CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020815, S003

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

SEP 27 1999

NDA#: 20-815/SE1-003

Applicant: Eli Lilly and Co.

Name of drug: Evista (raloxifene hydrochloride)

Documents Reviewed: Vols 22.14-22.16

Medical Officer: Eric Colman, M.D., HFD-510

Background

The sponsor has submitted the results of three (3) randomized trials to support the supplemental indication of "prevention of osteoporosis in postmenopausal woman". The major evidence comes from one Phase III trial (GGGK) and two smaller Phase II studies (GGGN and GGGP). The primary clinical endpoints reviewed for this indication are the incidence of new vertebral fractures as confirmed by x-ray and lumbar bone mineral density (BMD).

Study GGGK

This international trial (26 countries including the US) trial consisted of two separate substudies, each 3 years in length. Substudy I included patients with low BMD (at least 2.5 SD's below normal) while Substudy II included patients with at least one prevalent vertebral fracture. Patients were randomized 2:1 between Substudy I and Substudy II. There were a total of 5064 patients in Substudy I and 2641 patients in Substudy II. There were three treatment arms in each trial. In Substudy I there were 1689 in the PBO group, 1672 in the raloxifene 60-mg group (RLX-60), and 1703 in the raloxifene 120-mg group (RLX-120). In Substudy II, the respective sample sizes were 887, 885, and 869. Patients visited the clinic at months 3, 6, and 12 for the first year, and every 6 months thereafter.

The original protocol called for analyses of fracture rates, whereas the report refers to "regulatory guidelines [which] suggested that it is more appropriate to analyze the *proportion* of patients with an incident vertebral fracture" (italics added). Binary data was analyzed using the Pearson chi-square test. Change from baseline in lumbar BMD was analyzed using ANOVA with treatment and country in the model.

There were no important mean differences among the groups with respect to baseline variables.

Table 1 shows the amount of missing data from the trials. Post-baseline BMD measurements were missing in a total of 554 patients. Post baseline x-rays were missing in a total of 877 patients.

Table 2 displays the dropout rates pooling the two substudies. Note that RX patients terminated early more frequently than PBO patients due to adverse events, whereas PBO patients terminated early more frequently for 'protocol completion", defined by either 1) loss from baseline of more than 7% of lumbar BMD or more than 10% of femoral neck BMD at the 12-month visit or 2) loss from baseline of more than 11% of lumbar spine BMD or of more than 14% of femoral neck BMD at the 24-month visit, or (3) occurance of more than two incident vertebral fractures during the study.

New Vertebral Fractures

Table 3 displays the results of analyses on the incidence of new vertebral fractures (as opposed to a fracture in a previously fractured vertebra) by substudy. There are highly statistically significant differences between each dose of RX and placebo in each study. Analyses of rates using patient-years give similar results.

There was no evidence to suggest that RX was effective in preventing the worsening of existing lumbar fractures.

There were a substantial number (582 of the 5133 patients randomized to either to the placebo or RLX60 groups in the two substudies) who had missing fracture determinations. In order to gauge the impact of these missing patients, this reviewer did simulations of the missing data using the estimated common percentage of fracture incidence in the two groups pooled over the two substudies (6.8%). The Pearson chi-square statistic was computed for each simulation conditioning on the truly observed data. The percentage of times the p-value was greater than .05 was tabulated. The results were that among 1000 simulated trials, ~~no~~ 611 trials resulted in a p-value below .05. Thus, we can be confident that, should the null hypothesis be true, the trial would have resulted in a statistically significant result if the data on the 582 missing patients been collected **assuming that the patients were missing completely at random**.

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Bone Mineral Density

Tables 4 and 5 display the results for BMD in Substudies I and II, respectively. The statistically significant difference between each dose of RLX and placebo is approximately 2% in each substudy.

Conclusion

The sponsor has submitted two substudies which, when pooled according to prior agreement, shows a statistically significant difference between both Evista dose groups and placebo with respect to new vertebral fractures.

[redacted]

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cc:
Arch NDA# 20-815
HFD-510
HFD-510/EColman, SSobel, GTroendle
HFD-715/DHoberman, TSahlroot, DOB2, Chron

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Table 1

Table GGGK.5.7. Summary of Patients With Missing Baseline or Postbaseline BMD Scans or Spinal Radiographs
All Randomly Assigned Patients
H3S-MC-GGGK 36-Month Data

	BASELINE				POST-BASELINE			
	Placebo	Rlx 60	Rlx 120		Placebo	Rlx 60	Rlx 120	
Substudy I	(N= 1689)	(N= 1672)	(N= 1703)		(N= 1689)	(N= 1672)	(N= 1703)	
Substudy II	(N= 887)	(N= 885)	(N= 869)		(N= 887)	(N= 885)	(N= 869)	
Total	(N= 2576)	(N= 2557)	(N= 2572)	p-Value	(N= 2576)	(N= 2557)	(N= 2572)	p-Value
Femoral Neck								
Substudy I	8 (0.5%)	6 (0.4%)	8 (0.5%)	.848	107 (6.3%)	126 (7.5%)	123 (7.2%)	.368
Substudy II	5 (0.6%)	9 (1.0%)	15 (1.7%)a	.063	76 (8.6%)	87 (9.8%)	77 (8.9%)	.627
Totals	13 (0.5%)	15 (0.6%)	23 (0.9%)	.192	183 (7.1%)	213 (8.3%)	200 (7.8%)	.258
Lumbar Spine								
Substudy I	4 (0.2%)	6 (0.4%)	6 (0.4%)	.777	102 (6.0%)	118 (7.1%)	118 (6.9%)	.435
Substudy II	7 (0.8%)	5 (0.6%)	5 (0.6%)	.801	73 (8.2%)	76 (8.6%)	67 (7.7%)	.797
Totals	11 (0.4%)	11 (0.4%)	11 (0.4%)	1.000	175 (6.8%)	194 (7.6%)	185 (7.2%)	.546
Vertebral X-Rays								
Substudy I	6 (0.4%)	6 (0.4%)	6 (0.4%)	1.000	167 (9.9%)	182 (10.9%)	191 (11.2%)	.420
Substudy II	5 (0.6%)	1 (0.1%)	1 (0.1%)	.231	117 (13.2%)	116 (13.1%)	104 (12.0%)	.693
Totals	11 (0.4%)	7 (0.3%)	7 (0.3%)	.533	284 (11.0%)	298 (11.7%)	295 (11.5%)	.766

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

Data: RMP.SAS.H3SM.MCGGGKSC.LOCK04
Source: RMP.H3SSK3YR.SASPGM(PDMISS2) X5167 30NOV98
Output: RMT.H3SO.K3YR(PDMISS2N)

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Table GGGK.5.2. Reasons for Study Discontinuation
All Randomly Assigned Patients
H3S-MC-GGGK 36-Month Data

Table 2

Primary Reason for Discontinuation	Placebo (N= 2576)	Rlx060 (N= 2557)	Rlx120 (N= 2572)	Overall p-Value	Pooled Rlx p-Value
Total Discontinued	652 (25.3%)	585 (22.9%)a	567 (22.0%)b	.016	.005
Adverse Event	227 (8.8%)	279 (10.9%)a	248 (9.6%)	.039	.041
Personal conflict or other patient decision	185 (7.2%)	161 (6.3%)	160 (6.2%)	.302	.123
Protocol completed	101 (3.9%)	28 (1.1%)c	25 (1.0%)c	<.001	<.001
Protocol variance	29 (1.1%)	42 (1.6%)	45 (1.7%)	.145	.052
Protocol entry criteria not met	35 (1.4%)	29 (1.1%)	21 (0.8%)	.174	.128
Unable to contact patient (lost to follow-up)	29 (1.1%)	16 (0.6%)	21 (0.8%)	.146	.069
Death	23 (0.9%)	13 (0.5%)	28 (1.1%) d	.066	.670
Patient moved	22 (0.9%)	16 (0.6%)	19 (0.7%)	.634	.407
Patient completed protocol, but had an adverse event	1 (0.0%)	1 (0.0%)	0 (0.0%)		
Total Continuing	1924 (74.7%)	1972 (77.1%)a	2005 (78.0%)b	.016	.005

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

Data: RMP.SAS.H3SM.MCGGGKSC.LOCK04
Source: RMP.H3SSK3YR.SASPGM(DC000002) X5167 20NOV98

Output: RMT.H3SO.K3YR(DC00002N)

Table 3

Table GGGK.6.15. New Incident Vertebral Fracture Rates Overall and by Substudy
All Randomly Assigned Patients
H3S-MC-GGGK 36-Month Data

	Placebo	RLX060	RLX120	Pooled RLX Doses
Substudy I	n=1522	n=1490	n=1512	n=3002
Number of patients with ≥ one incident fracture (%)	68 (4.5%)	35 (2.3%)	42 (2.8%)	77 (2.6%)
Relative risk (95% CI) compared with placebo		0.53 (0.35, 0.79)	0.62 (0.43, 0.91)	0.57 (0.42, 0.79)
Pairwise comparison with placebo		p=0.001	p=0.013	p<0.001
Substudy II	n=770	n=769	n=765	n=1534
Number of patients with ≥ one incident fracture (%)	163 (21.2 %)	113 (14.7%)	82 (10.7%)	195 (12.7%)
Relative risk (95% CI) compared with placebo		0.69 (0.56, 0.86)	0.51 (0.40, 0.65)	0.60 (0.50, 0.73)
Pairwise comparison with placebo		p<0.001	p<0.001	p<0.001
Pooled Substudies	n=2292	n=2259	n=2277	n=4536
Number of patients with ≥ one incident fracture (%)	231 (10.1 %)	148 (6.6 %)	124 (5.4%)	272 (6.0%)
Relative risk (95% CI) compared with placebo		0.65 (0.53, 0.79)	0.54 (0.44, 0.67)	0.60 (0.50, 0.70)
Pairwise comparison with placebo		p<0.001	p<0.001	p<0.001

Abbreviations: RLX = raloxifene; RLX060 = raloxifene HCl 60 mg/day; RLX120 = raloxifene HCl 120 mg/day; CI = confidence interval; n = number of patients with evaluable radiographs at baseline and endpoint.

Table GGGK.6.29.

table 4

Summary of Percentage Change in BMD From Baseline to Endpoint
Randomly Assigned Substudy I Patients
H3S-MC-GGGK 36-Month Data

Region	Average n	Mean % Change From Baseline: Placebo 12 Mo	Placebo 24 Mo	Placebo 36 Mo	Mean Percentage Difference From Placebo: RLX060 12 Mo	RLX060 24 Mo	RLX060 36 Mo	RLX120 12 Mo	RLX120 24 Mo	RLX120 36 Mo
Lumbar Spine	1571	0.302	0.082	0.201	2.110 c	2.728 c	2.856 c	2.196 c	2.694 c	2.755 c
Femoral Neck	1566	0.067	-0.291	-1.025	1.336 c	1.827 c	2.088 c	1.445 c	2.202 c	2.401 c
Trochanter	1566	0.129	-0.193	-0.593	1.779 c	2.308 c	2.377 c	1.925 c	2.709 c	2.781 c
Intertrochanter	1010	-0.292	-0.528	-0.674	1.350 c	1.658 c	1.800 c	1.522 c	1.887 c	1.960 c
Ward's Triangle	1566	-0.144	-1.084	-2.332	2.148 c	3.269 c	3.203 c	2.045 c	3.511 c	3.459 c
Ultradistal Radius	496		-1.377			2.121 c			1.895 c	
1/3 Radius	497		-0.888			0.802 c			0.667 c	
Whole Body	450		-0.228			1.018 c			0.959 c	

Note: Average n=average number of patients per treatment group.
Forearm and body BMD were measured at baseline and 24 months only.
a - 0.01 < p-value of Raloxifene vs Placebo <=0.05
b - 0.001 < p-value of Raloxifene vs Placebo <=0.01
c - p-value of Raloxifene vs Placebo <=0.001
RMP.H3SSK3YR.SASPGM(BMDTB001) X4041 05MAR99 11:14:44

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Tab. 5.

Summary of Percentage Change in BMD From Baseline to Endpoint
Randomly Assigned Substudy II Patients
H3S-MC-GGGK 36-Month Data

Region	Average n	Mean % Change From Baseline: Placebo 12 Mo	Placebo 24 Mo	Placebo 36 Mo	Mean Percentage Difference From Placebo: RLX060 12 Mo	RLX060 24 Mo	RLX060 36 Mo	RLX120 12 Mo	RLX120 24 Mo	RLX120 36 Mo
Lumbar Spine	803	0.924	0.697	1.123	1.743 c	2.306 c	2.230 c	2.117 c	2.636 c	2.552 c
Femoral Neck	796	0.170	-0.493	-1.182	1.129 c	1.927 c	2.024 c	1.186 c	2.138 c	2.311 c
Trochanter	796	0.202	-0.264	-0.875	1.687 c	2.577 c	2.602 c	1.872 c	2.892 c	2.879 c
Intertrochanter	502	-0.302	-0.605	-0.830	1.024 c	1.666 c	1.646 c	1.197 c	1.731 c	1.943 c
Ward's Triangle	796	0.207	-1.096	-2.203	1.609 b	2.915 c	3.077 c	1.649 b	3.614 c	2.955 c
Ultradistal Radius	234		-1.428			2.344 c			1.715 a	
1/3 Radius	234		-0.806			1.180 c			0.767 a	
Whole Body	213		-0.563			1.140 c			1.431 c	

Note: Average n=average number of patients per treatment group.
Forearm and body BMD were measured at baseline and 24 months only.
a - 0.01 < p-value of Raloxifene vs Placebo <=0.05
b - 0.001 < p-value of Raloxifene vs Placebo <=0.01
c - p-value of Raloxifene vs Placebo <=0.001
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