CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-042

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-042 SUPPL # HFD # 150

Trade Name Evista®

Generic Name raloxifene hydrochloride

Applicant Name Eli Lilly and Company

Approval Date, If Known September 13, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-815 Evista (raloxifene HCl)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

(1) Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer, (2) Raloxifene Use for the Heart (RUTH), (3) Multiple Outcomes of Raloxifene Evaluation (MORE), and (4) Continuing Outcomes Relevant to Evista (CORE).

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Investigation #3 - Yes NDA 20-815 and Investigation #4 - No.

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #3 and # 4 - No.

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

(1) Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer, (2) Raloxifene Use for the Heart (RUTH), (3) Multiple Outcomes of Raloxifene Evaluation (MORE), and (4) Continuing Outcomes Relevant to Evista (CORE).

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 57,427 YES ☐ ! NO ☒
! Explain:
The National Surgical Adjuvant Breast and Bowel Project (NSABP) conducted and was the sponsor for this IND.

Investigation #2

IND # 57,137 and 39,503 YES ☒ ! NO ☐
! Explain:
Investigation # 3 - IND 39,503 and #4 - 57,137 and 39,503

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☒	! NO ☐
Explain:	! Explain:
STAR trial - Eli Lilly certified that they provided greater than 50% of the total clinical cost.	

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Patricia Garvey, R.Ph.
Title: Senior Regulatory Project Manager
Date: September 13, 2007

Name of Office/Division Director signing form: Robert Justice, M.D.
Title: Director, Division of Drug Oncology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Justice
9/13/2007 06:45:32 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA# : 22-042 **Supplement Type (e.g. SE5): _____** **Supplement Number: _____**

Stamp Date: November 14, 2006 **PDUFA Goal Date: September 14, 2007**

HFD-150 **Trade and generic names/dosage form: Evista (raloxifene HCl) 60mg Tablets**

Applicant: Eli Lilly and Company **Therapeutic Class: _____**

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

☑ **Yes. Please proceed to the next question.**

☐ **No. PREA does not apply. Skip to signature block.**

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only): The prevention and treatment of osteoporosis in postmenopausal women (NDA 20-815)

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 2

Indication #1: The reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis.

Is this an orphan indication?

☑ **Yes. PREA does not apply. Skip to signature block.**

☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**

☐ **Disease/condition does not exist in children**

☐ **Too few children with disease to study**

☐ **There are safety concerns**

☐ **Other: _____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: The reduction in risk of invasive breast cancer in postmenopausal women at high risk for breast cancer.

Is this an orphan indication?

☑ **Yes. PREA does not apply. Skip to signature block.**

☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Garvey
1/12/2007 11:16:02 AM

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 22-042	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type SE1	
Proprietary Name: Evista® Established Name: raloxifene hydrochloride Dosage Form: tablet		Applicant: Eli Lilly and Company	
RPM: Patricia Garvey, R.Ph.		Division: 150	Phone # 301-796-1356

NDAs: NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	September 14, 2007 September 13, 2007
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☒ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☒ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other – ASCO Burst, Information Advisory

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the

NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	Division Director – September 13, 2007
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	Not Applicable
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	Included
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	Included
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	Included
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	Included
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	

❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☐ DMETS ☒ DSRCS – August 31, 2007 ☐ DDMAC ☒ SEALD – August 28, 2007 ☒ Other reviews – DMEP August 14, 2007, RPM March 19, 2007 ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	RPM - January 18, 2007
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	Not Applicable
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☒ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg December 12, 2007 May 31, 2005 February 17, 1999
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	☐ No AC meeting
• Date of Meeting	July 24, 2007
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	Included
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	August 30, 2007
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	August 30, 2007
• ☐ Review & FONSI *(indicate date of review)*	

• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☒ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: ☐ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Not Applicable
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	Not Applicable
❖ Nonclinical inspection review Summary (DSI)	☒ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	TL – September 6, 2007 Reviewer #1 – September 7, 2007 Reviewer #2 – September 7, 2007
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	Included in September 7, 2007
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☒ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	Included in September 7, 2007
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	Not Applicable
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	June 21, 2007
• Bioequivalence Studies	Not Applicable
• Clin Pharm Studies	Not Applicable
❖ Statistical Review(s) *(indicate date for each review)*	☐ None Dep Dir/TL – September 10, 2007 Reviewer -September 10, 2007
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None September 5, 2007

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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/s/

Patricia Garvey
9/18/2007 01:57:21 PM

Harapanhalli, Ravi S

From: Garvey, Patricia
Sent: Thursday, September 13, 2007 12:35 PM
To: Harapanhalli, Ravi S
Cc: Pope, Sarah
Subject: RE: NDA 22-042 Evista - DRAFT approval letter

Thank you for your comments. I will send you the label when it is received.

From: Harapanhalli, Ravi S
Sent: Thursday, September 13, 2007 12:32 PM
To: Garvey, Patricia
Cc: Pope, Sarah; Harapanhalli, Ravi S
Subject: FW: NDA 22-042 Evista - DRAFT approval letter

Pat,
The letter looks good. I agree that the firm can submit the final printed carton and container labels, which are in compliance with 21CFR 208.24 (d) in an electronic format post-approval. It is my understanding that no other changes will be made to the previously-approved container labels other than including a statement on providing medication guide to patients at the time of dispensing. Please forward the electronic labels to us when they are received.

Thanks

Ravi S. Harapanhalli, Ph.D.
Chief, Branch V (CMC-Pre-marketing)
Division of Pre-market Assessment and Manufacturing Science
Office of New Drug Quality Assessment (ONDQA), CDER, FDA,
Bldg. 22, Room # 2414
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002
Phone: 301 796 1676; Fax: 301 796 9850

From: Garvey, Patricia
Sent: Thursday, September 13, 2007 12:00 PM
To: Cortazar, Patricia; Mann, Bhupinder; Pope, Sarah; He, Kun; Bullock, Julie
Cc: Pease, Dorothy W; Justice, Robert; Johnson, John R; Sridhara, Rajeshwari; Harapanhalli, Ravi S; Booth, Brian P
Subject: NDA 22-042 Evista - DRAFT approval letter

Hello Team,

Please review the attached DRAFT approval letter. Please send me your corrections/comments ASAP. If you do not have any corrections, please reply with your concurrence.

Also, if you have the action package, please continue to keep it circulation as we are trying to take an action late today or early tomorrow morning.

Thanks
Patty

<< File: Approval ltr.doc >>
Patty Garvey, R.Ph.
CDR, USPHS
Senior Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products

Center for Drug Evaluation & Research, FDA
P: (301) 796-1356
F: (301) 796-9845
E: patricia.garvey@fda.hhs.gov (**Please note my new e-mail address)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 30, 2007
To:	Robert Justice, MD., Director Division of Drug Oncology Products
Thru:	Toni Piazza-Hepp, Pharm.D., Deputy Director Division of Surveillance, Research and Communication Support
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Division of Surveillance, Research and Communication Support
Subject:	DSRCS Review of Patient Labeling (Medication Guide)
Drug Name(s):	Evista (raloxifene hydrochloride) Tablets for Oral Use
Application Type/Number:	N22-042
Applicant/sponsor:	Eli Lilly and Company
OSE RCM #:	2007-1783

1 INTRODUCTION

Evista (raloxifene hydrochloride) tablets, was granted a priority review and received its original approval under NDA #20-815 on December 9, 1997 as a new molecular entity. The approved indication at that time was for the prevention of osteoporosis in postmenopausal women. On September 30, 1999 Evista (raloxifene hudrochloride) tablets was approved for the treatment of osteoporosis in postmenopausal women.

Eli Lilly and Company submitted a Prior Approval Supplement sN20-815/S-018, on October 4, 2006 including proposed labeling changes that addressed unexpected findings of an increased risk from stroke in the RUTH study. DSRCS provided a review of the Patient Package Insert (PPI) that was included by the sponsor in the submission for this supplement on June 21, 2007. The supplement was approved with the revised Evista labeling by the Division of Metabolic and Endocrine Products on July 17, 2007.

The Division of Drug Oncology Products is currently reviewing a type 6 NDA (NDA# 22-042) efficacy supplement submitted by the sponsor on November 14, 2006 requesting two new indications: "reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis" and "reduction in risk of invasive breast cancer in postmenopausal women at high risk for breast cancer." The sponsor submitted an Information Amendment to this NDA on July 20, 2007, consisting of a revised Label in PLR format, with proposed language for safety and efficacy.

Based on discussions at the meeting of the Oncologic Drugs Advisory Committee on July 24, 2007, the Division of Drug Oncology Products met with the FDA Patient Information Subcommittee (PISC) on August 16, 2007, to discuss the need for a Medication Guide for EVISTA. The PISC agreed that Evista poses a serious and significant public health concern requiring distribution of FDA-approved patient labeling, as specified in 21 CFR 208.1 (c) (2): "The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect the patients' decision to use, or continue to use, the product." The Review Division requested that the sponsor submit a Medication Guide to address the serious and significant public health concern related to potential thromboembolic events, stroke and possible death from stroke. The sponsor submitted a proposed Medication Guide for Evista to NDA 22-042 as requested, on August 3, 2007. DSRCS has been requested to review the sponsor's proposed Medication Guide.

2 MATERIAL REVIEWED

The Sponsor proposed Medication Guide dated August 3, 2007 and Review Division revised Professional Information dated August 16, 2007 were reviewed.

3 DISCUSSION

Comments to the Review Division are ***bolded, underlined and italicized*** in the attached document. We are providing to the review division a marked up and clean copy of the revised Medication Guide.

4 CONCLUSIONS AND RECOMMENDATIONS

- Since we recently reviewed the Patient Package Insert (PPI), revisions to the proposed Medication Guide focused on making it consistent with the revised Professional Information and ensuring that it is consistent with the Medication Guide regulations specified in 21 CFR 208.

- Language was added to "What is the most important information I should know about Evista?" to reflect the proposed black box warning addressing thromboembolic events, that is being added to the PI. The Medication Guide must be consistent with the PI.
- [redacted] A statement was added under "What is EVISTA?" to indicate that Evista has not been studied in premenopausal women. b(4
- Refer to the Prescribing Information (PI). The bracketed information at the beginning of section 17 Patient Counseling Information refers to patient labeling and the first statement of that section in the PI still refers patients to the Patient Package Insert. Since a Medication Guide is now required for Evista, these should be revised to say Medication Guide as required under 21 CFR 201.57 (a) (14) and 21 CFR 201.57 (c) (18) respectively.
- Ensure that the sponsor complies with all distribution requirements including revisions of the carton and container labels as specified in 21CFR208.24 (d).

Please let us know if you have any questions.

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✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Sharon Mills
8/30/2007 06:50:03 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
8/31/2007 09:00:13 AM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: OSE/Samuel Chan

FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Division of Drug Oncology Products
Patty Garvey, Project Manager

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 15, 2007		NDA 22-042	New NDA	August 3, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Evista (raloxifene HCl) 60mg Tablets			September 1, 2007

NAME OF FIRM: Eli Lilly and Company

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This is type 6 NDA. Evista currently approved by DMEDP under NDA 20-815. Please review the attached sponsor proposed Medication Guide and attend relevant meetings. This is an electronic submission and path location is: \\CDSESUB1\NONECTD\N22042\N_000\2007-08-03

PDUFD DUE DATE: September 14, 2007
DDOP MO: Patricia Cortazar, MD and Bhupinder Mann, MD

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Patty Garvey	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

5 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Patricia Garvey
8/15/2007 08:05:54 PM

MEMORANDUM

Date: August 13, 2007

From: Brenda S. Gierhart, MD
Medical Officer, HFD-510

Through: Theresa Kehoe, MD
Team Leader, HFD-510

To: Mary Parks, MD
Director, HFD-510

Subject: DDOP Request for DMEP to review the DDOP revised PI for Evista® (raloxifene hydrochloride) re: Type 6 NDA 22-042

MATERIAL REVIEWED

1) Draft DDOP Revised Evista PI PLR labeling conveyed to this reviewer via e-mail on August 11, 2007.

BACKGROUND:

On July 17, 2007, Eli Lilly and Company was sent an approval letter for the Evista (raloxifene hydrochloride) NDA 20-815 SLR018 that added information regarding cardiovascular disease, death due to stroke, and renal impairment to the **WARNINGS AND PRECAUTIONS** section in labeling revised according to the Physicians Labeling Rule (PLR). The Revised Evista PLR PI and PPI labeling were attached to the approval letter.

Prior to sending Eli Lilly and Company their revised Evista PI based upon their review of the Evista type 6 NDA 22-042 for the new indications "reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis" and "reduction in risk of invasive breast cancer in postmenopausal women at high risk for breast cancer", DDOP has requested DMEP review their revised PI labeling. Some of the major changes proposed by DDOP include a new black box warning, new contraindications, significant changes to the **WARNINGS AND PRECAUTIONS** section of **HIGHLIGHTS** and a Medication Guide to replace the PPI. Because DDOP has not yet received approval from the OSE PISC committee regarding their request to convert the Evista PPI to a Medication Guide, DMEP was only asked to review the DDOP revised Evista PI.

LABELING REVIEW:

A detailed review was performed of the DDOP revised and currently approved PLR Evista PI.

DMEP strongly disagrees with the approach that DDOP is taking in several regards:

- The MORE (GGGK) trial data is currently in the Evista label in the sections entitled Osteoporosis Treatment Clinical Trial and the trial is defined by its primary endpoints-vertebral fracture and changes in lumbar spine and femoral neck BMD. Breast cancer was not a primary or a secondary endpoint in the GGGK protocol for either the planned initial 36 month treatment phase or for the 36 month extension phase. Thus, the primary outcome of the MORE trial was fracture and BMD. We do note that Lilly later transferred patients from MORE after approximately 4 years of treatment into the new extension study CORE (GGJY) which had the incidence of invasive breast cancer as the primary endpoint. We strongly disagree with presenting the safety data from MORE and CORE data in Section 14.4 as proposed to "match" the proposed Table 7 (i.e., presenting relative risk with 95% confidence

interval). It appears that DDOP has elevated the safety outcome of breast cancer to an efficacy endpoint. We disagree with this approach and recommend that the discussion of the breast effects in the Osteoporosis treatment trial remain in 14.1 "effects on the Breast", which has been removed and significantly elevated later in the label. We understand that a summary of the MORE breast safety data may be pertinent to your indications and advise using the currently approved 2 sentences that are proposed to be deleted [redacted] b(4)

- The Warnings and Precautions section has been carefully constructed based on what DMEP in close and careful negotiation with Lilly believe is the appropriate hierarchy. If there is a space problem in the label, then the hierarchy should be maintained and the lower W&P should be removed from the Highlights, not the highest W&P.
- We do not believe that the stroke data available can be elevated to a contraindication or even black box warning and this information should remain in W&P.

Recommendations for changes are:

1) The new Black Box **WARNING** references Section [redacted] (with the typo of ! instead of 1 in reference to Section 14.4) as supporting the Warning. However, no information in Section [redacted] (i.e., the RUTH study) currently supports this warning and the incidence of stroke in the RUTH trial was not statistically increased in the Evista arm compared to placebo. Recommend changing the boxed warning phrase from " [redacted] to [redacted] or add additional references to the data that supports the proposed boxed warning or deleting the phrase [redacted] from the Boxed Warning. b(4) b(4)

2) DDOP has deleted a carefully negotiated warning from the **WARNINGS AND PRECAUTIONS** section of **HIGHLIGHTS** pertaining to Death Due to Stroke [i.e., *Death Due to Stroke*: Increased risk of death due to stroke occurred in a trial in postmenopausal women with documented coronary heart disease or at increased risk for major coronary events. [redacted] Consider risk-benefit balance in women at risk for stroke. (5.3, [redacted] and replaced it with the phrase " [redacted] in the new Black Box Warning. This change significantly diminishes the warning. Recommend returning the Death Due to Stroke Warning to the **HIGHLIGHTS** section or revising the Black Box warning. b(4)

3) DDOP has deleted the warning [redacted] from the **WARNINGS AND PRECAUTIONS** section of **HIGHLIGHTS**. This is an important warning and should be returned to this section. b(4)

4) If space becomes an issue in the **HIGHLIGHTS** section when the above deleted warnings are returned to the **HIGHLIGHTS** section, possible methods for conserving space include (**NOTE**: these are ranked with #1 being the first recommended change to be made):
    1. In the **INDICATIONS AND USAGE** section of **HIGHLIGHTS**, in the first bullet change the phrase from "osteoporosis in postmenopausal women" to [redacted] as well as in the second and third bullets changing the phrase "postmenopausal women with osteoporosis" to [redacted] b(4)
    2. In the **WARNINGS AND PRECAUTIONS** section of **HIGHLIGHTS**, delete the last bullet [redacted] b(4)

3. In the **WARNINGS AND PRECAUTIONS** section of **HIGHLIGHTS**, delete the second to last bullet [redacted] b(4)
4. In the **WARNINGS AND PRECAUTIONS** section of **HIGHLIGHTS**, delete the third to last bullet [redacted]

5) In the **CONTRAINDICATIONS** section of **HIGHLIGHTS**, DDOP has added the phrase [redacted] to the end of the of venous thromboembolism, which is confusing since it now appears that these illnesses are VTEs. DDOP also added this same phrase to Section 4.1 which is entitled "Venous Thromboembolism", which is incorrect since these added illnesses are not VTEs. Recommend changing the bullet to:

• [redacted] b(4)

and also adding a new section 4.1 entitled [redacted], adding a new section 4.2 entitle [redacted] and [redacted]

6) DDOP has deleted the warning "[redacted] b(4) from the **WARNING AND PRECAUTIONS** section of the **HIGHLIGHTS**. This important warning should be returned to this section.

7) DDOP has deleted3 negotiated adverse reactions "flu syndrome, arthralgia, sweating" from the **ADVERSE REACTIONS** section of **HIGHLIGHTS**. Request DDOP clarify if this was based upon an analysis of all safety data from all long term clinical trials? If not, please reinsert.

8) **TABLE OF CONTENTS** typos: Section 1.3 recommend capitalizing the word "breast"; in Section 17.4 change [redacted] b(4) to "Osteoporosis".

9) **FULL PRESCRIBING INFORMATION, BOXED WARNING** typo: change (!4.4) to (14.4).

10) To 4 **CONTRAINDICATIONS,** add a new section 4.1 entitled [redacted] b(4) add a new section 4.2 entitle [redacted], change the current section 4.1 to sectior [redacted] and retain the approved language in this section, add a new section [redacted] and change the current section 4.2 to [redacted] b(4) ***Pregnancy, Women Who May Become Pregnant, and Nursing Mothers*** and retain the approved language in this section.

11) To Section 6.1, the word "between" was changed to "among" in section 6.1, subsection Osteoporosis Treatment Clinical Trial. This language has been carefully negotiated and should not be changed.

12) To section 6.1, DDOP inserted the adverse reactions from RUTH, STAR, and CORE studies in the middle of the adverse reactions from osteoporosis studies [redacted] b(4)

13) On pg. 18, it appears that the section currently listed as section 14.3 Reduction in Risk of Invasive Breast Cancer in Postmenopausal Women with Osteoporosis should be section 14.4.

ASSESSMENT:

Negotiations are now occurring with DDOP and the sponsor regarding the PLR Evista PI pertaining to type 6 NDA 22-042.

RECOMMENDATION:
Send DDOP the final DMEP comments regarding the DDOP revised PLR Evista PI.

cc: HFD-510: M. Parks/T. Kehoe/B. Gierhart/H. Seymour;
SEALD team: I. Masucci
Division of Drug Oncology Products (DDOP): B. Mann/P. Cortazar/J. Johnson/P. Garvey

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/s/

Brenda Gierhart
8/13/2007 09:52:50 AM
MEDICAL OFFICER

Theresa Kehoe
8/13/2007 09:55:52 AM
MEDICAL OFFICER

Mary Parks
8/14/2007 02:16:50 PM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 21, 2007

TO: Patty Garvey, R.Ph., Senior Regulatory Project Manager
Patricia Cortazar, M.D., Clinical Reviewer
Bhunpinder Mann, M.D., Clinical Reviewer
Division of Oncology Drug Products, HFD-150

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Lauren Iacono-Connors, Ph.D.
Reviewer, Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections, Pending Receipt of all EIRs

NDA: 22042/000

NME: No

APPLICANT: Eli Lilly and Company

DRUG: Evista® (raloxifene HCl)

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Reducing the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer. [P-2 STAR]

Reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis. [H3S-MC-GGIO RUTH]

CONSULTATION REQUEST DATE: January 9, 2007 & Amended on March 13, 2007

DIVISION ACTION GOAL DATE: August 14, 2007

PDUFA DATE: September 14, 2007

I. BACKGROUND:

Drug Product:

Evista is currently approved for the prevention and treatment of osteoporosis in post-menopausal Women; 1997 and 1999, respectively. The sponsor has provided clinical evidence to support the proposed indication of Evista for the reduction in risk of invasive breast cancer in high risk post-menopausal women, and for reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis. Evista is an orally (tablet) administered selective estrogen receptor modulator that was evaluated for efficacy in the prevention of invasive breast cancer in post-menopausal women at high risk for breast cancer (>35 years old) in the STAR study, and for prevention of invasive breast cancer in post-menopausal women with osteoporosis (≥55 years old) in the RUTH study. Two studies were targeted for inspection, P2 STAR and H3S-MC-GGIO RUTH.

The STAR study was a multicenter, randomized, double-blind, placebo-controlled, phase III study comparing two therapy regimens in the reduction in incidence rate of invasive breast cancer in high risk, post-menopausal women. The study was carried out at ~200 centers in North America. The study was opened for accrual July 1, 1999 and randomized a total of 19,747 post-menopausal women into the study. The final data analysis for the study was initiated after 327 incidents of invasive breast cancers were diagnosed. The cutoff date for data reported for analysis was December 31, 2005. The study remains open.

The clinical investigators, Dr. Moroose, Dr. Fehrenbacher, Dr. Grant and Dr. Robidoux, represent four of the many clinical investigators on the protocol P-2 STAR. According to the sponsor, Dr. Moroose, Dr. Fehrenbacher, Dr. Grant and Dr. Robidoux randomized 21 subjects, 357 subjects, 239 subjects and 316 subjects, respectively. The primary endpoint for this study was invasive breast cancer.

The RUTH study was a multicenter, randomized, double-blind, placebo-controlled, parallel phase III study. Approximately 10,000 subjects were to be enrolled and randomly assigned to one of two therapy groups comparing the each groups' reduction in incidence of the combined cardiac endpoint of coronary death, nonfatal MI, or hospitalization due to ACS other than MI, and invasive breast cancer.

The study was carried out at 192 centers in 26 counties. The study randomized the first subject on June 25, 1998 and randomized a total of 10,101 women into the study. Subjects were to be followed for up to 5 years; until a minimum of 1268 subjects experienced a coronary primary endpoint event. The observed rate of coronary primary endpoint was lower than predicted and ultimately the study was stopped early and after the last randomized subject had been followed for 5 years; the original final follow-up time point. The date for last subject completion was November 21, 2005.

The clinical investigators, Dr. Barrett-Connor, Dr. Cauley and Dr. Ensrud, represent three of 177 clinical investigators on the RUTH protocol. According to the sponsor, Dr. Barrett-Connor, Dr. Cauley and Dr. Ensrud randomized 74 subjects, 112 subjects and 105 subjects, respectively. The dual primary endpoints for this study were combined cardiac endpoint of coronary death, nonfatal MI, or hospitalization due to ACS and invasive breast cancer.

II. RESULTS:

Inspected Entity	City, State\Country	Protocol	Inspection Dates	EIR Received Date	Field Classification
Rebecca Moroose, M.D.	Orlando, Florida	P-2 (STAR)	April 2-11, 2007	May 2, 2007 FLA-DO	NAI
Michael Grant, M.D.	Dallas, Texas	P-2 (STAR)	March 27 – April 2, 2007	April 17, 2007 DAL-DO	NAI
Louis Fehrenbacher, M.D.	Vallejo, California	P-2 (STAR)	TBD	Pending SAN-DO	Pending
Andre Robidoux, M.D.	Montreal, QC, Canada	P-2 (STAR)	April 16-20, 2007	May 22, 2007 LOS-DO	NAI
Kristine Ensrud, M.D., M.P.H.	Minneapolis, MN	H3S-MC-GGIO (RUTH)	March 26 – April 10, 2007	May 15, 2007 MIN-DO	VAI
Elizabeth Barrett-Connor, M.D.	LaJolla, CA	H3S-MC-GGIO (RUTH)	March 27 – April 6, 2007	May 2, 2007 LOS-DO	NAI
Jane A Cauley, Dr.PH	Pittsburgh, PA	H3S-MC-GGIO (RUTH)	April 4-6, 2007	April 24, 2007 PHI-DO	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

1. **Rebecca Moroose, M.D. (Principal Investigator)**
Cancer Institute of Florida PA
2501 N Orange Ave. Ste 286
Orlando, FL 32804

Protocol Number	Subjects Randomized	Subjects Audited (BIMO Program)
P-2 STAR	22	9

a. What was inspected?

The study records of 9 subjects for the STAR study were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these audited subjects the record audit included comparison of source documentation for inclusion/exclusion criteria, completeness of CRFs, informed consent forms (for all 22 subjects), adverse events reported and drug accountability records.

b. Limitations of inspection: None

c. General observations/commentary:

The investigator was found to be generally adequate in the execution of the study. The study was found to be well controlled and well documented. No significant regulatory deviations were observed. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. Several AEs, a broken bone in one case and several cases of weight gain, were not properly reported to the local IRB per IRB SOPs. Minor record keeping deviations were also observed, but were corrected by site staff while the inspection was ongoing. The minor deficiencies were discussed with the investigator during the exit briefing. No Form FDA 483 was issued.

d. Assessment of data integrity: The data from Dr. Moroose's site, associated with protocol P-2 (STAR), submitted to the agency in support of NDA 22042, appear reliable.

2. **Michael Grant, M.D. (Principal Investigator)**
Baylor University Medical Center
3500 Gaston Ave., Ste 615 Collins
Dallas, Texas 75246

Protocol Number	Subjects Randomized	Subjects Audited (BIMO Program)
P-2 STAR	201 (by CI)	20

a. What was inspected?

The Baylor Dallas study location, under the responsibility of Dr. Grant randomized, 201 subjects. Another 84 subjects were randomized by subinvestigators at different local sites also under Dr. Grant as the PI. At the Baylor Dallas study location the study records of 20 subjects for the STAR study were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these audited subjects the record audit included comparison of source documentation for inclusion/exclusion criteria, completeness of CRFs, informed consent forms (for 10% of subjects), adverse events reported and drug accountability records.

b. Limitations of inspection: None

c. General observations/commentary

The investigator was found to be generally adequate in the execution of the study. The study was found to be well controlled and well documented. No significant regulatory deviations were observed. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. One sAE, a hip replacement, was not properly reported to the NCI/NSABP. The NSABP was responsible for reporting AEs to the FDA for the investigators in this study. Therefore, the FDA was not notified of this sAE. This reporting error was discussed with the investigator during the exit briefing. The CI and study coordinator indicated that this was an oversight and that the sAE should have been reported. No Form FDA 483 was issued.

d. Assessment of data integrity: The data from Dr. Grant's site, associated with protocol P-2 STAR submitted to the agency in support of NDA 22042, appear reliable based on available information.

3. **Louis Fehrenbacher, M.D., (Principal Investigator)**
Oncology
Kaiser Foundation Hospital
975 Sereno Drive
Vallejo, CA 94590

Protocol Number	Subjects Randomized	Subjects Audited
P-2 STAR	375	38

a. What was inspected? The study records of 38 (10%) subjects for study P-2 STAR were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these audited subjects the record audit included comparison of source documentation and CRFs to data listings submitted to the agency under NDA 22042, with particular attention paid to eligibility criteria satisfaction and efficacy endpoint achievement. The FDA investigator also assessed the date and cause of death, and any sAEs, informed consent forms and correspondence with the sponsor.

b. Limitations of inspection: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator.

c. General observations/commentary:

Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. No major deviations were observed. A Form FDA 483 was not issued.

The EIR is currently being finalized by the FDA investigator and will be submitted to DSI upon completion. The observations noted above are based on preliminary communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

d. Assessment of data integrity: The data from Dr. Fehrenbacher's site, associated with protocol P-2 STAR, appear to be reliable based on available information.

4. **Andre Robidoux, M.D., (Principle Investigator)**
Hotel-Dieu du CHUM
3840 St-Urbain Street
Montreal, QC H2W1T8
Canada

Protocol Number	Subjects Randomized	Subjects Audited
P-2 STAR	321	33

a. What was inspected? The study records of 33 of the 321 subjects for study P-2 STAR were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these audited subjects the record audit included comparison of source documentation and CRFs to data listings submitted to the agency under NDA 22042, with particular attention paid to eligibility criteria satisfaction and efficacy endpoint achievement. The FDA investigator also assessed the date and cause of death, and any sAEs, informed consent forms (33 subjects) and correspondence with the sponsor.

b. Limitations of inspection: None

c. General observations/commentary:

Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency, AE reporting practices, adherence to protocol and study discontinuations. CRFs were assessed for data consistency with the source documents. No Form FDA 483 was issued.

d. Assessment of data integrity: The data from Dr. Robidoux's site, associated with protocol P-2 STAR, appear reliable.

5. **Kristine Ensrud, M.D., M.P.H. (Principal Investigator)**
University of Minneapolis
Epidemiology Clinical Research Center
1100 Washington Avenue South, Suite 201,
Minneapolis, MN, 55415

Protocol Number	Subjects Randomized	Subjects Audited (BIMO Program)
H3S-MC-GGIO RUTH	105	23

a. What was inspected?

The study records of 23 subjects for the RUTH study were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these audited subjects the record audit included comparison of source documentation for inclusion/exclusion criteria, completeness of CRFs, informed consent forms (for all 23 subjects), adverse events reported and drug accountability records.

b. Limitations of inspection: None

c. General observations/commentary:

The investigator was found to be generally adequate in the execution of the study. The study was found to be reasonably well executed. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. One significant regulatory deviation was observed. Of the 23 subjects records reviewed 4 did not meet the inclusion/exclusion criteria as required by the protocol. Three of these protocol deviations were reported to the sponsor and subsequent waivers were issued. The 4 subjects' study identification numbers are 5652, 5751, 5882 and 5875.

Subject 5652 was participating in another clinical study at the time of randomization. The sponsor noted in a letter to the site dated June 4, 1999 (~ 2 months post subject randomization) the protocol deviation and authorized a waiver for this subject to continue in the RUTH study and cautioned the site.

Subject 5751 was randomized into the study and received drug but had taken estrogen or progesterone-containing compounds within 3 months prior to screening and within 6 months of study drug initiation. The sponsor waiver was on file.

Subject 5882 was taking a drug for hyperlipidemia at the time of the screening visit. LDL labs done at the time showed the subject had an LDL below 147. Because the subject was actively taking Zocor at that time the subject met entry criteria. Prior to the randomization visit the subject stopped

taking a drug for hyperlipidemia and therefore, based on available lab screening data, no longer met enrollment criteria. The sponsor waiver was on file.

Subject 5875 was reportedly a diabetic but was managed by dietary control and no other medication. The subject was randomized into the study based on an outdated blood glucose level indicating elevation within an inclusion criteria threshold. The subject did not return to the site for study enrollment until approximately 6 months after the initial screening labs were taken. A subsequent blood glucose level was taken at that time and showed that the current blood glucose level no longer supported subject enrollment. The study monitor was contacted by the site for guidance. The monitor stated that the subject had "boarder line" values for elevated glucose and suggested the site "retest again" if the subject was willing or if not to just use the outdated blood glucose test results to support randomization. The subject was randomized at that time without retesting for blood glucose levels. A study-required follow up blood glucose level showed that the subject had elevated glucose levels. The protocol deviation was never reported to the sponsor.

A Form FDA 483 was issued for one observation; the investigation was not conducted in accordance with the investigational plan.

d. Assessment of data integrity: The data from Dr. Ensrud's site, associated with the protocol RUTH, submitted to the agency in support of NDA 22042, appear reliable, however, the review division should take into consideration that the sample audit (23 subjects) suggests that approximately 17% of all randomized subjects may not have met one or more inclusion/exclusion criteria.

6. **Elizabeth Barrett-Connor, M.D. (Principal Investigator)**
University of California, San Diego School of Medicine
9500 Gilman Drive, Mail Code 0607
LaJolla, CA 92093-0607

Protocol Number	Subjects Randomized	Subjects Audited (BIMO Program)
H3S-MC-GGIO RUTH	74	20

a. What was inspected?

The study records of 20 subjects for the RUTH study were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these audited subjects the record audit included comparison of source documentation for inclusion/exclusion criteria, completeness of CRFs, informed consent forms (for 20 subjects), adverse events reported and drug accountability records.

b. Limitations of inspection: None

c. General observations/commentary:

The investigator was found to be generally adequate in the execution of the study. The study was reasonably well executed. No significant regulatory deviations were observed. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. A Form FDA 483 was not issued.

b. Assessment of data integrity: The data from Dr. Barrett-Connor's site, associated with the protocol RUTH, submitted to the agency in support of NDA 22042, appear reliable.

7. **Jane A. Cauley, Dr.PH (Principal Investigator)**
Univ Of Pittsburgh School Of Medicine,
130 DeSoto St., A524,
Pittsburgh, PA, 15261

Protocol Number	Subjects Randomized	Subjects Audited (BIMO Program)
H3S-MC-GGIO RUTH	112	21

a. What was inspected?

The study records of 21 subjects for the RUTH study were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these audited subjects the record audit included comparison of source documentation for inclusion/exclusion criteria, completeness of CRFs, informed consent forms (for 21 subjects), adverse events reported and drug accountability records.

b. Limitations of inspection: None

c. General observations/commentary:

The investigator was generally adequate in the execution of the study. The study was found to be well controlled, documented and executed. No significant regulatory deviations were observed. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. A Form FDA 483 was not issued.

d. Assessment of data integrity: The data from Dr. Cauley's site, associated with the protocol RUTH, submitted to the agency in support of NDA 22042, appear reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For the STAR study the data collected by Dr. Grant, Dr. Robidoux, Dr. Moroose, and Dr. Fehrenbacher appear reliable. Three of the four EIRs were available for review at the time this CIS was written. Observations noted above regarding the site of Dr. Fehrenbacher are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

For the RUTH study the data collected by Dr. Ensrud, Dr. Barrett-Connor and Dr. Cauley appear reliable. All 3 EIRs were available for review in support of the CIS. A Form FDA 483 was issued to Dr. Ensrud regarding her conduct of the RUTH study. No other Form FDA 483s were issued. Dr. Ensrud failed to conduct the study in accordance with the investigational plan. For Dr. Ensrud's site the sample audit revealed that approximately 17% of the subjects audited (4 of 23 subjects) did not meet the protocol-specified inclusion/exclusion criteria at the time they were enrolled. Therefore, the audit suggests that approximately 17% of all randomized subjects at this site may not have met one or more inclusion/exclusion criteria at the time of enrollment. The review division may wish to evaluate the sponsor-reported protocol deviations for this site relative to that reported by other sites for the RUTH study.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIR (STAR study) and the supporting inspection evidence and exhibits.

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Lauren Iacono-Connors
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Leslie Ball
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FAX

FOOD AND DRUG ADMINISTRATION
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To:	Dan Brady, Ph.D. – Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	301-796-1356
Phone:	317-276-8720	**Phone:**	301-796-9845
Pages (including cover):	3	**Date:**	May 24, 2007
Re:	NDA 22-042 Evista		

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• **Comments:**

Dear Dan,

Please refer to your NDA 22-042 Evista submission dated November 13, 2006 for two new proposed indications for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women at risk of breast cancer.

The statistical reviewer requests a copy of the SAS programs used in producing the results in the attached tables submitted. The information can be provided in any format, the SAS files, MS files, or PDF files, as long as we can get the information ASAP.

Please response via email then following up with the official submission later.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Senior Regulatory Project Manager
Division of Drug Oncology Products

RUTH Efficacy and Safety

Table 1. RUTH Efficacy and Important Safety Outcomes: Incidence Rates per 1,000 Patient-years and Absolute Risk Difference

	RLX 5,044	PLB 5,057	RLX IR	PLB IR
Endometrial cancer [a]	21/3900	17/3882	1.01	0.83
Ovarian Cancer [b]	17/4559	10/4606	0.70	0.41

Abbreviations: IR = Incidence Rate per 1000 Patient-years; PLB = Placebo; RLX = Raloxifene.
[a] Only patients with an intact uterus were considered for the denominator (raloxifene denominator = 3900, placebo denominator = 3882).
[b] Only patients with at least one ovary were considered for the denominator (raloxifene denominator = 4559, placebo denominator = 4606).

MORE Efficacy and Safety

Table 2. MORE Efficacy and Important Safety Outcomes: Incidence Rates per 1,000 Patient-years and Absolute Risk Difference

Events [a]	RLX 2,557	PLB 2,576	RLX IR	PLB IR
Clinical vertebral fracture	62	107	7.08	12.27
Death	64/5129	36	3.63	4.13
Death due to Stroke	9/5129	6	0.51	0.69
Stroke	91/5129	56	5.16	6.42
Deep vein thrombosis	44/5129	8	2.50	0.92
Pulmonary embolism	22/5129	4	1.25	0.46
Endometrial and uterine cancer [b]	8/3960	5/1999	0.59	0.74
Ovarian Cancer	6/5129	6	0.34	0.69

Abbreviations: IR = Incidence Rate per 1000 Patient-years; PLB = Placebo; RLX = Raloxifene.
[a] Breast cancer and clinical vertebral fracture events are for the raloxifene HCl 60 mg/day arm only, thus the denominator is 2557. For the safety events of death, death due to stroke, stroke, deep vein thrombosis, pulmonary embolism, and ovarian cancer, the raloxifene HCl 60 mg/day and 120 mg/day arms were pooled for analyses to have the greatest opportunity to detect safety signals; thus, the denominator for these events is 5129.
[b] Only patients with an intact uterus were considered for the denominator (raloxifene denominator = 3960, placebo denominator = 1999).

CORE Efficacy and Safety

Table 3. CORE Efficacy and Important Safety Outcomes: Incidence Rates per 1,000 Patient-years and Absolute Risk Difference

Events [a]	RLX 2,716	PLB 1,274	RLX IR	PLB IR
Clinical vertebral fracture [b]	65/2725	32/1286	8.28	8.56
Death	47/2725	29/1286	5.99	7.76
Death due to Stroke	6/2725	1/1286	0.76	0.27
Stroke	49/2725	14/1286	6.24	3.75
Deep vein thrombosis	17/2725	4/1286	2.17	1.07
Pulmonary embolism	9/2725	0/1286	1.15	0.00
Endometrial and uterine cancer [c]	4/2138	3/1008	0.65	1.02
Ovarian Cancer	2/2725	2/1286	0.25	0.54

Abbreviations: IR = Incidence Rate per 1000 Patient-years; PLB = Placebo; RLX = Raloxifene.
[a] Breast cancer events are for the patients who enrolled in CORE and had not been not diagnosed with breast cancer prior to Visit 1. For raloxifene, 2725 patients enrolled in CORE but 9 had been diagnosed with breast cancer prior to Visit 1, so the denominator is 2716. For placebo, 1286 patients enrolled but 12 had been diagnosed with breast cancer prior to Visit 1, so the denominator is 1274. The safety events of death, death due to stroke, stroke, deep vein thrombosis, pulmonary embolism, and ovarian cancer considered all patients who enrolled in CORE; thus, the denominators are 2725 for raloxifene and 1286 for placebo.
[b] Vertebral fractures were collected as adverse events.
[c] Only patients with an intact uterus were considered for denominator (raloxifene denominator = 2138, placebo denominator = 1008).

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/s/

Patricia Garvey
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CSO

FAX

FOOD AND DRUG ADMINISTRATION
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To:	Dan Brady, Ph.D. – Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	301-796-1356
Phone:	317-276-8720	**Phone:**	301-796-9845
Pages (including cover):	2	**Date:**	May 24, 2007
Re:	NDA 22-042 Evista – submission dated 3/13/2007		

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• **Comments:**

Dear Dan,

Please refer to your NDA 22-042 Evista submission dated March13, 2007, regarding the STAR clinical study report and the raw datasets.

Please see the following request for clarification. Please response to our request ASAP.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Senior Regulatory Project Manager
Division of Drug Oncology Products

We used the dataset submitted on March 13, 2007 to duplicate the table below. However, there are some discrepancies.

1) For "All breast cancer", the reviewer rounded up the 4th digit in p-value.
2) For "Death due to stroke", the reviewer used death code "COD" with range between 430-436 for stroke, which was defined in the program you submitted. There were only 9 in total using this convention.
3) For "Death", "Stroke", "DVT", "Endometrial cancer", and "Ovarian cancer", the reviewer's numbers for "Rate" matched the numbers in the Study Report, but did not match the numbers in the table.

Please confirm FDA's calculation? If there are any discrepancies, please identify which datasets, variables and SAS programs used in calculating the numbers, so that the reviewers can understand where the differences come from.

The Numbers in "Red" are FDA's calculation. Please check.

Type of Event	# events (%)		Rate/1000 women/year		RR 95% CI	p-value
	Tamoxifen 9736	Raloxifene 9751	Tamoxifen	Raloxifene		
All breast cancers	228 (2.3)	256 (2.6)	5.85	6.54	1.12(0.93,1.34)	0.221 .222
Invasive	168 (1.7)	173 (1.8)	4.30	4.40	1.02(0.82,1.27)	0.832
Non-invasive	60 (0.6)	83 (0.9)	1.54	2.12	1.38(0.98,1.95)	0.057
Clinical vertebral fracture	58	58	1.47	1.46	0.99(0.68,1.46)	0.968
Death	109	104	2.49 2.76	2.64 2.62	0.95(0.72,1.25)	0.678
Death due to stroke	7 5	5 4	0.18 0.13	0.13 0.1	0.71(0.18,2.60) 0.79 (0.16, 3.69)	0.552 0.728
Stroke	56	54	1.33 1.42	1.39 1.36	0.96(0.65,1.42)	0.819
DVT	92	67	1.69 2.35	2.29 1.69	0.72(0.52,1.00)	0.041
Pulmonary Embolism	58	38	1.47	0.96	0.65(0.42,1.00)	0.037
Endometrial Cancer	37	23	1.25 1.99	2.00 1.21	0.61(0.34,1.05)	0.055
Ovarian Cancer	14	18	0.68 0.52	0.45 0.66	1.27(0.60,2.76)	0.508
Cataracts	435	343	13.19	10.34	0.78(0.68,0.91)	<0.001

RR= Relative risk
p-value: log-rank test

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/s/

Patricia Garvey
5/24/2007 04:16:44 PM
CSO

FAX

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Pages (including cover):	2	**Date:**	May 23, 2007
Re:	NDA 22-042 Evista – submission dated 11/13/06		

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• **Comments:**

Dear Dan,

Please refer to your NDA 22-042 Evista submission dated November 13, 2006 for two new proposed indications for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women at risk of breast cancer.

Please see the following request from the clinical team.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Senior Regulatory Project Manager
Division of Drug Oncology Products

Please provide number of events, confidence intervals and p-values for the table below. Please indicated why the IRs provided in the P1 trial are different from the published article and the Tamoxifen label.

Table 2.5.6.1. Efficacy and Important Safety Outcomes Incidence Rates per 1000 Patient-years and Absolute Risk Difference Studies P-2 and P-1

	P-2			P-1 (≥50 years)		
	RLX IR	TMX IR	Absolute Risk Difference	TMX IR	PLB IR	Absolute Risk Difference
Invasive breast cancer	4.41	4.30	+0.11	**3.21**	**6.87**	**-3.66**
Noninvasive breast cancer	2.11	1.51	+0.60	1.58	2.04	-0.46
Clinical vertebral fracture	1.35	1.39	-0.04	1.25	1.76	-0.51
Death	2.49	2.64	-0.15	3.19	3.70	-0.51
Death due to Stroke	0.10	0.16	-0.06	0.19	0.13	+0.06
Stroke	1.33	1.39	-0.06	2.20	1.26	+0.94
Deep vein thrombosis	1.69	2.29	-0.60	1.51	0.88	+0.63
Pulmonary embolism	0.91	1.41	-0.50	**1.00**	**0.31**	**+0.69**
Endometrial cancer	1.25	2.00	-0.75	**3.05**	**0.76**	**+2.29**
Ovarian Cancer	0.68	0.45	+0.23	N/A	N/A	N/A

Note: Statistically significant differences are in bold.

Abbreviations: IR = incidence rate per 1000 patient-years; PLB = placebo; RLX = raloxifene; TMX = tamoxifen.

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/s/

Patricia Garvey
5/23/2007 06:58:16 PM
CSO

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To:	Dan Brady, Ph.D. – Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	301-796-1356
Phone:	317-276-8720	**Phone:**	301-796-9845
Pages (including cover):	2	**Date:**	May 16, 2007
Re:	NDA 22-042 Evista – submission dated 11/13/06		

☐ **Urgent** x **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Dear Dan,

Please refer to your NDA 22-042 Evista submission dated November 13, 2006 for two new proposed indications for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women at risk of breast cancer.

We also refer to your emails dated May 11 and 14, 2007 regarding questions about the Efficacy Safety tables.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Senior Regulatory Project Manager
Division of Drug Oncology Products

Sponsor response to FDA facsimile dated May 10, 2007:

We understand from your email: Both 60 and 120 mg arms in MORE were pooled for analyses in the Clinical Summary of Safety (CSS) to assess safety in the entire database, and that this approach may provide the greatest opportunity to detect safety signals. For efficacy analyses, in the Clinical Summary of Efficacy (CSE), you used only the 60 mg dose as this is the marketed dose for which you seek the indication. The MORE table of Efficacy and Safety correctly lists the events and incidence rates (IR) for the first 5 items (breast cancers and clinical fractures). These data and IRs reflect those patients that were enrolled in only the 60 mg arm of MORE. However, starting with the "Death" row and below, the number of events reflect a pooling of all raloxifene treated patients in MORE (60 mg + 120 mg)*, while the incidence rates reflect only the patients on the 60 mg dose. You can correct the table by either correcting the first RLX column to include only those patients on the 60 mg arm, or perform a new analysis on the pooled 60 and 120 mg arms to calculate an IR for each event.

FDA Response:

1. **Accordingly we ask: Please correct the IR in the MORE table (starting with the "Death" row) by: a new analysis on the pooled 60 and 120 mg arms to calculate an IR for each event as both 60 and 120 mg arms in MORE were pooled for analyses in the Clinical Summary of Safety (CSS) to assess safety in the entire database and this approach provides the greatest opportunity to detect safety signals. We can clarify this (the two denominators for efficacy and safety) further by a footnote.**

2. **We also propose to change "[redacted] in the 4th row of the tables to "[redacted]** b(4)

3. a) **Please complete the row "Clinical Vertebral fracture" in the MORE Efficacy-Safety table.**

   b) **Please complete the rows "Clinical vertebral fracture, Endometrial cancer, and Ovarian Cancer" in the CORE Efficacy-Safety table.**

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/s/

Patricia Garvey
5/23/2007 06:51:08 PM
CSO
Sent to the sponsor on May 16, 2007

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To: Dan Brady, Ph.D. – Eli Lilly and Company	**From:** Patty Garvey, R.Ph.
Fax: 317-276-1652	**Fax:** 301-796-1356
Phone: 317-276-8720	**Phone:** 301-796-9845
Pages (including cover): 2	**Date:** May 17, 2007
Re: NDA 22-042 Evista – submission dated 11/13/06	

☐ **Urgent** x **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Dear Dan,

Please disregard the clinical information request dated May 16, 2007, since there were errors in the document. This facsimile will supersede the previously requested facsimile dated May 16, 2007.

Please refer to your NDA 22-042 Evista submission dated November 13, 2006 for two new proposed indications for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women at risk of breast cancer.

The clinical team requests that you submit the following information as soon as possible.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Senior Regulatory Project Manager
Division of Drug Oncology Products

Clinical:

1. The following nine patients have a double entry on the P2 BREVT INV Breast Ca dataset. Please provide information ASAP on which is the appropriate data and submit a new dataset with the correct information.

   S01618J6H
   S02886ATR
   S05969IND
   S25701WPA
   S34639BAM
   S42323ROS
   S49646MOF
   S50720NCA
   S53832OTT

2. Please confirm the numbers and complete the table.
   The highlighted numbers show discrepancies between the clinical study report and the P2sump dataset submitted March 13, 2006. Please explain the discrepancies.

Type of Event	# events (%)		Rate/1000 women/year		p-value
	Tamoxifen 9736	Raloxifene 9751	Tamoxifen	Raloxifene	RR 95% CI
All breast cancers	228 (2.3)	256 (2.6)			
Invasive	168 (1.7)	173 (1.8)	4.30	4.40	
Non-invasive	60 (0.6)	83 (0.9)	1.54	2.12	
Clinical vertebral fracture	61	64			
Death	109	104	2.49	2.64	
Death due to stroke	3	4	0.10	0.16	
Stroke	56	54	1.33	1.39	
DVT	92	67	1.69	2.29	
Pulmonary Embolism	56	36	0.91	1.41	
Endometrial Cancer	37	23	1.25	2.00	
Ovarian Cancer	14	18	0.68	0.45	
Cataracts	435	344			

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/s/

Patricia Garvey
5/23/2007 06:44:40 PM
CSO
Sent to the sponsor on May 17, 2007

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To:	Dan Brady, Ph.D. – Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	301-796-1356
Phone:	317-276-8720	**Phone:**	301-796-9845
Pages (including cover):	2	**Date:**	May 1, 2007
Re:	NDA 22-042 Evista – submission dated 11/13/06		

☐ **Urgent** x **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Dear Dan,

Please refer to your NDA 22-042 Evista submission dated November 13, 2006 for two new proposed indications for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women at risk of breast cancer.

The clinical team requests that you submit the following information as soon as possible.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Senior Regulatory Project Manager
Division of Drug Oncology Products

Clinical:

1. Subgroup Analysis of invasive breast cancer in the MORE trial by Gail Score

2. Stage of invasive breast cancers by treatment group in the MORE, CORE and STAR trials

3. Datasets for MORE and CORE that include all breast cancer cases and the associated censoring times for subjects that did not experience breast cancer along with treatment codes for all subjects. These should be the same as the dataset submitted for the RUTH trial on December 11, 2006.

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/s/

Patricia Garvey
5/23/2007 06:38:20 PM
CSO
Sent to the sponsor on May 1, 2007

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To:	Dan Brady, Ph.D. – Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	301-796-1356
Phone:	317-276-8720	**Phone:**	301-796-9845
Pages (including cover):	2	**Date:**	May 22, 2007
Re:	NDA 22-042 Evista – submission dated 11/13/06		

☐ **Urgent** x **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Dear Dan,

Please refer to your NDA 22-042 Evista submission dated November 13, 2006 for two new proposed indications for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women at risk of breast cancer.

The clinical team requests that you provide the following information as soon as possible.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Senior Regulatory Project Manager
Division of Drug Oncology Products

CLINICAL:

1. Confirm all NSABP sites for the STAR trial are in North America.
2. Confirm that for the CORE Trial Table GGJY 11.1 Demography corresponds to the dataset used for the analysis of invasive breast cancer.
3. History of stroke is an exclusion criterion for the MORE trial, but is not an exclusion criterion for the CORE trial. Please confirm.
4. MORE trial patients did not have regularly scheduled breast exams during the trial. Did all patients have baseline breast exams?
5. Please confirm there were no prerandomization stratification factors for the MORE trial.
6. Please confirm there were no prerandomization stratification factors for the CORE trial.
7. Please confirm the only prerandomization stratification factor for the RUTH trial was investigator site.

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/s/

Patricia Garvey
5/23/2007 06:32:05 PM
CSO
Sent to the sponsor on May 22, 2007

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To:	Dan Brady, Ph.D. – Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	301-796-1356
Phone:	317-276-8720	**Phone:**	301-796-9845
Pages (including cover):	5	**Date:**	May 10, 2007
Re:	NDA 22-042 Evista – submission dated 11/13/06		

☐ **Urgent** x **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Dear Dan,

Please note that this facsimile request the same information as the May 9, 2007 facsimile. However, this facsimile contains the attached tables referred in the request.

Please refer to your NDA 22-042 Evista submission dated November 13, 2006 for two new proposed indications for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women at risk of breast cancer.

The clinical team requests that you submit the following information as soon as possible.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Senior Regulatory Project Manager
Division of Drug Oncology Products

Clinical:

Please review the attached tables and refer to the tables 2.5.6.2 and 2.5.6.3 in the Clinical Overview of Evista (Efficacy and Important Safety Outcomes; Incidence Rates per 1000 Patient-years and Absolute Risk Difference; for Study GGGK and Study GGIO, respectively).

The attached tables were developed from the above tables in the Clinical Overview by adding the data extracted from the NDA submission:

- Two columns are added to each table (one for raloxifene and one for placebo) and show the absolute number (n) of events for the efficacy and safety outcomes listed in the rows.
- A new row "All Cancers" is added following the current "Invasive breast cancer" and "Noninvasive breast cancer" rows and shows the respective numbers under the original and the new columns.

Please confirm the numbers appearing in the tables and provide the missing numbers.

RUTH Efficacy-Safety Table

Efficacy and Important Safety Outcomes (Incidence Rates per 1000 Patient-years and Absolute Risk Difference)

	RLX 5,044	PLB 5,057	RLX IR	PLB IR	Absolute Risk Difference
Invasive breast cancer	40	70	1.50	2.66	-1.16
Noninvasive breast cancer	11	5	0.41	0.19	+0.22
Invasiveness unknown	1	1			
All cancers	52	76	1.95	2.99	- 1.04
Clinical vertebral fracture	64	97	2.40	3.70	-1.30
Death	554	595	20.68	22.45	-1.77
Death due to Stroke	59	39	2.20	1.47	+0.73
Stroke	249	224	9.46	8.60	+0.86
Deep vein thrombosis	65	47	2.44	1.78	+0.66
Pulmonary embolism	36	24	1.35	0.91	+0.44
Endometrial cancer	17	16	1.01	0.83	+0.18
Ovarian Cancer	17	10	0.70	0.41	+0.29

IR = incidence rate per 1000 patient-years;

MORE Efficacy-Safety Table

Efficacy and Important Safety Outcomes (Incidence Rates per 1000 Patient-years and Absolute Risk Difference)

	RLX 2,557	PLB 2,576	RLX IR	PLB IR	Absolute Risk Difference
Invasive breast cancer	11	38	1.26	4.36	-3.10
Noninvasive breast cancer	3	5	0.34	0.57	-0.23
Invasiveness unknown	3	1			
All cancers	17	44	1.94	5.05	-3.11
Clinical vertebral fracture			7.08	12.27	-5.19
Death	64/5129	36	2.63	4.13	-1.50
Death due to Stroke	9/5129	6	0.34	0.69	-0.35
Stroke	91/5129	56	4.91	6.42	-1.51
Deep vein thrombosis	44/5129	8	2.28	0.92	+1.36
Pulmonary embolism	22/5129	4	1.26	0.46	+0.80
Endometrial cancer	5/5129	5	0.74	0.74	+0.00
Ovarian Cancer	6/5129	6	0.34	0.69	-0.35

IR = incidence rate per 1000 patient-years;

CORE Efficacy-Safety Table

Efficacy and Important Safety Outcomes (Incidence Rates per 1000 Patient-years and Absolute Risk Difference)

	RLX 2716	PLB 1274	RLX IR	PLB IR	Absolute Risk Difference
Invasive breast cancer	19	20	2.43	5.41	-2.98
Noninvasive breast cancer	5	2	0.64	0.54	+0.10
Invasiveness unknown	0	0			
All cancers	24	22	3.07	5.95	-2.88
Clinical vertebral fracture					
Death	47/2725	29/1286			
Death due to Stroke	6/2725	1/1286			
Stroke	49/2725	14/1286			
Deep vein thrombosis	17/2725	4/1286			
Pulmonary embolism	9/2725	0/1286			
Endometrial cancer					
Ovarian Cancer					

IR = incidence rate per 1000 patient-years;

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/s/

Patricia Garvey
5/10/2007 05:30:21 PM
CSO

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To:	Dan Brady, Ph.D. – Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	301-796-1356
Phone:	317-276-8720	**Phone:**	301-796-9845
Pages (including cover):	2	**Date:**	May 9, 2007
Re:	NDA 22-042 Evista – submission dated 11/13/06		

☐ **Urgent** x **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Dear Dan,

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The clinical team requests that you submit the following information as soon as possible.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Senior Regulatory Project Manager
Division of Drug Oncology Products

Clinical:

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Please confirm the numbers appearing in the tables and provide the missing numbers.

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/s/

Patricia Garvey
5/9/2007 10:07:30 PM
CSO