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

# REQUEST FOR CONSULTATION

TO *(Office/Division)*: OES/Samuel Chan, PM

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 |
|---|---|---|---|---|
| May 1, 2007 | | NDA 22-042 | New NDA | November 13, 2006 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| Evista (raloxifene HCl) 60mg Tablets | | | July 13, 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 provide postmarketing events for the following: endometrial and ovarian cancer, stroke, DVT and PE Myocardial infarction, death and death due to stroke. NDA is located at:\\CDSESUB1\N22042\N_000\2006-12-11V
This application will be presented at the ODAC meeting on July 24, 2007.
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 |

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/s/

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Patricia Garvey
5/1/2007 11:17:44 AM

# REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

## Division of Drug Oncology Products

**Application Number:** 22-042

**Name of Drug:** EVISTA® (raloxifene HCl) Tablets 60 mg

**Applicant:** Eli Lilly and Company

## Material Reviewed:

**Submission Date(s):** November 13, 2006

**Receipt Date(s):** November 14, 2006

**Submission Date of Structure Product Labeling (SPL):** November 13, 2006

**Type of Labeling Reviewed**: WORD

## Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

## Review

The following issues/deficiencies have been identified in your proposed labeling.

Highlights

1. Remainder that for recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d) (9) and Implementation Guidance].

2. Delete space under "ADVERSE REACTIONS" heading.

3. Do not include pregnancy category (e.g. X) under USE IN SPECIFIC POPULATION heading in Highlights. [See comment #34 Preamble]

4. Add ' [redacted] after See 17 for PATIENT COUNSELING INFORMATION. b(4)

5. Right justify the revision date.

6. Delete ' [redacted], since this information is not needed. b(4)

Full Prescribing Information: Content*

7. Add space under [redacted] to separate from *Sections or subsections omitted from the full prescribing information are not listed" statement. b(4)

Full Prescribing Information

8. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]

9. Do not refer to adverse reactions as "adverse events". Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, "available at hhtp://www.fda.gov/cder/guidance.

10. Under 17 PATIENT COUNSELING INFORMATION, replace '[redacted] b(4)

11. Under [redacted] delete [redacted] b(4)
[redacted] statement.

Patient Packing Insert

12. The patient package insert should follow immediately after the end of the package insert full prescribing information.

13. Delete the "[redacted] date. The revision date at the end of the Highlights is intended to replace the date at the end of the label. b(4)

**Recommendations**

Please address the identified deficiencies/issues and re-submit labeling by April 16, 2007. This updated version of labeling will be used for further labeling discussions.

Patricia Garvey, R.Ph.
Senior Regulatory Project Manager

Supervisory Comment/Concurrence:

Dotti Pease
Chief, Project Management Staff

Drafted: PNG/2/16/07
Revised/Initialed: R. Anderson (SEALD)/3-1-07; D.Pease/3-14-07
Finalized: PNG/3-16-07

**PM LABELING REVIEW OF PLR FORMAT**

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/s/

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Patricia Garvey
3/18/2007 08:59:51 PM
CSO

Dotti Pease
3/19/2007 07:35:34 AM
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:** | 301-796-9845 |
| **Phone:** | 317-276-8720 | **Phone:** | 301-796-1356 |
| **Pages (including cover):** | 3 | **Date:** | March 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.

Please find attached the PLR deficiencies for your package and patient inserts. Please make the following appropriate revisions to your labeling and submit the revised inserts by April 13, 2007.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Senior Regulatory Project Manager
Division of Drug Oncology Products

**LABELING**

Highlights

1. Remainder that for recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d) (9) and Implementation Guidance].

2. Delete the space under "ADVERSE REACTIONS" heading.

3. Do not include pregnancy category (e.g. X) under USE IN SPECIFIC POPULATION heading in Highlights. [See comment #34 Preamble]

4. Add "and FDA Approved Patient Labeling" after See 17 for PATIENT COUNSELING INFORMATION.

5. Right justify the revision date.

6. Delete [redacted], since this information is not needed. b(4)

Full Prescribing Information: Content*

7. Add space under [redacted] to separate from *Sections or subsections omitted from the full prescribing information are not listed" statement. b(4)

Full Prescribing Information

8. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]

9. Do not refer to adverse reactions as "adverse events". Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, "available at hhtp://www.fda.gov/cder/guidance.

10. Under 17 PATIENT COUNSELING INFORMATION, replace ' [redacted] statement with [redacted] b(4)

11. Under [redacted] delete " [redacted] statement. b(4)

Patient Packing Insert

12. The patient package insert should follow immediately after the end of the package insert full prescribing information.

13. Delete the [redacted] date. The revision date at the end of the Highlights is intended to replace the date at the end of the label. b(4)

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/s/

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Patricia Garvey
3/17/2007 08:53:22 PM
CSO

# DSI CONSULT: Request for Clinical Inspections

**Date:** March 13, 2007

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
Leslie K. Ball, M.D., Branch Chief, GCP2, HFD-47

**Through:** Gary Della'Zanna, D.O., M.Sc., Director
Division of Scientific Investigations, HFD-45

Robert Justice, M.D., Director
Division of Drug Oncology Products, HFD-150

**From:** Patty Garvey, R.Ph., Senior Regulatory Project Manager
Division of Drug Oncology Products, HFD-150

**Subject:** **Request for Clinical Site Inspections**
Application: NDA 22-042
Sponsor: Eli Lilly and Company
Drug: Evista (raloxifene HCl)

**Protocol/Site Identification:**

As discussed with Dr. Lauren Iacono-Connors, the following site has been added to our original clinical site inspection request dated January 9, 2007. Please note that this application will be presented at the ODAC meeting in late July 2007.

This drug is not a New Molecular Entity (NME).

| Site # (Name, Address, Phone number) | Protocol # | Number of Subjects | Indication |
|---|---|---|---|
| Michael Grant<br>Baylor University Medical Center<br>3909 Worth St., Ste 300<br>Dallas, TX 75246<br>214-826-7300 | P-2 (STAR: Study of Taxmoxifen and Raloxifene) | 239 | Reducing the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer |

**Domestic Inspections:**

We have requested inspections because (please check all that apply):

__X__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

**International Inspections:**

We have requested inspections because (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
__X__ Other (specify): Important site with the highest enrollment

**Five or More Inspection Sites:**

We have requested these sites for inspection (international and/or domestic) because of the following reasons:

1. The domestic data are insufficient.
2. We need at least 6 inspection sites because we have clinical data on more than 36,000 women. We are requesting 3 inspections sties for the STAR trial and 3 inspection sites for the RUTH trial. Each trial has a different indication.
3. Prioritize sites according to the table.

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

**Goal Date for Completion:**

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **July 1, 2007**. We intend to issue an action letter on this application by (division action goal date) **August 14, 2007**. The PDUFA due date for this application is **September 14, 2007.**

Should you require any additional information, please contact Patty Garvey, Regulatory Project Manager at 301-796-1356.

Concurrence: (as needed)

Patricia Cortazar, M.D., Medical Reviewer/3-14-07
John Johnson, M.D., Medical Team Leader/3-14-07
Robert Justice, M.D., Division Director (for foreign inspection requests only)/3-15-07

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/s/

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Robert Justice
3/16/2007 04:28:33 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-042

Eli Lilly and Company
Attention: Daniel R. Brady, Ph.D., RAC
Manager, US Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brady:

Please refer to your November 13, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Evista® (Raloxifene HCl) 60mg Tablets.

We also refer to your submissions dated December 11 and 18, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on January 13, 2007 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

The raw data and full study report for the STAR trial were not submitted.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. The full study report for the STAR trial to include the following additional information:
   clinical sites information and number of patients enrolled, demographics, patients removed from study, protocol violations, non-allowed concomitant medications, patient characteristics including prognostic factors, on study therapy (compliance and treatment delays).

2. The raw data for the STAR trial to allow FDA reviewer to independently assess efficacy and safety.

3. Please submit the derived datasets which were used to do time to event analyses in the MORE, CORE and RUTH trials.

4. For all studies, please submit the SAS codes for efficacy analyses, including baseline demographic, primary analyses, and secondary analyses and the SAS codes for efficacy analyses across studies, including 8 years analysis GGGK/GGJY.

Please respond to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Patricia Garvey, Regulatory Project Manager, at (301) 796-1356.

Sincerely,

*{See appended electronic signature page}*

Robert L. Justice, M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

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Robert Justice
1/26/2007 03:29:31 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-042

Eli Lilly and Company
Attention: Daniel R. Brady, Ph.D., RAC
Manager, US Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brady:

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   clinical sites information and number of patients enrolled, demographics, patients removed from study, protocol violations, non-allowed concomitant medications, patient characteristics including prognostic factors, on study therapy (compliance and treatment delays).

2. The raw data for the STAR trial to allow FDA reviewer to independently assess efficacy and safety.

3. Please submit the derived datasets which were used to do time to event analyses in the MORE, CORE and RUTH trials.

4. For all studies, please submit the SAS codes for efficacy analyses, including baseline demographic, primary analyses, and secondary analyses and the SAS codes for efficacy analyses across studies, including 8 years analysis GGGK/GGJY.

Please respond to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Patricia Garvey, Regulatory Project Manager, at (301) 796-1356.

Sincerely,

*{See appended electronic signature page}*

Robert L. Justice, M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

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Robert Justice
1/26/2007 03:29:31 PM

# NDA REGULATORY FILING REVIEW
**(Including Memo of Filing Meeting)**

NDA # 22-042 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Evista
Established Name: raloxifene hydrochloride
Strengths: 60mg Tablets

Applicant: Eli Lilly and Company
Agent for Applicant (if applicable): N/A

Date of Application: November 13, 2006
Date of Receipt: November 14, 2006
Date clock started after UN: N/A
Date of Filing Meeting: December 18, 2006
Filing Date: January 13, 2007
Action Goal Date (optional): N/A User Fee Goal Date: September 14, 2007

Indication(s) requested: (1) The reduction in risk of invasive breast cancer in post menopausal women with osteoporosis and (2) the reduction in risk of invasive breast cancer in post menopausal women at high risk of breast cancer.

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

***NOTE:***
*(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) N/A
Other (orphan, OTC, etc.) Orphan

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☐ Exempt (orphan, government) ☒
Waived (e.g., small business, public health) ☐

***NOTE:*** *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.*

*Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain: Evista is currently approved for the prevention and treatment of osteoporosis in postmenopausal women by the Division of Metabolic and Endocrine Drug Products (NDA 20-815).

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  **If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES ☐ NO ☒
  If no, explain: The sponsor did not submit the STAR trial raw datasets and clinical study report. For additional information, please see Regulatory Conclusions/Deficiencies in the Memo of Filing Meeting.

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☒
   This application is: All electronic ☒ Combined paper + eNDA ☐
   This application is in: NDA format ☒ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐
   **If an eNDA, all forms and certifications must be in paper and require a signature.**

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☐
**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐
- Exclusivity requested? YES, _____ Years NO ☒
***NOTE:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

***NOTE:*** *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☒ NO ☐
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**
**NOTE:** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☒
- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 57,137
- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 11/15/2005; 5/25/2005; 1/28/1999 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO ☒

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☒ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☒ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

## Chemistry

| | | | | | |
|---|---|---|---|---|---|
| • | Did applicant request categorical exclusion for environmental assessment? | YES | ☒ | NO | ☐ |
| | If no, did applicant submit a complete environmental assessment? | YES | ☐ | NO | ☐ |
| | If EA submitted, consulted to EA officer, OPS? | YES | ☐ | NO | ☐ |
| • | Establishment Evaluation Request (EER) submitted to DMPQ? | YES | ☐ | NO | ☐ |
| • | If a parenteral product, consulted to Microbiology Team? YES | | ☐ | NO | ☐ |

ATTACHMENT

## MEMO OF FILING MEETING

**DATE:** December 18, 2006

**NDA #:** 22-042

**DRUG NAMES:** Evista (raloxifene hydrochloride) 60mg Tablets

**APPLICANT:** Eli Lilly and Company

**BACKGROUND:** This is type 6 NDA submission. Evista is currently approved for the prevention and treatment of osteoporosis in postmenopausal women by the Division of Metabolic and Endocrine Drug Products under NDA 20-815. This NDA provides for two new indications. Primary clinical data to support the reduction in risk of invasive breast cancer indication was submitted from three Eli Lilly sponsored placebo controlled clinical studies which included 17,000 postmenopausal women, and an active control trial, NSABP P-2 in 19,747 postmenopausal women.

**ATTENDEES:** Robert Justice, Ramzi Dagher, John Johnson, Patricia Cortazar, Bhupinder Mann, Rajeshwari Sridhara, Kun He, Brian Booth, Julie Bullock, Sarah Pope, Patricia Garvey

**ASSIGNED REVIEWERS (including those not present at filing meeting) :**

| Discipline/Organization | Reviewer |
|---|---|
| Medical: | Patricia Cortazar, MD |
| Secondary Medical: | Bhupinder Mann, MD |
| Statistical: | Kun He, PhD |
| Pharmacology: | ----- |
| Statistical Pharmacology: | ----- |
| Chemistry: | Sarah Pope, PhD |
| Environmental Assessment (if needed): | Sarah Pope, PhD |
| Biopharmaceutical: | Julie Bullock, PharmD |
| Microbiology, sterility: | ----- |
| Microbiology, clinical (for antimicrobial products only): | ----- |
| DSI: | Lauren Iacono-Connor, MD |
| OPS: | ----- |
| Regulatory Project Management: | Patricia Garvey, RPh |
| Other Consults: | DDMAC, DSCRS, OES, SEALD |

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known TBD NO ☐

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A ☒ YES ☐ NO ☐

| | | | | | | |
|---|---|---|---|---|---|---|
| CLINICAL MICROBIOLOGY | N/A | ☒ | FILE | ☐ | REFUSE TO FILE | ☐ |
| STATISTICS | N/A | ☐ | FILE | ☒ | REFUSE TO FILE | ☐ |
| BIOPHARMACEUTICS | | | FILE | ☒ | REFUSE TO FILE | ☐ |

- Biopharm. study site audits(s) needed? ☐ NO ☒
  YES

| | | | | | | |
|---|---|---|---|---|---|---|
| PHARMACOLOGY/TOX | N/A | ☒ | FILE | ☐ | REFUSE TO FILE | ☐ |

- GLP audit needed? YES ☐ NO ☐

| | | | | | | |
|---|---|---|---|---|---|---|
| CHEMISTRY | | | FILE | ☒ | REFUSE TO FILE | ☐ |

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
**(Refer to 21 CFR 314.101(d) for filing requirements.)**

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing. (see comments below)

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional):

**Comments:**

The FDA requested the following in previous communications and at the December 12, 2006 applicant orientation meeting:

1. The full study report for the STAR trial to include the following additional information: clinical sites information and number of patients enrolled, demographics, patients removed from study, protocol violations, non-allowed concomitant medications, patient characteristics including prognostic factors, on study therapy (compliance and treatment delays).

2. The raw data for the STAR trial to allow FDA reviewer to independently assess efficacy and safety.

3. Submit the derived datasets which were used to do time to event analyses in the MORE, CORE and RUTH trials.

4. For all studies, submit the SAS codes for efficacy analyses, including baseline demographic, primary analyses, and secondary analyses and the SAS codes for efficacy analyses across studies, including 8 years analysis GGGK/GGJY.

The sponsor responded to FDA's request to complete the NDA submission and proposed a timeline submission of mid-February 2007 for the STAR trial raw datasets and mid-March 2007 for the STAR trial clinical study report.

FDA will file NDA 22-042 based on the sponsor's commitment to submit the NDA information that are missing at the proposed timelines.

**ACTION ITEMS:**

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Patricia Garvey, RPh
Regulatory Project Manager

## Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
(3) 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) 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, and.

(3) 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) 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, or

(3) 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.

**Appendix B to NDA Regulatory Filing Review**
**Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☐

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☐

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   *If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

*(b)* Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

***NOTE:*** *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

**NOTE:** *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

  YES ☐ NO ☐

  *If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
  *Was this listed drug product(s) referenced by the applicant? (see question # 2)*

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

  N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

| Application No. | Product No. | Exclusivity Code | Exclusivity Expiration |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

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/s/

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Patricia Garvey
1/18/2007 04:19:19 PM
CSO

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

# REQUEST FOR SEALD CONSULTATION

TO *(Division/Office)*:
Study Endpoints and Label Development Team (SEALD)
CDER/OND-IO White Oak Bldg 22, Mail Drop 6411

FROM *(Division/Office)*:
Division of Drug Oncology Products
Patty Garvey, Project Manager

| DATE of REQUEST | NDA/BLA/IND NO. | SERIAL NO/SUPPL. NO | TYPE OF DOCUMENT | DATE OF DOCUMENT |
|---|---|---|---|---|
| January 16, 2007 | | | New NDA | November 13, 2006 |

| NAME OF DRUG | MEETING DATES FOR SUBMISSION | CLASSIFICATION OF DRUG | REQUESTED COMPLETION DATE |
|---|---|---|---|
| Evista (raloxifene HCl) 60mg Tablets | Internal: Sponsor: | | July 13, 2007 |

NAME OF SPONSOR or INVESTIGATOR (for investigator Initiated INDs): Eli Lilly and Company

**DRUG DEVELOPMENT PHASE & MILESTONE**

| | | |
|---|---|---|
| ☐ pre-IND/pre-BBIND<br>☐ PHASE II<br>☐ PHASE III<br>☐ PRE-NDA/BLA MEETING | ☐ NDA/BLA/sNDA/SBLA REVIEW<br>☐ NDA/BLA SAFETY/EFFICACY UPDATE<br>☐ RESPONSE TO DEFICIENCY LETTER<br>☐ NDA/BLA/sNDA/SBLA RESUBMISSION REVIEW<br>☐ ADVISORY COMMITTEE MEETINGS<br>☐ LABELING (INITIAL OR REVISION)<br>☐ ADVERTISING REVIEW | ☐ OTHER ( Specify) |

**STUDY ENDPOINT OR LABELING To BE REVIEWED**

| STUDY ENDPOINT REVIEW | | LABELING REVIEW |
|---|---|---|
| ☐ TYPE A MEETING PACKAGE<br>☐ CLINICAL HOLD/DISPUTE RESOLUTION<br>☐ SPA RESPONSE<br>☐ TYPE B MEETING PACKAGE<br>☐ PRE-IND MEETING<br>☐ END OF PHASE II/Pre-PHASE III<br>☐ PRE-NDA/BLA<br>☐ TYPE C MEETING PACKAGE | ☐ SPECIAL PROTOCOL ASSESSMENT REVIEW<br>☐ STANDARD PROTCOL REVIEW<br>☐ PROGRESS REPORT<br>☐ STATISTICAL ANALYSIS PLAN REVIEW<br>☐ ENDPOINT DEVELOPMENT/VALIDATION DOSSIER<br>☐ NDA / BLA REVIEW<br>☐ AC MEETING | **X PROPOSED LABELING**<br>☐ FINAL PRINTED LABELING<br>☐ LABELING REVISION<br>☐ DRUG ADVERTISING<br>☐ OTHER (SPECIFY): |

**CONSULT REVIEW REQUESTED**

This is a type 6 NDA submission. Evista is currently approved by DMEDP under NDA 20-815. Please review the attached PLR labeling and attend any relevant meetings. This is an electronic submission and the path location is \\CDSESUB1\N22042\N_000\2006-12-11V

**PDUFD DUE DATE: September 14, 2007**

DDOP MO: Patricia Cortazar, MD and Bhupinder Mann, MD
DDOP PM: Patty Garvey

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one) |
|---|---|
| Patty Garvey | ☐ INTEROFFICE MAIL **DFS/ E-MAIL** ☐ HAND -CARRIED X |
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

24 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

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Patricia Garvey
1/16/2007 02:34:43 PM

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

# REQUEST FOR CONSULTATION

TO *(Office/Division)*: DSRCS/Mary Dempsey

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 |
|---|---|---|---|---|
| January 16, 2007 | | NDA 22-042 | New NDA | November 13, 2006 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| Evista (raloxifene HCl) 60mg Tablets | | | July 13, 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 PLR labeling and PPI and attend relevant meetings. This is an electronic submission and path location is: \\CDSESUB1\N22042\N_000\2006-12-11V

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 |

# 24 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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Patricia Garvey
1/16/2007 02:07:35 PM

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

# REQUEST FOR CONSULTATION

TO *(Office/Division)*: DDMAC/Joseph Grillo, PharmD

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 |
|---|---|---|---|---|
| January 16, 2007 | | NDA 22-042 | New NDA | November 13, 2006 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| Evista (raloxifene HCl) 60mg Tablets | | | July 13, 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 labeling, attend relevant meetings and review any advertising materials that may be submitted. This is an electronic submission and path location is: \\CDSESUB1\N22042\N_000\2006-12-11V

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 |

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✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

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Patricia Garvey
1/16/2007 01:09:53 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-042

**NDA ACKNOWLEDGMENT**

Eli Lilly and Company
Attention: Daniel R. Brady, Ph.D., RAC
Manager, US Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brady:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

| | |
|---|---|
| Name of Drug Product: | Evista® (Raloxifene HCl) 60mg Tablets |
| Review Priority Classification: | Standard (S) |
| Date of Application: | November 13, 2006 |
| Date of Receipt: | November 14, 2006 |
| Our Reference Number: | NDA 22-042 |

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 13, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 14, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact me at (301) 796-1356.

Sincerely,

*{See appended electronic signature page}*

Patricia N. Garvey, R.Ph.
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

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Patricia Garvey
1/12/2007 10:29:47 AM

# DSI CONSULT: Request for Clinical Inspections

**Date:** January 9, 2007

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
Leslie K. Ball, M.D., Branch Chief, GCP2, HFD-47

**Through:** Gary Della'Zanna, D.O., M.Sc., Director
Division of Scientific Investigations, HFD-45

Robert Justice, M.D., Director
Division of Drug Oncology Products, HFD-150

**From:** Patty Garvey, R.Ph., Senior Regulatory Project Manager
Division of Drug Oncology Products, HFD-150

**Subject:** **Request for Clinical Site Inspections**
Application: NDA 22-042
Sponsor: Eli Lilly and Company
Drug: Evista (raloxifene HCl)

**Protocol/Site Identification:**

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

This NDA provides data for the following: 1. Reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis, and 2. Reducing the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer

This drug is not a New Molecular Entity (NME).

| Site # (Name, Address, Phone number) | Protocol # | Number of Subjects | Indication |
|---|---|---|---|
| André Robidoux, M.D.<br>Hôtel-Dieu du CHUM<br>3840 St-Urbain Street<br>Montreal, QC H2W1T8<br>514-890-8000 Ext 14195 | P-2 (STAR: Study of Taxmoxifen and Raloxifene) | 316 | Reducing the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer |

| | | | |
|---|---|---|---|
| Rebecca Moroose, M.D.<br>Cancer Institute of Florida PA<br>2501 N Orange Ave. Ste 286<br>Orlando, FL 32804<br>407-898-2343 | **P–2** (STAR: Study of Taxmoxifen and Raloxifene) | 212 | Reducing the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer |
| Louis Fehrendacher, M.D.<br>Oncology<br>Kaiser Foundation Hospital<br>975 Sereno Drive<br>Vallejo, CA 94590<br>707-651-2787 | **P-2** (STAR: Study of Taxmoxifen and Raloxifene) | 357 | Reducing the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer |
| Jane Cauley, M.D.<br>University of Pittsburgh<br>130 N. Bellefield<br>Pittsburgh, PA<br>412-624-0218 | **H3S-MC-GGIO** (RUTH: Raloxifene Use for The Heart) | 112 | Reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis |
| Kristine Ensrud, M.D., MPH<br>University of Minnesota<br>Suite 201<br>1100 Washington Ave.South<br>Minneapolis, MN<br>612-725-2158 | **H3S-MC-GGIO** (RUTH: Raloxifene Use for The Heart) | 105 | Reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis |
| Elizabeth Barrett-Connor, M.D.<br>University of California, San Diego<br>Dept of Family & Preventive Medicine<br>9500 Gilman Drive<br>La Jolla, CA<br>858-534-0511 | **H3S-MC-GGIO** (RUTH: Raloxifene Use for The Heart) | 74 | 1. Reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis |

**Domestic Inspections:**

We have requested inspections because (please check all that apply):

__X__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

**International Inspections:**

We have requested inspections because (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
__X__ Other (specify): Important site with the highest enrollment

**Five or More Inspection Sites:**

We have requested these sites for inspection (international and/or domestic) because of the following reasons:

1. The domestic data are insufficient.
2. We need at least 6 inspection sites because we have clinical data on more than 36,000 women. We are requesting 3 inspections sties for the STAR trial and 3 inspection sites for the RUTH trial. Each trial has a different indication.
3. Prioritize sites according to the table.

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

**Goal Date for Completion:**

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **August 1, 2007**. We intend to issue an action letter on this application by (division action goal date) **August 14, 2007**. The PDUFA due date for this application is **September 14, 2007.**

Should you require any additional information, please contact Patty Garvey, Regulatory Project Manager at 301-796-1356.

Concurrence: (as needed)

Patricia Cortazar, M.D., Medical Reviewer/ 1-8-07
Bhupinder Mann, M.D., Medical Reviewer/ 1-4-07
John Johnson, M.D., Medical Team Leader/1-8-07
Robert Justice, M.D., Division Director (for foreign inspection requests only)/ 1-8-07

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/s/

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Robert Justice
1/9/2007 05:56:36 PM

# 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:** | January 8, 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 have the following request for information from the clinical pharmacology reviewer. Please reply to the request 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 Pharmacology**

To support the population analyses, please submit the datasets for studies GGGK, GGHW and the data for the Pop PK/PD analysis of GGGF, GGGG and GGGH:

- All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

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/s/
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Patricia Garvey
1/9/2007 04:10:03 PM
CSO
Sent to the sponsor on January 8, 2007

# MEETING MINUTES

**MEETING DATE:** December 12, 2006 **TIME:** 10:00 am

**NDA** 22-042 **Briefing Document Submission:** 12-8-06

**DRUG:** Evista (raloxifene HCl)

**SPONSOR/APPLICANT:** Eli Lilly and Company

**TYPE OF MEETING:**

1. Applicant Orientation Presentation

2. **Proposed Indication:**
   (1) The reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and
   (2) the reduction in risk of invasive breast cancer in postmenopausal women at high risk for breast cancer.

**FDA PARTICIPANTS:**

| | | |
|---|---|---|
| Richard Pazdur, M.D. | -- | Director, Office of Oncology Drug Products (OODP) |
| Karen Weiss, M.D. | -- | Deputy Director, OODP |
| Robert Justice, M.D. | -- | Director, Division of Drug Oncology Products (DDOP) |
| Ramzi Dagher, M.D. | -- | Acting Deputy Director, DDOP |
| John Johnson, M.D. | -- | Medical Team Leader, DDOP |
| Patricia Cortazar, M.D. | -- | Medical Reviewer, DDOP |
| Bhupinder Mann, M.D. | -- | Medical Reviewer, DDOP |
| Rajeshwari Sridhara, Ph.D. | -- | Statistical Team Leader, Division of Biometrics I (DBEI) |
| Brian Booth, Ph.D. | -- | Deputy Director, Division of Clinical Pharmacology V |
| Sarah Pope, Ph.D. | -- | Pharmaceutical Assessment Lead, Branch V, Division III of Office of New Drug Quality Assessment |
| Patty Garvey, R.Ph. | -- | Senior Regulatory Project Manager, DDOP |

**INDUSTRY PARTICIPANTS:**

| | | |
|---|---|---|
| Gregory Enas, Ph.D. | -- | Director, US Reglatory Affairs |
| Vijayapal Reddy, DVM, Ph.D. | -- | Regulatory Specialist |
| Daniel Brady, Ph.D. | -- | Manager, US Reglatory Affairs |
| Toni Shepard-Mustaklem, BS | -- | Regulatory Submissions Coordinator |
| Gwen Krivi, Ph.D. | -- | Osteoporosis Team Leader |
| Bruce Mitlak, M.D. | -- | Senior Medical Fellow II |
| Maria Rivas, M.D. | -- | US Affiliate Medical Director |
| John Mershon, M.D. | -- | US Affiliate Medical |
| Michelle McNabb, M.S. | -- | Statistical Team Leader |
| Jingli Song, Ph.D. | -- | Principal Research Statistician |
| Daniel Masica, M.D. | -- | Global Product Safety |
| Joseph Costintino, Ph.D. | -- | Director, NSABP Biostatistical Center |
| Worta McCaskill-Stevens, M.D. | -- | Program Director, National Cancer Institute |

**MEETING OBJECTIVE:**

To provide orientation to the New Drug Application (NDA) number 22-042 Evista for the proposed indications (1) the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and (2) the reduction in risk of invasive breast cancer in postmenopausal women at high risk for breast cancer.

**BACKGROUND:**

On November 13, 2006, the sponsor submitted their NDA for Evista for the proposed indications (1) the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and (2) the reduction in risk of invasive breast cancer in postmenopausal women at high risk for breast cancer.

Evista is currently approved for the prevention and treatment of osteoporosis in post-menopausal women in the Division of Metabolic and Endocrine Drug Products.

**DISCUSSION:**

The sponsor presented a review of the data supporting approval of Evista for the reduction of risk of invasive breast cancer in postmenopausal women at high risk of breast cancer, or postmenopausal women with osteoporosis.

On November 30, 2006, FDA requested the sponsor to submit the raw data sets and clinical study report for the P-2 study (STAR) to their NDA. On November 15, 2005, the FDA and the sponsor met for a pre-NDA meeting. From that meeting, the sponsor had understood that the STAR (NSABP P-2) trial manuscript and summary data files were acceptable in lieu of the clinical study report. . Apparently, the sponsor misunderstood what the FDA conveyed at the meeting.

However, the sponsor agreed to submit the raw data sets by first week of February and the STAR trial clinical study report by mid of March. They indicated that they would try their best to submit these items earlier if possible.

FDA indicated that this NDA would highly likely be reviewed by ODAC because this is for chemoprevention with widespread implications.

FDA indicated that a priority review would not be possible since the sponsor did not submit all the required items to complete the NDA review, such as raw data sets and CSR for the NSABP P-2 study. The sponsor understood the FDA concerns and accepted a standard review for their NDA.

Dr. Constintino stated that NSABP is different from other cooperative groups because they conduct medical review and ongoing cleaning of the data when submitted by the investigative sites rather than collecting the data at the end of the trial.

FDA was also concerned about the negative perception of another government employee, in this case NCI employee, representing or participating in FDA meetings on behalf of a sponsor. Dr. McCaskill-Stevens indicated that she had received approval to participate in the meeting from NCI Ethics Office. She also indicated she will have NCI Ethics Office discuss this issue with the FDA Ethics Office as well.

FDA concluded that a quality review of an application is more important than meeting regulatory timelines.

**ACTION ITEMS:**

1. The sponsor will submit the complete raw data for the P-2 study by the end of the first week of February 2007.

2. The sponsor will submit the clinical study report for the P-2 study as soon as possible after they have reviewed the raw data sets from NSABP.

**ADDENDUM:**

On December 15, 2006, the sponsor submitted their meeting minutes and included the following updated to commitments made during the December 12, 2006 meeting.

1. After more fully assessing the requirements for data conversion and validation, Lilly plans to submit to NDA 22-042 the complete P-2 raw data sets by 15 February 2007. Lilly and NSABP will work hard to deliver these data sets earlier if possible.
2. Some appendices of the CSR are dependent on analyses using the data sets generated by NSABP. In order to provide a CSR for regulatory review, Lilly proposes submitting the P-2 CSR by mid-March 2007.

*{See appended electronic signature page}* *{See appended electronic signature page}*

Patty Garvey, R.Ph.
Regulatory Project Manager/Facilitator

Concurrence Chair:
John Johnson, M.D.
Medical Team Leader, DDOP

*Attachment: Sponsor presentation slides*

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_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/
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Patricia Garvey
12/22/2006 06:36:16 AM

John Johnson
12/22/2006 10:31:57 AM

**Pease, Dorothy W**

**From:** Pease, Dorothy W
**Sent:** Thursday, November 30, 2006 12:26 PM
**To:** 'drbrady@lilly.com'
**Cc:** Garvey, Patricia
**Subject:** NDA 22-042 Evista

Hope you don't mind an e-mail communication. I am covering in Patty's absence.

We received your submission for NDA # 22042 dated November 13, 2006. We need to get the following additional items which are essential to the NDA review:

**STAR Trial:**

1) We need a full study report. The study manuscript does not provide enough detail for an NDA review. At the November 15, 2005 Pre-NDA meeting you asked if the package described as (study protocol, manuscript, summary of adverse events and blood tests and data files) was acceptable in lieu of a CSR and FDA responded: "The proposed package is incomplete. You need to submit the following additional information:

- clinical sites information and number of patients enrolled
- demographics
- Patients removed from study
- protocol violations
- non-allowed concomitant medications
- patient characteristics including prognostic factors
- on study therapy: compliance and treatment delays

2)We need to have raw data for the STAR trial that will allow FDA reviewers to independently assess efficacy and safety. The datasets that you submitted have all derived data.

**RUTH Trial:**

1)We need datasets based on all patients enrolled in the trial which should allow us to do time-to-event analyses for breast cancer events in this trial. This must include the censoring information. Data only on 130 patients (BRCADATA) who developed breast cancer is not sufficient.

2) Please also submit the derived datasets which were used to do time to event analyses in the MORE, CORE, and RUTH trials.

**For ALL Studies:**

1) Please submit the SAS codes for efficacy analyses, including baseline, demographic, primary analyses, and secondary analyses.

2) Please also submit the SAS codes for efficacy analyses across studies, including 8 year analysis GGGK/GGJY.

Format could be pdf or word file in email version (preferred) or hard copy. A formal submission going through EDR is not necessary if hard copy is submitted.

Thanks

Dotti Pease for Patty Garvey
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
301 796-1434 fax 301 796-9845

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/s/
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Dotti Pease
11/30/2006 01:32:57 PM
CSO

# MEETING MINUTES

**MEETING DATE:** November 15, 2005 **TIME:** 11:00 am **LOCATION:** WO 1309

**IND** 57,137 **Meeting Request Submission Date:** 8-30-05; sn058
**Briefing Document Submission:** 10-18-05; sn062

**DRUG:** Evista® (raloxifene HCl)

**SPONSOR/APPLICANT:** Eli Lilly and Company

**TYPE OF MEETING:**

1. Pre-sNDA #2

2. **Proposed Indication:**
   Evista is indicated as a first-line therapy for the reduction in risk (primary prevention) of invasive breast cancer in postmenopausal women.

**FDA PARTICIPANTS:**

| | | |
|---|---|---|
| Robert Justice, M.D. | -- | Acting Director, Division of Drug Oncology Products (DDOP) |
| Ramzi Dagher, M.D. | -- | Acting Deputy Director, DDOP |
| Patricia Cortazar, M.D. | -- | Medical Reviewer, DDOP |
| Rajeshwari Sridhara, Ph.D. | -- | Statistical Team Leader, Division of Biometrics I (DBEI) |
| Shenghui Tang, Ph.D. | -- | Statistical Reviewer, DBEI |
| Patty Garvey, R.Ph. | -- | Regulatory Project Manager, DDOP |

**INDUSTRY PARTICIPANTS:**

| | | |
|---|---|---|
| Daniel R. Brady, Ph.D. | -- | Regulatory Scientist, US Regulatory Affairs |
| Gregory G. Enas, Ph.D. | -- | Director, US Regulatory Affairs |
| Mary Jane Geiger, M.D., Ph.D. | -- | Medical Advisor |
| Mark Lakshmanan, M.D. | -- | Medical Director, Osteoporosis Medical Team |
| John Mershon, M.D. | -- | Medical Advisor |
| Toni Shepard-Mustaklam | -- | Global Operations Submissions Coordinator |
| Vijayapal Reddy, DVM, Ph.D. | -- | Regulatory Scientist, US Regulatory Affairs |
| Matthew Rotelli, Ph.D. | -- | Head, Statistics Team |
| Gregory Sides, M.D. | -- | Medical Director |
| Jingli Song, Ph.D. | -- | Research Scientist, Statistics |

| | | | |
|---|---|---|---|
| Consultants: | Joseph Costantino, Ph.D. | -- | Director, NSABP Biostatistical Center |
| | Lawrence Wickerham,M.D | -- | Associate Chair, NSABP |
| | Leslie G. Ford, M.D. | -- | Associate Director for Clinical Research, NCI |

**MEETING OBJECTIVES:**

To discuss detailed contents of the sNDA, details of the National Surgical Adjuvant Breast and Bowel's Project's (NSABP's) P-2 study of tamoxifen and raloxifene (STAR), outstanding issues relative to Study H3S-MC-GGIO (Ruth), and administrative information.

**BACKGROUND:**

Raloxifene HCL is one of a series of benzothiophene compounds, previously described as antiestrogens, for their ability to inhibit estrogen-responsive breast epithelial cell growth (Black et al. 1982; Jones et al. 1984). Raloxifene is now classified as a SERM, based on its ability to act as an estrogen agonist in bone and on lipid metabolism, while acting as an estrogen antagonist in tissues-selective estrogen agonist/antagonist effects have not been complete elucidated, it is now clear that differential binding to estrogen receptor subtypes results in conformational changes, which subsequently induces various genomic and nongenomic activities involved in these differential effects.

Raloxifene HCL was developed for the prevention and treatment of osteoporosis under IND 39,503 in the Division of Metabolic and Endocrine Drug Products (DMEDP). Raloxifene was approved on December 9, 1997, under the trade name Evista ®, for prevention in postmenopausal women. On September 30, 1999, a supplemental new drug application for Evista was approved for the treatment of osteoporosis in postmenopausal women.

The sponsor opened an IND 57,137 with the Division of Oncology Drug Products (DODP) on October 21, 1998, with the intention of establishing the safety and efficacy of raloxifene to support the additional indication of reduction in risk of invasive breast cancer. The sponsor anticipates raloxifene HCl to be indicated as a first-line therapy for the reduction in risk (primary prevention) of invasive breast cancer in postmenopausal women.

Four Phase 3 clinical studies will support this new indication. The DMEDP reviewed a 3-year placebo-controlled study of 7705 women, H3S-MC-GGGK (GGGK), for approval of the treatment of osteoporosis in postmenopausal women (NDA 20-815). Study GGGK was extended for an additional 12 months and contains additional breast cancer data that will be included in the sNDA. Approximately 4000 women continued in this study extension, H3S-MC-GGJY, for further evaluation of raloxifene's effect on risk reduction of invasive breast cancer. Clinical study H3S-MC-GGIO (GGIO) is a placebo-controlled study of 5+ years in 10,101 postmenopausal women at risk for coronary heart disease and has two primary endpoints: (1) reduction in risk of invasive breast cancer and (2) reduction in risk of major acute coronary events. This study will close after the last patient has completed their scheduled 5- year visit, anticipated in August 2005. The final study is an active comparator trial of 19,747 women on either raloxifene HCL or tamoxifen citrate conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and is identified as the P-2 trial, or STAR. It is anticipated that this trial will conclude in the spring of 2006.

On May 25, 2005, the sponsor had a meeting with the Division to discuss clinical issues regarding the sNDA submission. This is the second sNDA meeting mainly to discuss formatting the sNDA submission.

**QUESTIONS for DISCUSSION with FDA RESPONSES and DECISIONS REACHED:**

CONTENTS of the sNDA

1a. Is the proposed format of the sNDA (see Appendix 2), which incorporated Common Technical Document (CTD) elements in the electronic NDA format, as described in Section 2.1 of this briefing document, acceptable to the FDA?

**FDA: Yes.**

1b. Is the draft table of contents outlined in Section 2.1 of this briefing document and provided in Appendix 2 acceptable to the FDA?

**FDA: Yes.**

1c. As described in Section 2.1 of this briefing document, does the FDA agree that it is acceptable to present the clinical efficacy data in the Summary of Clinical Efficacy and not include a separate Integrated Summary of Efficacy (ISE)?

**FDA: Please include the Summary of Clinical Efficacy and a separate ISE. Please follow the guidance.**

*Discussion:*

*The FDA will accept the Summaries of Clinical Efficacy and Clinical Safety in lieu of the ISE and ISS as long as there are links to these reports. Comparative results will be presented even if not integrated from a statistical standpoint.*

*FDA will check with IT regarding format and will follow-up with the sponsor.*

1d. As described in Section 2.1 of this briefing document, does the FDA agree that it is acceptable to present the clinical safety data in the Summary of Clinical Safety and not include a separate Integrated Summary of Safety (ISS)?

**FDA: Please include the Summary of Clinical Safety and a separate ISS. Please follow the guidance.**

*Discussion:*

*The FDA will accept the Summaries of Clinical Efficacy and Clinical Safety in lieu of the ISE and ISS as long as there are links to these reports. Comparative results will be presented even if not integrated from a statistical standpoint.*

*FDA will check with IT regarding format and will follow-up with the sponsor.*

1e. Does the FDA agree with the proposal described in Section 2.1 of this briefing document to provide an electronic review aid of the archival copy of the application?

**FDA: Yes.**

REGISTRATION TRIALS

2a. Is the NSABP P-2 study statistical analysis (SAP) described in Section 3.1.2 of this briefing document and Section 13.0 of the NSABP P-2 Protocol (Appendix 3) adequate to support filing and review of this sNDA?

**FDA: The SAP appears to be acceptable for testing superiority.**

*Discussion:*

*FDA clarified that superiority is with respect to efficacy.*

*The FDA statistical team will follow-up on the adaptive randomization scheme and whether other sensitivity analyses should be conducted. The FDA will follow-up within a month.*

2b. As described in Section 3.1.3 of this briefing document, Lilly proposes that the following package serve as the clinical study report (CSR) for the NSABP P-2 study:

- the study protocol (see Appendix 3)
- the final draft (i.e., the draft submitted for publication) of a manuscript written by the NSABP reporting the primary and secondary endpoint results and adverse events of interest, as determined by the NSABP
- summary tables for the adverse event, self-reported symptom, and blood tests results
- the data files described in Section 3.1.4 of this briefing document.

Does the FDA agree that the package defined above is acceptable to submit in lieu of a CSR?

**FDA: The proposed package is incomplete. You need to submit the following additional information:**

- **clinical sites information and patients enrolled**
- **demographics**
- **removal from study**
- **protocol violations**

- **non-allowed concomitant medications**
- **patient characteristics including prognostic factors**
- **on study therapy: compliance and treatment delays**

*Discussion:*

*FDA agrees that removal from study refers to patients who have withdrawn consent.*

*FDA wants to have protocol unblinding information. The tabular form is acceptable.*

*Demographics as described in section 3.1.4 are acceptable.*

2c. For the NSABP P-2 study, the data files for endpoints, adverse events, self-reported symptoms, and blood test results will be provided with the submission. Is the information contained in these files, as described in section 3.1.4 of this briefing document, sufficient for the filing and review of this sNDA?

**FDA: The proposed data files appear to be acceptable.**

2d. As discussed in Section 3.1.5 of this briefing document, adverse events for the NSABP P-2 study are being reported in accordance with the policy and procedures agreed to for this study (see Appendix 7: NSABP Policy and Procedures for Reporting Adverse Events (AEs) Occurring on NSABP Protocol P-2, 5/5/99, IND 57,427), and as described in Section 12.0 of the protocol (see Appendix 3). The NSABP is providing written reports of adverse events requiring prompt reporting, but is not writing additional patient narratives. For the submission, Lilly does not intend to resubmit these reports, but will refer to the FDA to the NSABP's IND 57,427 for these reports. Does the FDA agree that this is sufficient to support the review and approval, in principle, of the sNDA?

**FDA: Yes. However, the written reports or patient narratives of events requiring prompt reporting should be provided with the NDA submission.**

2e. For the NSABP P-2 study, case report forms (CRFs) will be provided for participants who have experienced any of the events listed in Section 3.1.6 of this briefing document. Does the FDA agree that the proposed CRFs for the NSABP P-2 study are sufficient to support review and approval, in principle, of this sNDA?

**FDA: Yes.**

2f. Although there may be many possible "positive" outcomes of the NSABP P-2 study, does DDOP agree that at least either of the two scenarios described in Section 3.1.7 of this briefing document would constitute a "positive" outcome for the NSABP P-2 study and in combination with the safety and efficacy results of Study GGIO, Study GGGK, and Study GGJY, would, in principle, be sufficient to register raloxifene for the proposed indication?

**FDA: Your SAP does not include a non-inferiority hypothesis testing in P-2 and any claim for non-inferiority is unlikely. What would constitute a positive outcome depends on the review of the data as well as a possible ODAC discussion.**

*Discussion: FDA recommends that the sponsor request a meeting be held prior to filing the sNDA to discuss results of all the trials. The sponsor agrees.*

3a. At the 60-day DDOP filing meeting, does DDOP anticipate that it will be able to provide Lilly with an initial request for scanned CRFs on individual patients in Study GGIO, as discussed in Section 3.2.1 of this briefing document, so that Lilly can initiate the scanning preparation of CRFs for DDOP review?

**FDA: No. It will be premature for FDA reviewers to determine at the filing meeting, if additional CRFs are needed. We will try to let you know as soon as we review the data if additional CRFs are needed.**

*Discussion: The sponsor is committed to submitting the CRFs for breast cancer cases with the sNDA and sending additional CRFs upon FDA request. The turn around time will be 20 patient files within a 3 week period.*

3b. Does the FDA agree that the format of the sample datasets for Study GGIO submitted on 6 October 2005 (serial number 061) is acceptable (see Section 3.2.2 of the briefing document)?

**FDA: The datasets appear to be adequate.**

3c. In the event that there are outstanding, unadjudicated endpoint events at the planned 30 January 2006 datalock for Study GGIO, does the FDA agree with Lilly's plan, outlined in Section 3.2.3 of this briefing document, to use the data from the relock as the basis for the submission and the United States Package Insert (USPI)?

**FDA: No. There should be only one datalock.**

*Discussion: The sponsor agreed that there will be one datalock.*

ADMINISTRATIVE INFORMATION

4a. Does the FDA agree that positive outcomes on safety and efficacy from Study GGIO and the NSABP P-2 study along with the data from Study GGGK and Study GGJY, as discussed in Section 4.2.1 of this briefing document, would meet the criteria for the designation of the sNDA for a Priority Review?

**FDA: Whether or not this will be a priority review will be determined at the time of filing.**

4b. As discussed in Section 4.2.2 of this briefing document, does the FDA agree that a 4-month safety update will not be necessary for this sNDA review?

**FDA: Unless all studies are complete, a 4-month safety update should be submitted.**

*Discussion: The 4-month safety update will be provided for the STAR trial. The other trials have been completed and a safety update will not be required.*

4c. Is the financial certification or disclosure proposal for Studies GGGK, GGJY, and GGIO, and the NSABP P-2 study described in Section 4.2.3 of this briefing document adequate?

**FDA: Yes.**

4d. Does the FDA agree that it is appropriate to use the Indication and Usage section (see Appendix 9, section[c]) of the label to define "first-line therapy" and "primary prevention" for invasive breast cancer risk reduction, as discussed in Section 4.2.4 of this briefing document?

**FDA: First line therapy and primary prevention should not be used as terms in the label.**

4e. Does the FDA agree that it is appropriate to maintain the current adverse event table for osteoporosis treatment and prevention using Coding Symbol and Thesaurus for Adverse Reaction Terminology (COSTART), and to add appropriate text and/or a table(s) for Study GGJY and Study GGIO using Medical Dictionary for Regulatory Activities (MedDRA) terms (see Appendix 9, section [g] Adverse Reactions)?

**FDA: Yes.**

4f. As the Common Toxicity Criteria (CTC) is the standard terminology used by the NCI for adverse events, does the FDA agree that it is appropriate to add text and/or a table(s) for the NSABP P-2 study using CTC version 2 terminology (see Appendix 9, section [g] Adverse Reactions)?

**FDA: Yes.**

**ACTION ITEM:** None

1. FDA will check with IT regarding sNDA CTD formatted submission, specifically if there are any problems when a module contains only a link or left blank.

2. FDA statistical team will follow-up on the adaptive randomization scheme and whether other sensitivity analyses should be conducted.

**ADDENDUM:**

FDA follow-up to the above action items.

Action item #1 – It is acceptable for the sponsor to leave a module blank or contain a link.

Action item #2 – The sponsor primary analysis plan appears to be acceptable and no more analyses are required at this moment.

There were no unresolved issues. The meeting concluded at 12:00 p.m.

*{See appended electronic signature page}*

Patty Garvey, R.Ph.
Regulatory Project Manager

*{See appended electronic signature page}*

Concurrence Chair:

Ramzi Dagher, M.D.
Acting Deputy Director, DDOP

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/s/

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Ramzi Dagher
12/12/2005 09:05:49 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

July 14, 2005

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Re: Designation Request # 04-1975

Attention: David R. McAvoy, J.D., M.S.E.S.
Director
Office of Scientific and Regulatory Affairs

Dear Mr. McAvoy:

Reference is made to your request for the orphan-drug designation dated November 8, 2004, of raloxifene (trade name: Evista®) for "reduction of the risk of breast cancer in postmenopausal women." Please also refer to our acknowledgement letter of November 10, 2004, and to your submissions dated January 19, February 22, May 24 and 25, June 8 and June 10, 2005.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan drug designation of raloxifene (trade name Evista®) is granted for *reduction of the risk of breast cancer in postmenopausal women.* Specifically, orphan-drug designation is being granted on the basis that there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States for seven years after approval of a marketing application [21 CFR 316.20(8)(ii)].

We acknowledge your agreement to provide additional information as described in your commitment letter of June 10, 2005, and as outlined below.

1. Provide updated information related to the assumptions on patent status reflected in section 8.4.2 of your Application. This includes information on any new patents or other significant intellectual property rights that would impact Evista for the orphan indication.

2. Provide information identifying new competitor product launches since the date of application (section 8.4.5.2).

JUL 26 2005
G.G. Enas

3. Provide a current and projected net price for the next 12-month period for Evista.

4. Provide updated estimates for projected marketing investment for the orphan indication as reflected in section 3.2, Supplement #1 of the Application.

5. Provide a description of Evista's prescription growth for the previous 12-month period and, for the first report, compare to the 12-month period immediately prior to launch.

6. Provide Evista's net revenue for the previous 12-month period and, for the first report, compare to the 12-month period immediately prior to launch.

As agreed to in your June 10, 2005 letter, the above information will be submitted within 90 days following the first full year of marketing Evista for the orphan indication in the United States, and thereafter annually for an additional two years.

It should be noted that this Office reserves the right to revoke the orphan drug designation of Evista, and exclusive marketing rights if approved, as stipulated under 21 CFR 316.29.

If you have any questions, please contact Jeffrey Fritsch, R.Ph., in this Office at (301) 827-3666.

Sincerely yours,

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

Appears This Way
On Original

JUL 26 2005
G.G. Enas

## MEETING MINUTES

**MEETING DATE:** May 25, 2005 **TIME:** 1:00 pm **LOCATION:** WOC2/rm 3004

**IND:** 57,137 **Meeting Request Submission Date:** 3-24-05; sn054
**Briefing Document Submission Date:** 4-25-05; sn055

**DRUG:** Evista® (raloxifene HCl)

**SPONSOR/APPLICANT:** Eli Lilly and Company

**TYPE of MEETING:**

1. Pre-sNDA

2. **Proposed Indications (from briefing package):**
   Evista is indicated as a first-line therapy for the reduction in risk (primary prevention) of invasive breast cancer in postmenopausal women.

**FDA PARTICIPANTS:**

| | | |
|---|---|---|
| Robert Justice, M.D. | -- | Deputy Director, DODP |
| Ramzi Dagher, M.D. | -- | Medical Team Leader |
| Patricia Cortazar, M.D. | -- | Medical Reviewer |
| Ning Li, Ph.D. | -- | Statistical Reviewer |
| Yong-Cheng Wang, Ph.D. | -- | Statistical Reviewer |
| Patty Garvey, R.Ph. | -- | Regulatory Project Manager |

**INDUSTRY PARTICIPANTS:**

| | | |
|---|---|---|
| Daniel Brady, Ph.D. | -- | Manager, U.S. Regulatory Affairs |
| Per Cantor, M.D. Ph.D. | -- | Medical Director |
| Gregory Enas, Ph.D. | -- | Director, U.S. Regulatory Affairs |
| Mary Jane Geiger, M.D., Ph.D. | -- | Clinical Research Physician |
| Patricia Martin | -- | Executive Direct, Osteoporosis Products |
| [redacted] | -- | [redacted] |

b(4)

**BACKGROUND:**

Raloxifene HCL is one of a series of benzothiophene compounds, previously described as antiestrogens, for their ability to inhibit estrogen-responsive breast epithelial cell growth (Black et al. 1982; Jones et al. 1984). Raloxifene is now classified as a SERM, based on its ability to act as an estrogen agonist in bone and on lipid metabolism, while acting as an estrogen antagonist in tissues-selective estrogen agonist/antagonist effects have not been complete elucidated, it is now clear that differential binding to estrogen receptor subtypes results in conformational changes, which subsequently induces various genomic and nongenomic activities involved in these differential effects.

Raloxifene HCL was developed for the prevention and treatment of osteoporosis under IND 39,503 in the Division of Metabolic and Endocrine Drug Products (DMEDP). Raloxifene was approved on December 9, 1997, under the trade name Evista®, for prevention in postmenopausal women. On September 30, 1999, a supplemental new drug application for Evista was approved for the treatment of osteoporosis in postmenopausal women.

The sponsor opened an IND 57,137 with the Division of Oncology Drug Products (DODP) on October 21, 1998, with the intention of establishing the safety and efficacy of raloxifene to support the additional indication of reduction in risk of invasive breast cancer. The sponsor anticipates raloxifene HCl to be indicated as a first-line therapy for the reduction in risk (primary prevention) of invasive breast cancer in postmenopausal women.

Four Phase 3 clinical studies will support this new indication. The DMEDP reviewed a 3-year placebo-controlled study of 7705 women, H3S-MC-GGGK (GGGK), for approval of the treatment of osteoporosis in postmenopausal women (NDA 20-815). Study GGGK was extended for an additional 12 months and contains additional breast cancer data that will be included in the sNDA. Approximately 4000 women continued in this study extension, H3S-MC-GGJY, for further evaluation of raloxifene's effect on risk reduction of invasive breast cancer. Clinical study H3S-MC-GGIO (GGIO) is a placebo-controlled study of 5+ years in 10,101 postmenopausal women at risk for coronary heart disease and has two primary endpoints: (1) reduction in risk of invasive breast cancer and (2) reduction in risk of major acute coronary events. This study will close after the last patient has completed their scheduled 5-year visit, anticipated in August 2005. The final study is an active comparator trial of 19,747 women on either raloxifene HCL or tamoxifen citrate conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and is identified as the P-2 trial, or STAR. It is anticipated that this trial will conclude in the spring of 2006.

**MEETING OBJECTIVES (from briefing document):**

To inform the Division on the status of studies completed and those concluding that will support the new indication, and to reach agreement with the Division on the initial organization and inclusion of materials in the sNDA.

**QUESTION for DISCUSSION with FDA RESPONSES and DECISIONS REACHED:**

Clinical Studies

1a. Section 3.3 of this briefing document outlines the studies to be included in the sNDA submission, specifically, Study GGGK, Study GGJY, Study GGIO, and the National Surgical Adjuvant Breast and Bowel Project's (NSABP's) P-2 Study of Tamoxifen and Raloxifene (STAR). These studies support the indication of first-line therapy for the reduction in risk (primary prevention) of invasive breast cancer in postmenopausal women for raloxifene hydrochloride (HCl). Does FDA agree that these studies will support the proposed label indication?

FDA: Yes. It is possible that data from the STAR trial, if positive, can be used in conjunction with the results from the MORE/CORE and RUTH trials to support the reduction in the incidence of invasive breast cancer indication.

1b. Does FDA agree with inclusion of only the 4-year clinical study report (CSR) for Study GGGK in the sNDA, as described in Section 3.3 of this briefing document?

FDA: No. You should submit a complete 4-year CSR to include the data from the 48 month treatment and the extension phase. This CSR should include patient narratives and CRFs through the 4th year. In addition to your proposed definition for notable patients for studies GGGK (MORE), GGJH (CORE) and GGIO (RUTH) you should include CRFs and patient narratives for patients with invasive breast cancer. Please submit baseline mammogram reports, abnormal mammogram and pathology reports (for benign or malignant processes) at the time of the NDA submission.

*Discussion:*

- *The sponsor will submit the clinical study reports for the treatment and extension phase for GGGK trial.*
- *The sponsor will submit 48 months of patient narratives and CRFs for GGGK for deaths, breast cancer events and SAEs.*
- *The FDA will get back to the sponsor regarding the benign datasets. The sponsor will provide the algorithm used in determining the benign processes.*
- *The sponsor and FDA agreed that all information regarding malignant processes will be provided.*

Study–Specific Questions

2a. Does FDA agree with the criteria proposed in Section 3.4.1.2 of this briefing document to define notable patients for Study GGIO?

**FDA: No. Notable deaths should include all patients who died on study regardless of the cause. Please also include CRFs and patient narratives for patients with invasive breast cancer.**

*Discussion:*

- *The sponsor agreed to submit notable deaths for all patients who died on study regardless of the cause.*
- *CRFs and patient narratives are not required for discontinuation due to non-serious AEs. A line listing identifying these patients will be provided.*

2b. Does FDA agree with the proposal in Sections 3.4.1.1 and 3.4.1.2 of this briefing document for providing CRFs for Studies GGGK, GGJY, and GGIO?

FDA: Please send a blank CRF sample for each study so we can determine which sections are critical for the NDA review and which sections could be available upon request.

*Discussion:*

- *The sponsor will provide a hard copy of a CRF sample for the RUTH trial. CRF's for MORE and CORE studies have already been scanned so selectively submitting certain sections only will not be practical.*

Format of Study Datasets

3. Does FDA agree that submission of datasets from Studies GGGK, GGJY, and GGIO (see Section 3.4.2 of this briefing document) in the Study Data Tabulation Model (SDTM) format is not required?

FDA: Yes. SDTM is an allowable format, not a required one. Please send a sample of one of the studies datasets, (preferable a dataset containing the primary endpoint,) so we can give you feedback regarding the format.

*Discussion;*

- *The sponsor will submit a sample of the studies datasets.*

Administrative Issues

4a. Given the intended patient population of postmenopausal women, Lilly seeks a waiver from conducting pediatric studies for this indication, as described in section 3.4.3.1 of this briefing document. Does FDA agree that Lilly's request for a waiver will be granted?

FDA: Yes, please submit a formal request.

4b. Does FDA agree that there is no need for a thorough QT/QTc study to support this sNDA, based on the extensive patient exposure and available safety data of raloxifene (see Section 3.4.3.2 of this briefing document)?

FDA: Yes.

Statistical Analysis Plan

5a. Does FDA agree with the censoring rules for the purposes of the time-to-first-event analyses, as defined in Section 3.4.4.1.1 in this briefing document and in Section 9.7.1.1.1 of the SAP for Study GGIO (Appendix 4)?

FDA: The censoring rule for non-mortality time-to-event analyses is acceptable. However, for the time-to-event analyses of mortality, if patients fail to complete the protocol, we suggest that the censoring date will be defined as the last date at which the patient is known to be alive (visits or other form of contact).

*Discussion:*

- *The sponsor agreed to the FDA's response to add additional clarity to the SAP.*

5b. Does FDA agree with the planned sensitivity analyses to support the efficacy analysis of the breast cancer primary endpoint, as outlined in Section 3.4.4.1.2 of this briefing document, and in Section 9.7.1.12.1.1.3 of the SAP for Study GGIO (Appendix 4)?

FDA: Yes. The planned sensitivity analyses can be considered as exploratory only. If the breast cancer primary endpoint analysis is positive, these sensitivity analyses can be used to support the efficacy analysis of the breast cancer primary endpoint.

5c. Does FDA agree with use of a Fisher's Exact test instead of the Cochran-Mantel-Haenszel (CMH) test for comparison of the occurrence of treatment emergent adverse events (TEAEs), as outlined in Section 3.4.4.1.3 of this briefing document, and in Section 9.7.1.13.1 of the SAP for Study GGIO (Appendix 4)?

FDA: Since the CMH test is specified for comparison of the occurrence of TEAEs in the original protocol, we strongly suggest keeping this test to avoid a post-hoc definition in the statistical analysis plan.

*Discussion:*

- *The sponsor agrees to maintain the CMH test. The statistical analysis plan specified prior to data lock and before unblinding will not be considered as post-hoc. No need to report Breslow –Day.*

5d. Does FDA agree with use of a ranked one-way analysis of variance (ANOVA) model instead of the two-way ANOVA model for analyses of the changes from baseline of the safety laboratory data and vital signs, as outlined in Section 3.4.4.1.3 of this briefing document, and in Sections 9.7.1.13.2 and 9.7.1.13.3 of the SAP for Study GGIO (Appendix 4)?

FDA: For the same reason in our response to Q 5c, we strongly suggest keeping the two-way ANOVA model for analyses of the changes from baseline of the safety laboratory data and vital signs to avoid a post-hoc definition in the statistical analysis plan.

*Discussion:*

- *The FDA agreed with the sponsor proposal to change the current SAP from the 2-way ANOVA to the ranked 1-way ANOVA.*

5e. Lilly has provided the statistical analysis plan (SAP) for the GGIO CSR in Appendix 4. Does FDA have any comments on the SAP?

FDA: We have the following comments for the proposed SAP.

1. If you plan to make claims based on secondary endpoints, you need to specify an adjustment for the multiple comparisons of secondary endpoints or a priority analysis procedure for the secondary endpoint analyses.

2. Some additional analyses for the primary efficacy endpoints are planned in the SAP. You need to be aware that any additional analysis is for supportive purposes only. The final efficacy claim should be based on the non-stratified log-rank test for the primary endpoints which have been specified in the protocol.

3. Some secondary endpoints and subgroup analyses plan are also included in the protocol. However, the secondary endpoints and subgroup analyses should be considered as the exploratory analyses only. You need to be aware that no efficacy results can be claimed based on any secondary or subgroup analysis if the primary endpoint fails to show statistical significance.

Integrated Review of Safety

6a. Lilly plans to report adverse events (AEs) from Study GGGK, as described in Section 3.4.4.2 of this briefing document, using events re-coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA), as part of the Integrated Review of Safety. Does FDA have any comment?

FDA: We agree with the proposed plan.

6b. Based on the differences among the studies noted in Section 3.4.4.2 of this briefing document, does FDA agree that it is acceptable to present safety data from Studies GGGK, GGJY, GGIO, and the NSABP Study P-2 in a side-by-side format to facilitate comparison of safety results across these major trials, rather than pooling the study data?

FDA: We agree with the proposed plan.

**ACTION ITEMS:**

1. The sponsor will submit the clinical study reports for the treatment and extension phase for GGGK trial.

2. The sponsor will submit 48 months of patient narratives and CRF's for GGGK for deaths, breast cancer events and SAEs.

3. The FDA will get back to the sponsor regarding the benign datasets. The sponsor will provided the algorithm used in determining the benign processes.

4. The sponsor will submit notable deaths for all patients who died on study regardless of the cause.

5. The sponsor will provide a hard copy of a CRF sample for the RUTH trial.

6. The sponsor will submit a sample of the studies datasets.

7. The sponsor will add additional clarity to the SAP.

8. The sponsor will submit a proposal for the closed testing procedure for the RUTH trial.

There were no unresolved issues. The meeting concluded at 2:10 p.m.

*{See appended electronic signature page}*

Patty Garvey, R.Ph.
Regulatory Project Manager

Concurrence Chair:

*{See appended electronic signature page}*

Ramzi Dagher, M.D.
Medical Team Leader

*Concurrence: N. Li/Y. Wang – 5/27/05*

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/s/

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Ramzi Dagher
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# MEETING MINUTES

**MEETING DATE:** January 28, 1999 **TIME:** 2:00 PM **LOCATION:** Conf. Rm."G"

**IND:** 57,137

**Meeting Request Submission Date:** October 22, 1998
**Briefing Document Submission Date:** January 6, 1999
**Additional Submission Dates:** January 19, 1999

**DRUG:** Evista® (raloxifene hydrochloride)

**SPONSOR/APPLICANT:** Lilly Research Laboratories

**TYPE of MEETING:**

1. pre-NDA

2. Proposed Indication: For the reduction of the incidence of breast cancer in postmenopausal women with osteoporosis.

**FDA PARTICIPANTS:**

Robert Justice, M.D. -Acting Director, Division of Oncology Drug Products
Julie Beitz, M.D. -Acting Deputy Director
Richard Simon, D.Sc. -ODAC Consultant (via teleconference)
Grant Williams, M.D.- Medical Team Leader
Susan Honig, M.D. -Medical Officer
Gang Chen, Ph.D. -Statistical Team Leader
Alvis Dunson -Project Manager

**FDA PARTICIPANTS (Pre-Meeting Only):**

Robert Temple, M.D. -Director, Office of Drug Evaluation 1

**INDUSTRY PARTICIPANTS:**

Kapil Dhingra, M.D. -Senior Clinical Research Physician, Cancer Reseach
Stephen Eckert, Ph.D. -Senior Statistician
Gregory G. Enas, Ph.D. -Director, U.S. Regulator Affairs
Paul D. Gesellchen, Ph.D. -Senior Regulatory Scientist, U.S. Regulatory Affairs
Hunter Heath, M.D. -Director, Medical Division,
Gary V. Kaiser, Ph.D. -Director, Evista Product Team
Yili Lu, Ph.D. -Senior Statistician
Douglas B. Muchmore, M.D. -Physician Group Leader, Evista Product Team
Leo Plouffe Jr., M.D. -Senior Clinical Research Physician, Medical Division

| | |
|---|---|
| Teri Scott, MSN | -Clinical Research Adninistrator, Evista Product Team |
| Vikram Sinha, Ph.D. | -Senior Pharmacokineticist, Bioavailability and Pharmacokinetics |
| John D. Termine, Ph.D. | -Vice President, Lilly Research Laboratories |

**MEETING OBJECTIVES:**

To review breast cancer data that LILLY has collected during clinical trials with raloxifene hydrochloride.

**QUESTIONS for DISCUSSION with FDA RESPONSE, and DECISIONS REACED:**

**QUESTION 1:**

We believe the data presented in this briefing document provide compelling evidence that raloxifene reduces the incidence of breast cancer in postmenopausal women with osteoporosis and that it is highly unlikely that this evidence will lose statistical significance if data continue to be collected for several more years. Does the Agency concur with these conclusions?

**ANSWER 1:**

The answer to this question should be considered in several parts.

A. We have concerns about the credibility of the finding (fewer cases on the raloxifene arms compared to the placebo arm). The following issues represent critical problems in the clinical trial design that probably cannot be addressed retrospectively:

- Breast cancer incidence was not prospectively defined as an endpoint
  - ➢ It was included with a series of neuropsychiatric, cardiovascular, and cancer endpoints as the 7th "secondary objective"
- The protocol did not contain a prospectively defined statistical plan for this endpoint
- The FDA statisticians and the ODAC consultant, Richard Simon, have concerns about the validity of the statistical analysis, including but not limited to inappropriate pooling of the data
- The findings reported in the meeting package represent a premature analysis for this endpoint

- LILLY indicated that a pre-clinical model supported the hypothesis that the drug would prevent breast cancer.(i.e., there is a biologic rationale for the observed effect)

- LILLY suggests patient follow-up may be similar to the P-1 trial.

- Study H3S-MC-GGGK is the pivotal trial. Analysis will be limited to this study rather than based on pooled data.

B. The safety and efficacy data are inadequate to support the reported findings (additional data may be able to be retrieved by the sponsor):

- Mammographic evaluation at 1 year was optional. Participants may have had a mammogram up to 12 months prior to study entry. Thus, some participants may have had a 3-year gap in mammographic screening. This factor is of concern, since the follow-up on trial GGGK (as reported at ASCO and on page 1001) is approximately 3 years.
- Patients could refuse a mammogram and undergo breast ultrasound instead, an unreliable screening tool
- Breast examinations were optional during the trial, as was the physical examination
- Few breast cancer cases were diagnosed overall
- There is no information about baseline breast cancer risk factors nor any risk assessment results (such as a score calculated from the Gail model) that demonstrates comparability of the treatment groups, in terms of breast cancer risk, at baseline. This information is also important to ensure that the effect (if real) is seen across the study population and is not limited to a high-risk subset.
  - Information needed to calculate risk includes age at study entry, age at menarche, age at first live birth, presence/absence of lobular carcinoma in situ or atypical hyperplasia at study entry, number of breast biopsies prior to study entry, and family history. Calculation of a Gail model score is highly desirable. This information ensures that the level of risk was balanced between treatment arms
- After 3 years of treatment, the data safety monitoring board could recommend re-randomization for patients in ineffective treatment groups. We do not have information on the extent of cross-over in this trial.
- A risk-benefit assessment has not been provided, and may not be available from the collected data:
  - In the P-1 study, antiestrogen therapy with tamoxifen was shown to increase the incidence of deep vein thrombosis, pulmonary embolism, cataracts, stroke, and endometrial cancer.
  - The meeting package states that thromboembolic events were increased with raloxifene, but the numbers and types of events are not reported. No information is given about the rigor of follow-up of these potential adverse events.

- It is not known whether data on stroke were prospectively collected.
- The meeting package states that there was no increase in cataract formation or the need for cataract surgery, but it is not known whether reports of eye examinations were systematically and prospectively collected or whether spontaneous self-reporting was used.
- Gynecologic examinations were optional during the course of the study. Six cases of endometrial cancer were diagnosed on the raloxifene arms in study GGGK, compared to 4 on placebo (2:1 randomization in favor of raloxifene). It is not known how rigorously women were screened for endometrial cancer by their physicians or whether all cases were reported to the sponsor. It is unknown how many women entered the trial with a hysterectomy, and whether hysterectomized women were equally distributed between treatment arms.

- We do not have information on the drop-out rate and the reasons for study discontinuation. Unbalanced drop-out may affect ascertainment rates for breast cancer and for adverse events.

C. Even if data to address the items in part B were collected, there are additional limitations of the data:

- Follow-up is 3 years. Longer follow-up with a larger cohort of breast cancer cases will be needed to demonstrate a significant effect of raloxifene. Additional follow-up will only be helpful if the placebo group did not cross over to the raloxifene arms.
- Although not statistically significant, there were more cases of ER(-) breast cancer diagnosed on the raloxifene arms compared to the placebo arm, both in the pooled analysis and in the analysis of GGGK alone. This finding may reflect a non-significant difference that resulted from small numbers, or may represent an important adverse effect of raloxifene. The possibility that raloxifene induces a more aggressive breast cancer phenotype is of concern.
- The proposed indication would include the entire population of postmenopausal women with osteoporosis. Safety remains a major public health concern in potentially broadening the indication beyond that approved for tamoxifen. Thromboembolic events in particular need to be documented, and a risk-benefit analysis would be required to demonstrate a net benefit of raloxifene therapy in women whose major risk is for complications of osteoporosis, not breast cancer.

- LILLY will submit information that addresses some of the points in Part B.

**QUESTION 2:**

Based on the information that has been provided in this briefing document, would the Agency support an NDA submission which would seek an indication for the reduction in incidence of invasive breast cancer in postmenopausal women with osteoporosis (e.g., the patient population that has been studied)?

**ANSWER 2:**

No, we would not. This trial might be supportive if all questions/deficiencies are adequately addressed. We believe that the results of the STAR trial are necessary to support an application.

**QUESTION 3:**

If the Agency does believe that a submission is warranted at this time, what specific information would be required in the submission?

**ANSWER 3:**

Not applicable.

**QUESTION 4:**

If the Agency believes that a submission is not warranted at this time, what additional information would be required before a submission would be appropriate?

**ANSWER 4:**

See question 1.

**QUESTION 5:**

As discussed in Section 5 of the briefing document, the sponsor considers the intent-to-treat analysis to be the most appropriate method for reporting these data. Does the Agency believe that the sponsor should continue to report results from the adjudication process in addition to the primary intent-to-treat analysis? Is so, are there any aspects of the adjudication process which are not essential?

**ANSWER 5:**

The intent-to-treat analysis is generally considered as the primary analysis by the Agency. However, in study GGGK, the largest trial with the majority of the reported breast cancer cases, there were gaps in mammographic screening. For this reason, the adjudication process is important in assessing whether or not the cancers pre-dated study entry and whether there is an imbalance in the number of women with breast cancer at baseline between treatment arms.

The other responsibilities of the adjudication panel include confirmation of a breast cancer diagnosis and determining whether the cancer is invasive or non-invasive. These functions are an integral part of evaluating the endpoint of interest.

Analyses should be performed using the intent-to-treat population and the adjudicated ("evaluable") population.

- Adjudication process should be used as the primary analysis for breast cancer.
- FDA will review the RUTH trial to determine the adequacy of breast cancer data collection and analysis plans.
- LILLY will propose a final breast cancer analysis plan for the MOORE trial.

The meeting was concluded at 3:40 pm.

2/17/99
Alvis Dunson, Project Manager
Minutes preparer

Concurrence Chair: Susan Honig M.D.
Susan Honig, M.D. 2/17/99
Medical Officer