Safety Outcome

No specific information is provided regarding the incidence of cognitive, psychiatric and behavioral adverse events in the 3 treatment groups. However the following is stated:

- Only 1 death was reported by Month 12
- There were no significant differences between treatment groups in the incidence of serious adverse events, and adverse events leading to treatment discontinuation
- The only differences between treatment groups were in the incidence of arthralgia, dizziness, and respiratory system adverse events: these differences were not considered clinically relevant

SPONSOR'S CONCLUSIONS

- The sponsor has concluded from the initial 12-month double-blind period of treatment that "overall, there was no evidence that raloxifene affected cognitive performance when administered to post-menopausal women for 12 months at dosage levels of 60 mg or 120 mg daily." The sponsor does concede that given the numerous comparisons that were performed any seemingly statistically significant differences between treatment groups are more likely to have been due to chance
- The sponsor has further concluded from the double-blind extension study that they "see little evidence that raloxifene alters cognitive performance when administered to post-menopausal women in dosage levels of 60 mg or 120 mg daily".
- The sponsor has also expressed the following opinions:
  - Determining the cognitive effects of a drug does not only amount to counting the number of statistically significant differences that are found between groups on multiple comparisons, since in a given individual drugs may impair, improve or not affect specific aspects of cognitive functioning. Even a small number of differences found in multiple comparisons of treatment groups or even contradictory findings on different variables may be significant
  - Such differences might be considered more significant if consistency was noted both within a test battery and over time. The lack of consistency between the differences noted in this study makes it unlikely that they are of significance
  - Since there was no attempt to limit the range of cognitive functioning in those enrolled in the study, this increased baseline variability would greatly increase the sample size needed to detect drug effects. The sponsor does not however feel that the lack of consistency in the statistically significant differences noted between treatment groups can be accounted for by increased baseline variability.
- No safety concerns were noted in this study that were not evident in Study GGGK.

COMMENTS

- No analysis plan or primary outcome measure was specified in the original protocol in regard to the cognitive and affective parameters. The Walter Reed

Performance Assessment Battery described in the study report was not listed in the version of the protocol provided to us

- The protocol-specified sample size estimate for this study was not based upon the cognitive or affective outcome measures.
- It is possible that the number of patients enrolled in this study is inadequate to demonstrate a statistically significant difference (at even a $p < 0.05$ level) between treatment groups for the many comparisons that were made for which a statistically significant difference was not demonstrated; under those circumstances an even larger sample would have been needed if α was adjusted downwards to account for multiple comparisons. **Thus this study also may be lacking in power to support the sponsor's conclusions regarding the effect of the above doses of raloxifene on cognition and affect.**
- Any "statistically significant" ($p < 0.05$)differences actually apparent from the above comparisons are rendered less meaningful by the lack of adjustment for such multiple comparisons; i.e., these differences are much more likely to have been due to chance than a p-value of < 0.05 might suggest.
- Although the treatment groups analyzed were compared with respect to age, no comparisons were made between these groups in respect to other demographic variables or baseline cognitive function. It is noteworthy that patients with pre-existing cognitive impairment were not excluded from the study.
- No formal comparison has been made between the 2 Year Treatment Group and the Placebo Crossover Group, when assessing the results of the double-blind extension phase of the study
- On account of the multiple deficiencies noted, and especially because the power of the study to detect differences between the treatment groups is likely to have been low, the results of the study cannot be used to support the sponsor' s contention in draft labeling that reads as follows: "Evista® has not been associated with deterioration of cognitive function or a change in affect. Any such change during Evista® use is unlikely to be related to therapy, and should be investigated as clinically indicated"

APPEARS THIS WAY
ON ORIGINAL

5. Overall Comments

- Because of the many deficiencies in Studies H3S-MC-GGGK and H3S-MC-GGGN, they cannot be used to support the statement in the submitted draft package insert that is as follows: "Evista® has not been associated with deterioration of cognitive function or a change in affect. Any such change during Evista® use is unlikely to be related to therapy, and should be investigated as clinically indicated"
- The above statement should, therefore, be deleted from the package insert

6. Recommendations

The "Precautions" section of the draft package insert contained in this submission contains the following statement:

[redacted]

The entire statement should be deleted

/S/

APPEARS THIS WAY ON ORIGINAL

Ranjit B. Mani, M.D.
Medical Reviewer

R. Levin, M.D. /S/

rbm 7/16/99
cc:
HFD-120
HFD-510
Division Consult File 20815 (S-003)
electronic copy-Levin

See attached page

APPEARS THIS WAY ON ORIGINAL

Medical Officer—Review of Consultation Material

NDA:	20-815/S-003	**Requesting Division:**	HFD-510
Drug:	Raloxifene	**Consult Date:**	July 15, 1999
Sponsor:	Eli Lilly	**Additional Material:**	August 24, 1999
		Review Date:	September 14, 1999

I. Regulatory Background

Raloxifene was approved to prevent osteoporosis in postmenopausal women in December 1997, after review of 3 randomized placebo-controlled trials. During the conduct of these and other supportive studies, information on breast cancer cases was collected. Fewer cases were observed in women treated with raloxifene compared to women treated with placebo. The Division of Oncology Drug Products was consulted in March 1998 to evaluate the cases and to determine whether information about breast cancer should be included in the label. The review stated that the quality of these data did not support an indication for reduction in the incidence of breast cancer. However, the DODP review stated that it was appropriate to list the number of FDA-adjudicated cases identified on the raloxifene and placebo arms of the trials in the approved labeling for raloxifene.

In order to obtain an indication for the treatment of osteoporosis, study GGGK, a 7700-patient multicenter trial of raloxifene at several doses compared to placebo, was completed and has been submitted for review to HFD-510 as supplement 003. The goal date for this application is September 30, 1999. DODP has been consulted to evaluate the sponsor's request to update the number of breast cancer cases in the revised product label.

It should be noted that the applicant has met with DODP separately to discuss the possibility of an indication for reduction in the incidence of breast cancer for raloxifene. After review of the updated data submitted in the briefing document, the DODP again concluded that the quality of the data does not support this indication at this time. A development plan for the reduction in incidence of breast cancer indication was discussed and agreed upon with the applicant.

II. Sponsor's Adjudication Methods

Documentation of all breast cancer cases reported to the sponsor was collected. Mammograms, breast ultrasounds, and pathology slides were sent to an independent blinded consultant for secondary review. The results of the institutional readings of these materials and of the independent consultant's readings were transcribed verbatim into a "Breast Cancer Case" form. An adjudication board, convened by the sponsor, reviewed these results and determined whether or not the case represented breast cancer, specified whether it was invasive or non-invasive, and whether or not it was pre-existing. Only new cancer cases were included in the analysis.

The adjudication board met on December 5, 1996 and October 23, 1997. Forty-nine cases (per medical officer's review, 3/98) were reviewed at these meetings and were subsequently reviewed by Karen Johnson, M.D., DODP in 3/98. The results of these reviews formed the basis for the original labeling claim.

In the sNDA currently under review, the procedure was amended slightly. The blinded review of the baseline films was used as the basis for determining whether a cancer was pre-existing or not. Second, the board was asked whether a diagnosed cancer arose from the same area as the abnormality identified on the baseline film. These guidelines prevented the board from retrospectively identifying lesions that were not obvious from the context of a single baseline film, and from classifying a cancer as pre-existing if in fact it developed in a different part of the breast.

The current application includes one case that was reviewed October 23, 1997 but did not meet the data lock date for the original submission, 19 cases reviewed on March 30, 1998, and 18 cases reviewed October 28, 1998.

III. Summary of the Case Reviews, 3/98

In the original application, 57 cases were reported by the sponsor. Six cases were excluded, because they occurred in patients on the estrogen arm of trials in which women were randomized to receive estrogen, raloxifene, or placebo (Study GGGH 5 patients; study GGGM 1 patient). Two additional cases were excluded from analysis: patient 5415 in study GGGX received raloxifene 60 mg in a non-placebo-controlled study (the trial compared raloxifene to estrogen) and patient 0416 in study GGGN received raloxifene 120 mg in an unblinded extension phase.

Of the remaining 49 cases, 7 were incomplete and were not adjudicated at the time of the NDA submission. Seven of the 42 reviewed cases were classified as DCIS and were excluded. Thirty-five cases were classified as invasive breast cancer, 21 in the placebo arm and 14 in the raloxifene arms.

The following table summarizes the serial review process:

Table 1. Breast cancer cases in all raloxifene trials, 11/97

Therapeutic arm	Sponsor-reported cases	Cases reviewed by adjudication board	New cases per adjudication board	New cases per FDA	Cases permitted in the label
Estrogen	6	Not evaluated	Not evaluated	Not evaluated	Not reported
Placebo	26	21[c]	13[d]	10	10
Raloxifene:		14[c]	5[e]	6	6 (not reported by raloxifene dose)
30 mg	3				
60 mg	9[a]				
120 mg	10[b]				
150 mg	3				

[a] One excluded from analysis; not a placebo-controlled study

[b] One excluded from analysis; occurred on open-label extension phase

[c] Cases reviewed after exclusion of 7 incomplete cases and 7 DCIS cases; treatment arms not given in the 3/98 medical officer's review

[d] One case was indeterminant; 7 were pre-existing

[e] One case was indeterminant; 8 were pre-existing

Table 2. Patients (by ID) included in the original labeling

Therapeutic arm	Study	Patient ID	Raloxifene Dose
Placebo	GGGF	3601	[redacted]
	GGGK	3971	
		7618	
		4534	
		5905	
		9451	
		4730	
		0083	
		6687	
		0946	
Raloxifene	GGGF	3622	30 mg
	GGGG	2971	30
	GGGH	0969	150
		0419	150
	GGGK	0032	120
		2333	120

IV. Case reviews, 9/99

The current supplement was submitted to HFD-510 for the treatment of osteoporosis. The sponsor updated the number of cases in the label, based on additional follow-up data, to 17 cases on placebo and 11 on raloxifene, for a total of 28 cases. DODP has been consulted to review the updated figures.

A. Materials Submitted

1. Copy of the sponsor's revisions to the label
2. Clinical study summary, pages 5-16
3. Breast-Related Endpoints, from the Integrated Summary of Safety, pages 288-311

B. Additional Materials:

After a request by the DODP for primary breast cancer data, the applicant submitted a list of breast cancer cases identified since 11/97 and copies of the documents used by the adjudication committee.

The DODP sent a second set of questions and received a response on 9/17/99. In this response, the applicant changed the number of cases for labeling to 16 on placebo and 11 on raloxifene. The patient ID numbers and justifications for the changes were included in the response and are discussed below.

C. Case Review

As noted above, the current dataset includes one case that was reviewed October 23, 1997 but did not meet the data lock date for the original submission, 19 cases

reviewed on March 30, 1998, and 18 cases reviewed October 28, 1998. A total of 38 cases were reported in this submission.

Three cases were excluded from analysis, because these trials did not have placebo controls (patient 0146 from study GGGN; patient 4708 from study GGHF; patient 5829 from study GGHV).

Nine cases were excluded because they represented DCIS, 5 on placebo (0388 right-sided lesion, 4101, 4731, 0072, 7464) and 4 on raloxifene (0238, 3026, 2631, 1302). The reviewer agrees with the classification of non-invasive cancer for these patients.

Table 3. Serial breast cancer case exclusions

Therapeutic arm	All sponsor-reported cases	Invasive cancer cases	Evaluable cases	New cases per adjudication board	New cases per FDA	Cases permitted in the label
Estrogen[a]	1	1	0	N/A	Not evaluated	Excluded
Alendronate[b]	1	1	0	N/A	Not evaluated	Excluded
Placebo	17[c]	12	12	6[e]	See Tables 4 and 5	
Raloxifene:	19	15	14	6[f]	See Tables 4 and 5	
60 mg	9	7	7	3		
120 mg	8[d]	6[d]	5	1		
150 mg	2	2	2	2		

[a] Pt 4708 on trial GGHF, estrogen v. raloxifene; randomized to HRT. Excluded from analysis because of lack of placebo control and allocation to the estrogen arm

[b] Pt 5829 on trial GGHV, alendronate + placebo; excluded from analysis

[c] One patient (pt 0388 on GGGK) with bilateral breast cancer, 1 invasive and 1 non-invasive

[d] One case excluded (pt 0146 on GGGN); included in non-placebo-controlled study

[e] 3 were pre-existing (pt 2469, 4267, 3975); in 3, an assessment could not be made (pt 8162, 6637, 8736)

[f] 7 cases were pre-existing (3 at 60 mg [pt 3035, 5215, 0331] and 4 at 120 mg [8938, 2756, 7880, 2333]); 1 patient did not have cancer on pathology review (pt 6480 on RLX 60)

Each case was reviewed by the FDA reviewer. The reviewer was not blinded to the treatment assignment or to the assessment of the adjudication board for the evaluable cases. The following table summarizes the results of the adjudication board and FDA assessments.

Table 4. Comparison of Adjudication Board and FDA reviewer assessments—patients with invasive evaluable cancer

Treatment arm	Study/ Dose mg	Patient ID	Adjudication Board Assessment	FDA Assessment	Comments
Placebo	GGGF	0860	New	Agree	New breast mass 4 years after study entry. ER +; PR not done
	GGGK	0108	New	Agree	New mass 2 yrs after study entry. ER 90%; PR 60%
		0388	New	Agree	Left evaluated only (pt had synchronous right DCIS that was excluded from review). Mass 1 year after randomization. ER 100%; PR 50%
		2469	Pre-existing	Agree	Inc. dens. UOQ was present at baseline. ER/PR-
		3011	New	Agree	New mass on 1-year f/u mammogram. ER +, PR-
		3975	*Pre-existing*	Agree	Mass present at baseline. 2 invasive cancers. ER+, PR-
		*3975**	*Pre-existing*		
		4267	Pre-existing	Agree	Abnormal baseline mammogram. ER 100%; PR 80%
		6637*	Unable to assess	Pre-existing	Abnormal baseline mammogram (1.5 cm lateral mass right breast). Receptors not done
		6662*	New	Pre-existing	Abnormal masses that correlate to subsequent area of cancer were identified on the baseline mammogram. ER/PR +
		8162	Unable to assess	Pre-existing	Baseline mammogram notes abnormality in left UOQ. Tumor subsequently diagnosed as axillary mass with extension into "lateral breast" and second focus in LIQ. ER/PR +
		8736	Unable to assess	Agree	No baseline films or reading. Abnormal mammogram at 2-yr f/u (1st film after study entry). ER+/PR-
		9228	New	Agree	New mass at 3-yr f/u mammogram. ER/PR -
Raloxifene	GGGG 60	3035	Pre-existing	Agree	Dx made 1.5 mo after study entry. ER/PR not done
	GGGF 60	1008	New	Agree	New calcifications 2 years after study entry. ER/PR -
	GGGH 150	1406	New	Agree	New mass 3 years after study entry. ER/PR both "weakly +"
	GGGK				
	60	0282	New	Disagree; pre-existing	The 2-year f/u mammogram states that the mass is bigger than it was at baseline, although the baseline film was read as normal. ER strong +, PR weak +

	60	0331	Pre-existing	Agree	Baseline abnormal mammogram and palpable mass. ER 0, PR 21.8
	120	2333*	Pre-existing	Agree	Right subareolar Ca^{2+} seen at baseline. No receptors performed
	120	2756	Pre-existing	Agree	Baseline abnormal mammogram. ER/PR +
	60	4469	New	Agree	New mass 2 yrs after study entry. ER/PR -
	60	5215	Pre-existing	Agree	Abn mass and Ca^{2+} on baseline film in L subareolar area. The bx was performed because of Ca^{2+} and mass in L UIQ; probably the same abnormality as at baseline. ER 50%; PR not given
	60	6480*	Not cancer	Agree	Second path review showed ADH but no DCIS
	120	7871	New	Agree	New Ca^{2+} at 2-yr f/u. ER/PR -
	120	7880	Pre-existing	Agree	Abnormal baseline mammogram. ER 90%; PR 30%
	120	8938	Pre-existing	Agree	Baseline mammogram abnormal. No receptors performed
	GGGP 150	2409	New	Agree	New finding on the 2-year f/u mammogram. Second reviewer thought cellular smears might represent DCIS, but local pathologist, using excisional bx material, called it invasive. Reviewer agrees with the invasive categorization. ER +6/7; PR + 5/7

* Adjudicated twice:

- Pt 3975 called pre-existing both times, but pathology information was incomplete the first time.
- Pt 6637 reviewed prior to 12/97 and deemed a new cancer by the adjudication board; called a pre-existing cancer by the FDA reviewer in 3/98; excluded from labeling.
- Pt 6662 reviewed prior to 12/97 by the adjudication board and deemed a new cancer; called pre-existing by the FDA reviewer and excluded from labeling.
- Pt 6480 reviewed prior to 12/97; adjudication board was unable to assess the timing of the cancer; called DCIS by the FDA reviewer and excluded from labeling
- Pt 2333 reviewed prior to 12/97 and called pre-existing cancer by the adjudication board; FDA reviewer called this a new cancer; patient included in the original breast cancer labeling

In all cases, the reviewer agreed that the cancer was invasive.

D. Reviewer disagreements with the adjudication board

Placebo:

Patient 6637*: The board could not assess whether the tumor was pre-existing. The reviewer believes it was, as a 1.5 cm lateral right breast mass was identified on the baseline mammogram. (This finding agrees with that of the previous FDA reviewer. The applicant did not include this patient in current labeling as of 9/17/99 submission).

Patient 8162: The board could not assess whether the lesion was pre-existing. The reviewer believes it was. The baseline mammogram noted a left UOQ abnormality. The tumor was subsequently diagnosed as arising from breast tissue in the axilla and was found at mastectomy to extend into the lateral aspect of the breast. A separate area of tumor, consistent with its invasive lobular histology, was found in the lower inner quadrant. [Not included in current labeling by the applicant.]

Patient 6662: This case was reviewed prior to 12/97 by the adjudication board and was deemed a new cancer. The reviewer believes it was pre-existing, as abnormal masses that correlate with the location of the cancer were identified at baseline. This finding is in agreement with that of the previous FDA reviewer. [Included in labeling by the applicant]

Raloxifene:

Patient 0282: The board adjudicated this cancer as new. The reviewer disagrees. The two-year follow-up mammogram indicates that the mass has increased in size since the baseline film, even though the baseline film was read as normal.

E. Reviewer disagreements with the previous FDA reviewer (patients adjudicated twice; the current reviewer did not re-review the original material)

Patient 2333: This patient's case was reviewed prior to 12/97 and was classified as a pre-existing cancer by the adjudication board. The previous FDA reviewer called this a new cancer and included the case in the original breast cancer labeling. The current reviewer believes this cancer was pre-existing, because right subareolar microcalcifications were present on the baseline examination. [Not included in current labeling by the applicant]

F. Unable to assign timing of the cancer

Patient 8736 did not have a baseline mammogram; no films or report were available to the local investigator or to the outside second reader. The cancer was found on the first follow-up mammogram, obtained 2 years after study entry. Because it is not possible to determine whether the cancer was pre-existing, it should be excluded from analysis. The purpose of this labeling is to report only those cancers on placebo and on raloxifene that we are sure occurred during the course of the study, as data for this endpoint were not prospectively and rigorously collected.

G. Reviewer disagreements with the applicant

The applicant and the reviewer agree on all cases listed in Table 5, with the following exceptions:

Placebo:

The applicant added patient 6662. As described in Table 4 and section D, the reviewer does not agree that this case represents a new cancer. This case should be removed from labeling.

Raloxifene:

The applicant added patient 0282. The committee was asked to use the baseline assessment to determine whether the cancer was pre-existing or not. For this patient, baseline films were not available for a second, central blinded reading. The local radiologist identified irregular parenchyma without tumors on the baseline film, but stated on the second available film that the suspicious mass had grown compared to baseline. Review of all submitted cases suggests that the reports of the blinded central reviewer are more accurate and descriptive than those available from the local radiologist. Since the lesion was present at baseline, even in retrospect, and given the limitations of the local readings, the FDA reviewer believes that this case should be classified as pre-existing.

V. Conclusions

The following table summarizes the patient ID numbers of those cases appropriate for inclusion in the label. In order to obtain totals, this table includes the patient identifiers, if appropriate, of the original (3/98) labeling.

Table 5. Cases of breast cancer, with patient ID, appropriate for labeling

Therapeutic arm	Study	Patient ID
Placebo	GGGF	3601
	GGGK	3971
		7618
		4534
		5905
		9451
		4730
		0083
		6687
		0946
	GGGF	0860
	GGGK	0108
		0388
		9228
		3011
Raloxifene	GGGF	3622
		1008
	GGGG	2971
	GGGH	0969
		1406
		0419
	GGGK	0032
		4469
		7871
		2409

The accepted totals for labeling are 15 cases on placebo and 10 on raloxifene.

VI. Recommendations

1. The total number of labeled cases in "Effects on the Breast" should be 15 for placebo and 10 for raloxifene.

2. The labeling under "Effects on the Breast" (page 25 of the sample label submitted to DODP) reads:

The word should be deleted from this sentence.

/S/

Susan Flamm Honig, M.D.
Medical Reviewer

/S/ 9/22/99

Julie Beitz, M.D.
Team Leader

APPEARS THIS WAY
ON ORIGINAL