.5. Cardiovascular Discussion and Conclusions

Raloxifene has not been associated with an increased risk of MI or stroke (Ettinger et al. 1999, Delmas et al. 2002). Cardiovascular events were collected as a secondary endpoint in Study GGGK (MORE), and the protocol specified the collection of a physician's written report whenever possible for the following adverse events: myocardial infarction, sudden cardiac death, stroke, coronary bypass surgery, and percutaneous transluminal coronary angioplasty. Further, serial 12-lead electrocardiograms (ECGs) were prespecified and centrally evaluated to detect sub-clinical MIs. After 4 years of study drug, there was no statistically significant difference between either raloxifene treatment group (60 and 120 mg/day) and the placebo group or between the pooled raloxifene groups and placebo for any of the identified cardiovascular events. Also, ECG analysis did not indicate any statistically significant difference between the treatment groups in the incidence of ECG-diagnosed MI. However, when the raloxifene data were pooled, there was a non-statistically significant trend toward a decrease in ECG-diagnosed MI (RR 0.812, 95% CI 0.644, 1.025) (Study H3S-MC-GGGK 4-Year Study Report).

Post-hoc analyses of the effects of raloxifene on cardiovascular events in Study GGGK have been published (Barrett-Connor et al. 2002). Briefly, following 4 years of therapy, the incidence of any adjudicated coronary event in Study GGGK was similar across the three treatment groups (2.1% in the placebo group, 1.8% in the raloxifene 60-mg/day group, and 2.2% in the raloxifene 120-mg/day group [overall p=0.51]). Cerebrovascular events were also reported similarly among the three treatment groups (1.6% in the placebo group, 1.4% in the raloxifene 60-mg/day group, and 1.5% in the raloxifene 120-mg/day group [overall p=0.91]). However, in an analysis of a subgroup of women considered to be at increased risk of cardiovascular disease (based on modified criteria from Mosca et al. 2001), there was a statistically significant reduction in cardiovascular disease (RR 0.60, 95% CI 0.38 - 0.96) and stroke (RR 0.38, 95% CI 0.15- 0.94) in pooled raloxifene-treated women compared with placebo-treated women.

As in Study GGGK, data from Study GGJY do not support an association between raloxifene and myocardial infarction, stroke, or atrial fibrillation. Secondary analyses of these cardiovascular events that included only patients who received study drug do not result in an increased risk for any of these events. The ongoing randomized clinical trial, Study GGIO, is specifically designed to evaluate the effects of raloxifene on cardiovascular endpoints.

12.4. Clinical Laboratory Evaluation

Extensive laboratory evaluations were conducted during Study GGGK and have been presented in all clinical study reports pertaining to Study GGGK. No further laboratory evaluations were conducted during Study GGJY.

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

12.5.1. Vital Signs

Table GGJY.12.17 summarizes the change of weight, height, and body mass index (BMI) from Study GGJY baseline for all enrolled Study GGJY patients. No statistically significant differences between treatment groups were observed for any of the three variables (see Table GGJY.12.20). However, there were statistically significant within group decreases from baseline through study termination for both weight and height ($p<0.1$ for all comparisons). Also, there were very small, but statistically significant, within-group increases in BMI from baseline through study termination ($p=0.021$ and $p<0.001$ for the placebo and raloxifene groups, respectively).

Table GGJY.12.20. Vital Signs Change from CORE Baseline (All Patients Enrolled in Study GGJY)

Variable analyzed: Weight: kg (CWGTKNNO)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	PLACEBO	1246	63.89	63.00	10.47	63.52	62.63	10.75	-0.38	0.00	3.73
2)	RLX060	2648	64.26	63.30	10.40	63.97	63.00	10.97	-0.29	0.00	4.02

		p-Values		
			Pairwise*3	
No.	Therapy	Within Group*1	Overall*2	vs.(2)
1)	PLACEBO	.009	.925	.925
2)	RLX060	<.001		

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model=treatment.
*3 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
SOURCE IS RMP.H3SP.SASMACRO(LAS3M) V1002 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
XLAS0003

Variable analyzed: Weight: kg (CWGTENNO)

			Baseline			Minimum			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	PLACEBO	1246	63.89	63.00	10.47	62.15	61.20	10.44	-1.75	-1.20	3.12
2)	RLX060	2648	64.26	63.30	10.40	62.59	61.80	10.49	-1.68	-1.10	3.16

		p-Values	
			Pairwise*3
No.	Therapy	Within Group*1	Overall*2	vs.(1)
1)	PLACEBO	<.001	.330	.330
2)	RLX060	<.001		

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model=treatment.
*3 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
SOURCE IS RMP.H3SP.SASMACRO(LAS3M) VI002 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
XLAS0003

Variable analyzed: Weight: kg (CWGTENNO)

			Baseline			Maximum			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	PLACEBO	1246	63.89	63.00	10.47	65.36	64.50	11.02	1.47	1.00	3.07
2)	RLX060	2648	64.26	63.30	10.40	65.90	64.92	11.34	1.64	1.14	3.92

		p-Values	
			Pairwise*3
No.	Therapy	Within Group*1	Overall*2	vs.(1)
1)	PLACEBO	<.001	.154	.154
2)	RLX060	<.001		

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model=treatment.
*3 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
SOURCE IS RMP.H3SP.SASMACRO(LAS3M) VI002 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
XLAS0003

Variable analyzed: Height: cm (CHGTENNO)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	PLACEBO	1243	158.24	158.10	6.67	157.66	157.50	6.71	-0.58	-0.50	1.24
2)	RLX060	2646	158.29	158.45	6.67	157.66	157.70	6.71	-0.64	-0.50	1.39

		p-Values	
			Pairwise*3
No.	Therapy	Within Group*1	Overall*2	vs.(1)
1)	PLACEBO	<.001	.276	.276
2)	RLX060	<.001		

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model=treatment.
*3 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
SOURCE IS RMP.H3SP.SASMACRO(LAS3M) VI002 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
XLAS0003

Variable analyzed: Height: cm (CHGTENMO)

			Baseline			Minimum			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	PLACEBO	1241	158.24	158.10	6.67	157.41	157.30	6.70	-0.83	-0.70	1.08
2)	RLX060	2646	158.29	158.45	6.67	157.40	157.48	6.73	-0.89	-0.70	1.34

		p-Values		
			Pairwise*1	
No.	Therapy	Within Group*1	Overall*2	vs.(2)
1)	PLACEBO	<.001	.225	.225
2)	RLX060	<.001		

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model-treatment.
*3 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
SOURCE IS RMP.H3SP.SASMACRO(LAS3M) VI002 000
DATA FROM RMP.SAS.H38M.MCGGJYSC.FINAL
KLAS0003

Variable analyzed: Height: cm (CHGTENMO)

			Baseline			Maximum			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	PLACEBO	1241	158.24	158.10	6.67	158.35	158.20	6.64	0.11	0.00	1.01
2)	RLX060	2646	158.29	158.45	6.67	158.37	158.40	6.66	0.08	0.00	0.98

		p-Values		
			Pairwise*3	
No.	Therapy	Within Group*1	Overall*2	vs.(2)
1)	PLACEBO	<.001	.323	.323
2)	RLX060	<.001		

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model-treatment.
*3 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
SOURCE IS RMP.H3SP.SASMACRO(LAS3M) VI002 000
DATA FROM RMP.SAS.H38M.MCGGJYSC.FINAL
KLAS0003

Variable analyzed: BMI: kg/m^2 (BMI)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	PLACEBO	1241	25.52	25.15	4.03	25.55	25.15	4.11	0.03	0.15	1.52
2)	RLX060	2645	25.66	25.30	4.00	25.75	25.31	4.26	0.09	0.12	1.70

		p-Values		
			Pairwise*1	
No.	Therapy	Within Group*1	Overall*2	vs.(2)
1)	PLACEBO	.011	.911	.911
2)	RLX060	<.001		

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model-treatment.
*3 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
SOURCE IS RMP.H3SP.SASMACRO(LAS3M) VI002 000
DATA FROM RMP.SAS.H38M.MCGGJYSC.FINAL
KLAS0003

Variable analyzed: BMI: kg/m^2 (BMI)

			Baseline			Minimum			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	PLACEBO	1241	25.52	25.15	4.03	24.92	24.50	1.99	-0.60	-0.40	1.25
2)	RLX060	2645	25.66	25.30	4.00	25.10	24.75	4.00	-0.56	-0.38	1.26

		p-Values		
			Pairwise*3	
No.	Therapy	Within Group*1	Overall*2	vs.(1)
1)	PLACEBO	<.001	.250	.250
2)	RLX060	<.001		

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model-treatment.
*3 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
SOURCE IS RMP.H3SP.SASMACRO(LAS3M) VI002 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
XLAS0003

Variable analyzed: BMI: kg/m^2 (BMI)

			Baseline			Maximum			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	PLACEBO	1241	25.52	25.15	4.03	26.24	25.84	4.25	0.72	0.57	1.27
2)	RLX060	2645	25.66	25.30	4.00	26.47	25.97	4.41	0.80	0.60	1.67

		p-Values		
			Pairwise*3	
No.	Therapy	Within Group*1	Overall*2	vs.(1)
1)	PLACEBO	<.001	.172	.172
2)	RLX060	<.001		

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
*2 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model-treatment.
*3 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
SOURCE IS RMP.H3SP.SASMACRO(LAS3M) VI002 000
DATA FROM RMP.SAS.H3SM.MCGGJYSC.FINAL
XLAS0003

12.6. Safety Conclusions

Study GGJY (N=4011) was an approximately 3.5-year study in postmenopausal women with osteoporosis who were previously enrolled in Study GGGK (N=7705). The primary objective of Study GGJY was to assess the efficacy of raloxifene to reduce the risk of invasive breast cancer in postmenopausal women with osteoporosis. Study GGJY also provides long-term safety data for raloxifene. Generally, safety data observed during Study GGJY were consistent with the known safety profile of raloxifene and support that raloxifene is well-tolerated through 8 years of treatment. The adverse events considered to be associated with raloxifene treatment are muscle cramps (especially leg cramps) and flushing (hot flushes). Edema may also be a minor adverse event of raloxifene therapy, but it is not considered clinically relevant.

An increase in benign uterine findings was observed during Study GGGK and in the Study GGJY cohort observed from Study GGGK baseline through Study GGJY termination. The clinical significance of this finding is unclear given that neither vaginal bleeding nor endometrial cancer was increased among raloxifene users during the approximately 8 years of follow-up. These events are likely related to prospectively defined uterine surveillance procedures conducted during Study GGGK.

The only serious adverse event associated with raloxifene treatment is venous thromboembolism (VTE), with an approximately 2-fold overall increase in risk that was observed throughout all 8 years of follow-up. VTE data from Study GGJY do not alter the previously known effects of raloxifene on the incidence rate of these events.

12.6.1. Exposure

Mean exposure to study drug was 2.66 patient-years, and exposure was similar between the two treatment groups in Study GGJY.

Approximately 20% of patients did not elect to resume study drug during Study GGJY.

For all Study GGJY patients, there was a delay between Study GGGK termination and Study GGJY enrollment. The gap between studies was at least 2.6 months for all patients who participated in Study GGJY. The mean time between studies for all Study GGJY participants was 11.9 months and was similar between treatment groups. Whether the interruption in study drug had any effect on the safety profile observed during Study GGJY is difficult to ascertain.

12.6.2. Treatment-Emergent Adverse Events

Two TEAEs were common (> 2%) and statistically significantly different between treatment groups: "pneumonia NOS" and "depression". "Pneumonia NOS" were reported less frequently in raloxifene-treated patients than in placebo-treated patients during the study. Pneumonia is unlikely to be a clinically relevant finding due to the lack of a plausible biological mechanism of raloxifene to elicit the event. "Depression" was reported more frequently in raloxifene-treated

patients compared with placebo-treated patients. The increased reporting of depression is inconsistent with raloxifene data from other studies, including Study GGGK, in which depression was prospectively assessed (Study H3S-MC-GGJY 3-Year Study Report; Nickelsen et al. 1998; Jarkova et al. 2002).

Furthermore, depression was not prospectively assessed in Study GGJY and it is difficult to analyze depression based on adverse event reporting because many adverse events could have been, but were not necessarily, used to describe depression. Given these facts, the increased reporting of depression is probably not related to raloxifene treatment.

Three other TEAEs were statistically significantly increased with raloxifene treatment: "allergies to foods, food additives, drugs and other chemicals"; "drug hypersensitivity"; and "post-procedural pain". Review of the actual terms for these events did not suggest any pattern. The increased reporting of these events is probably due to multiple statistical comparisons to determine significance.

TEAEs were also analyzed for the Study GGJY cohort from Study GGGK baseline through Study GGJY termination. During this observation period, the events increased by raloxifene corresponded well with the safety profile observed during Study GGGK.

Influenza-like illness, muscle cramp, and flushing (hot flushes) were all statistically significantly increased with raloxifene use. Because neither muscle cramp nor flushing were increased during Study GGJY, these two events are considered to be associated with raloxifene treatment primarily during the early part of the treatment regimen, with rates similar to placebo after the first 2 years of treatment.

Edema was increased in Study GGGK and in the Study GGJY cohort observed from Study GGGK baseline through Study GGJY termination. In Study GGGK, a statistically significant increase in the reporting of peripheral edema was observed in the raloxifene 120 mg/day group compared with the placebo group. Though there was no statistically significantly increase in the raloxifene 60 mg/day group compared with placebo, the incidence of peripheral edema appeared to be dose-related. The increase in edema among raloxifene patients seen in the Study GGJY cohort from Study GGGK baseline through Study GGJY termination is the result of increased reporting of the event during Study GGGK. While there is no clear biological mechanism to explain the increase in peripheral edema seen in Study GGGK, edema (in particular, peripheral edema) may be an adverse event associated with raloxifene administration.

Benign uterine events were observed more frequently in raloxifene-treated patients compared with placebo-treated patients in the Study GGJY cohort from Study GGGK baseline through Study GGJY termination. Specifically, "uterine neoplasms", "reproductive tract disorders NEC (excluding neoplasms)", "biopsy endometrium", "uterine polyp NOS", "uterine disorder NOS", and "ultrasound scan vagina" were all statistically significantly increased among raloxifene patients. Two of these terms, "biopsy endometrium" and "ultrasound scan vagina", are procedures, not adverse events.

Importantly, this increase in uterine investigations did not result in an increased reporting of any malignancies. The high level term "uterine neoplasms" contained only the preferred terms of "uterine polyp NOS" and "uterine cyst" and did not contain any malignancies. Benign uterine findings (for example, endometrial fluid and polyps) were observed in Study GGGK, though there were no statistically significant between-group differences during Study GGJY for any uterus-related adverse event. The clinical relevance of these events is uncertain. Vaginal bleeding, which is the most common clinical symptom of these events that would lead to uterine assessment and/or imaging, was never increased among raloxifene patients during the 8 years of follow-up. Thus, most of these abnormalities would not have been identified in a normal clinical setting, but were found primarily as a result of the uterine surveillance plan in place during Study GGGK.

There were statistically significant decreases in two skin-cancer related events during Study GGJY ("skin lesion excisions" and "skin neoplasms malignant and unspecified [excluding melanoma]") and in one skin cancer-related event in the Study GGJY cohort from Study GGGK baseline through Study GGJY termination ("Bowen's disease"). A protective effect of raloxifene on skin cancer has not been previously observed in clinical trials; however, an effect of raloxifene on the development of various skin malignancies cannot be ruled out.

12.6.3. Deaths and SAEs

Seventy-six deaths were reported during Study GGJY (CORE), and the number of deaths was similar between the placebo and raloxifene treatment groups. As previously observed through 4 years of treatment in Study GGGK (MORE), there were proportionately fewer deaths in the raloxifene group compared with the placebo group.

Two deaths of raloxifene-treated patients were considered to be possibly related to study drug. The cause of death for these two patients was "ovarian cancer NOS" and "sudden death".

Safety data from both Study GGGK and Study GGJY have shown that raloxifene does not increase the incidence of ovarian cancer, and this death was not likely to have been caused by raloxifene treatment. The sudden death was deemed by a coroner to be "accidental", but not enough information is available to rule out a causal relationship of raloxifene for this death.

Overall, serious adverse events (SAEs) were reported similarly between the two treatment groups. Only three SAEs were reported statistically significantly more often in raloxifene patients than placebo patients: "spinal fractures and dislocations", "osteoarthropathies", and "breathing abnormalities".

Spinal fractures and dislocations is unlikely to be a true effect of study drug because:
1) The event rate was not reflective of the expected event rate in this population;
2) Study GGJY was not designed to analyze vertebral fractures, and supporting documentation to validate these events is unavailable; and

3) Raloxifene has proven efficacy to prevent vertebral fractures in postmenopausal women with osteoporosis (see Study H3S-MCGGGK 3-Year Study Report).

Osteoarthropathies have not been increased with raloxifene treatment in previous clinical studies. Currently available clinical data are inconsistent (Nevitt et al. 1996; Vingard et al. 1997; Von Muhlen et al. 2002; Karlson et al. 2003), but some data suggest that estrogens and selective estrogen receptor modulators (SERMs) may actually have a protective effect on such events.

With respect to "breathing abnormality", no similar event was observed among raloxifene patients in Study GGGK. The between-group difference for this event is probably due to multiple statistical comparisons and not reflective of a true treatment effect.

12.6.4. Other Events of Interest

Eighty-four patients discontinued Study GGJY due to an adverse event. Discontinuations due to an adverse event were similar between the raloxifene and placebo treatment groups. There were no remarkable findings concerning any of these events.

Ovarian cancer, endometrial cancer, and venous thromboembolism (VTE) events were identified as adverse events of interest based on prior experience during Study GGGK.

As in Study GGGK, there were no statistically significant differences between groups in the incidence of either ovarian or endometrial cancer, either during Study GGJY or in the Study GGJY cohort from Study GGGK baseline through Study GGJY termination. In fact, both of these events were numerically decreased over both observation periods, though this decrease did not reach statistical significance. Thus, long-term administration of raloxifene is safe with respect to ovarian and endometrial cancer.

A VTE event was reported in 28 patients during Study GGJY (Table GGJY.12.10).

When the Study GGJY cohort was observed from Study GGGK baseline through Study GGJY termination, 62 patients had a VTE event (Table GGJY.12.11); 10 of these patients (12 events) occurred during the time interval between Study GGGK termination and Study GGJY enrollment when patients were not receiving study drug. There were no statistically significant between-group differences for VTEs overall or for any specific category of VTE during either observation period. However, numerical increases in the raloxifene group compared with the placebo group were seen for VTEs overall and for each category during both observation periods.

Raloxifene therapy confers a small, but clinically important, excess risk of VTE that appears to be similar in magnitude, and perhaps pathogenesis, to the risk conferred by estrogens and other SERMs. The greatest risk occurs during the first 4 months of raloxifene treatment (see Study GGGK 4-Year Study Report), with an approximate doubling of risk present throughout the duration of therapy up to 8 years. Study GGJY data do not indicate that resumption of raloxifene therapy after an approximately 2- to 12-month washout period is associated with an increased

risk of VTE (>2-fold) in the first 4 months of treatment such as was observed during the initial few months of therapy in Study GGGK.

Given the known effects of estrogen on the risk of cardiovascular events, the numeric (but not statistically significant) increase in myocardial infarction (MI) and cerebrovascular accident (stroke) were further investigated. For each of these events, a search category was used that included all MedDRA preferred terms that were likely to represent a diagnosis of either event. Using the search categories, neither MI nor stroke was increased during Study GGJY or in the Study GGJY cohort observed from Study GGGK baseline through Study GGJY termination. When only patients who resumed study drug in Study GGJY were analyzed, there was no increase in relative risk of either event compared with the entire Study GGJY cohort, which suggests that a drug effect is not present. Treatment groups were also similar with respect to the number of MI or stroke events that were classified as serious.

12.6.5. Vital Signs

No statistically significant differences between treatment groups were observed for height, weight, or BMI. However, there were statistically significant within-group decreases from baseline through study termination for both weight and height. Also, there were very small, but statistically significant, within-group increases in BMI from baseline through study termination.

12.6.6. Conclusions

CORE provides up to 8 years of safety data on the use of raloxifene in postmenopausal women and the safety profile remains consistent with what was previously known for the drug. The safety profile of raloxifene based on CORE data has not been appreciably altered from what was previously known of the drug.

Muscle cramps and flushing were not common or increased among raloxifene users in CORE and are most closely associated with raloxifene early in the treatment regimen, as seen in MORE. Other TEAEs that emerged during CORE (drug hypersensitivity and post-procedural pain) were not likely to be related to study drug. The only serious adverse event related to raloxifene treatment is VTE, which has been previously established.

Raloxifene is safe with respect to ovarian and endometrial cancers for up to 8 years of therapy. Vaginal bleeding was not increased among raloxifene patients. However, intensive uterine surveillance during Study GGGK identified an increase in benign uterine events, although these events were not associated with any malignancies. Long-term administration of raloxifene 60 mg/day to reduce the risk of invasive breast cancer is well tolerated by postmenopausal women with osteoporosis.

Discussion and Overall Conclusions (13)

CORE was designed to evaluate the long-term efficacy of raloxifene compared with placebo on the reduction in risk of invasive breast cancer as seen by the end of 4 years of raloxifene treatment in MORE.

CORE enrolled a cohort from the MORE population. A secondary endpoint of CORE was to determine the efficacy of raloxifene on the reduction in risk of invasive ER (+) breast cancer.

The primary observation period was from 1 January 1999 through CORE termination and consisted of patients whose investigators enrolled patients in CORE. An additional secondary endpoint of CORE was to determine the effect of raloxifene on nonvertebral fractures from enrollment in MORE through termination of CORE in patients enrolled in CORE.

The two treatment groups in CORE were well balanced with respect to breast cancer risk; however, the two treatment groups in CORE differed in severity of osteoporosis. Furthermore, the cohort who enrolled in CORE was younger, had less severe osteoporosis, particularly in the placebo group, and fewer cardiovascular risk factors (Mosca et al. 2001) than patients who did not enroll in CORE, although there was a similar family history of breast cancer (defined as breast cancer occurring in a first degree relative of the patient) in the two populations.

Approximately 20% of patients enrolled in CORE never took study drug.

Compliance in CORE, defined as taking at least 80% of study drug, was 55%.

The mean exposure to study drug was 2.66 years and was similar between the two treatment groups.

Furthermore, more patients in the placebo group took bone-active agents and lipid-lowering agents than patients in the raloxifene group. Although use of the allowed concomitant medications would not be expected to have an effect on the incidence of breast cancer, use of bone-active agents could and likely did have an effect on the ability to differentiate a treatment effect on nonvertebral fractures by raloxifene.

Raloxifene treatment resulted in a significant reduction of adjudicated invasive breast cancer (59% risk reduction, hazard ratio 0.41 [95%CI 0.24, 0.71] [p<0.001]) and invasive estrogen receptor positive ER (+) breast cancer (66% risk reduction, hazard ratio 0.34 [95%CI 0.18, 0.66] [p<0.001]) in the PAD from 1 January 1999 through study termination.

Also, there were statistically significant reductions in adjudicated invasive breast cancer and invasive ER (+) breast cancer in every population at every treatment duration studied. There was no difference between the treatment groups in the risk of estrogen receptor negative (ER-) breast cancer or in the risk of noninvasive breast cancer. Time-to-event analyses demonstrated a continuous separation between placebo and raloxifene-treated patients for invasive and invasive

ER (+) breast cancer cases over 4.5 and 8 years of treatment duration. Every sensitivity analysis conducted confirmed that the primary analysis on adjudicated invasive breast cancer results was robust.

Subgroup analyses (5-year predicted breast cancer risk according to the Gail model, baseline estradiol, baseline age, baseline BMD, previous use of hormone replacement therapy, and family history of breast cancer [defined as breast cancer occurring in a first degree relative of the patient]) demonstrated that patients at increased risk of invasive breast cancer had an overall decrease in the incidence of breast cancer with raloxifene treatment. Furthermore, raloxifene-treated patients with lower risk factors for developing invasive breast cancer generally had a lower incidence of invasive breast cancer than placebo-treated patients, although the difference may not have been significant.

Raloxifene treatment had a neutral effect on nonvertebral fractures (hazard ratio 1.000 [95%CI 0.870, 1.149]) and on nonvertebral-six fractures (hazard ratio 1.007 [95%CI 0.859, 1.180]).

There was an imbalance between raloxifene and placebo-treated arms of the Study GGJY population in the severity of osteoporosis by prevalent vertebral fracture and SQ score (semi-quantitative visual assessment [Genant et al. 1993] by a radiologist for presence of fractures in the T4-L4 vertebral bodies, of which scoring includes 0 [no fracture], 1.0 [mild], 2.0 [moderate], or 3.0 [severe]) at baseline of Study GGGK.

Moreover, patients in the placebo group received more bone-active agents than patients in the raloxifene group. The likelihood of determining an effect of raloxifene on nonvertebral fractures was also diminished by the safety provision that patients were allowed to use other bone-active agents after the 3rd year of Study GGGK and continuing through Study GGJY. Furthermore, patients were allowed to remain in Study GGJY even though they never took study drug.

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

Generally the safety data observed during Study GGJY was consistent with the known safety profile of raloxifene. The adverse events previously defined as being associated with raloxifene treatment are venous thromboembolism, the only serious adverse event, and muscle cramps and flushing (hot flushes), two non-serious events. Peripheral edema may also be associated with raloxifene treatment since previous studies showed a dose relationship, although the incidence at the marketed raloxifene dose (raloxifene HCl 60 mg/day, the dose used in Study GGJY) was not statistically significant.

Raloxifene treatment appeared to be well tolerated during Study GGJY, and there was no difference in discontinuations due to adverse events between the treatment groups.

During Study GGJY, depression was the only common treatment emergent adverse event that was reported significantly more frequently by raloxifene-treated patients than placebo-treated patients. Depression was not observed as a treatment-related adverse event in other clinical trials, and analysis of preferred terms likely to indicate a diagnosis of depression revealed no between-group differences. Review of other events significantly increased in the raloxifene treatment group did not suggest a relationship to raloxifene treatment. Thus, depression is unlikely to be related to raloxifene treatment.

There were 76 deaths in Study GGJY. As previously observed through 4 years of treatment in Study GGGK, there were fewer deaths in the raloxifene group compared with the placebo group.

The overall incidence of serious adverse events (SAEs) was similar between the two treatment groups. Although three SAEs were reported more frequently by raloxifene treated patients (spinal fractures and dislocations, osteoarthropathies, and breathing abnormalities), none were considered likely to be related to raloxifene treatment.

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

There was no increased risk of ovarian cancer, endometrial cancer, or cardiovascular-related events with raloxifene treatment compared with placebo treatment.

Evaluation of the Study GGJY cohort from Study GGGK baseline through the termination of Study GGJY showed no adverse events not already previously evaluated; evaluation was consistent with events observed through 4 years of treatment in Study GGGK.

Vital sign evaluation of patients in Study GGJY showed no significant differences between treatment groups for height, weight, or body mass index.

In conclusion, raloxifene treatment significantly reduced the risk of invasive breast cancer and invasive ER (+) breast cancer in every population studied over any treatment duration. Raloxifene had a neutral effect on nonvertebral fractures in Study GGJY, which was likely due to multiple confounders. The safety profile of raloxifene based on Study GGJY was not altered from that which was previously known. Specifically, raloxifene is associated with only one serious adverse event: venous thromboembolism.

Non-serious adverse events also associated with raloxifene treatment are muscle cramps and flushing, with peripheral edema also likely associated with raloxifene treatment. The combined safety data from enrollment in Study GGGK through termination of Study GGJY continues to

confirm that raloxifene has a good safety profile over 8 years of treatment. Furthermore, the benefits of raloxifene treatment to reduce the risk of vertebral fractures, invasive breast cancer, and invasive ER (+) breast cancer in post-menopausal women with osteoporosis outweighs the risk of raloxifene-associated adverse effects in women not at elevated risk for venous thrombotic events.

10.2 Line-by-Line Labeling Review

- Labeling review is ongoing.

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