Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

March 20, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attn: Mr. Alvis Dunson, Project Manager
1451 Rockville Pike
Rockville, Maryland 20852-1448

Meeting Minutes

LY231514 (MTA, MultiTargeted Antifolate); IND # 40,061 Serial No.: 216
Meeting Minutes from the March 1, 2000 Meeting to Discuss Vitamin Supplementation in the Ongoing Mesothelioma Registration Trial

Reference is made to the meeting between the Division of Oncology Drug Products (DODP) and Eli Lilly on March 1, 2000 to discuss the issue of vitamin supplementation in the mesothelioma registration trial (H3E-MC-JMCH; JMCH for brevity) for LY231514. We thank the FDA for granting this meeting and for their valuable suggestions at the meeting.

Enclosed are meeting minutes from the March 1 meeting (Attachment 1). These minutes reflect the agreed-to minutes that were shown on the acetates during the minutes and also provided to Lilly in hard copy by Alvis Dunson of DODP at the conclusion of the meeting.

In addition as DODP works toward providing the official meeting minutes of the March 1 meeting, Lilly would like to ask for consideration of the following clarifications and additions to the minutes:

For Response to Question 1a:

Lilly would ask that it be noted that the FDA agreed that if a survival benefit for the LY231514 arm be shown at the interim analysis for the mesothelioma registration trial (where 150 patients have been supplemented with vitamins) that

a submission may be made for this indication based on these data provided that vitamin supplementation did not have any negative impact on survival.

For Response to Question 2:

Lilly is attempting to provide standardized doses of folic acid for each country in which the trial is being conducted, and the dose of folic acid will be captured on the patients' case report forms. Protocol JMCH(d) states for the folic acid dose: "Folic acid will be supplied locally as one of the following options, with preference in order from option #1 to option #3: 1.) 350 – 600 μg folic acid. 2.) A multivitamin containing folic acid in the range of 350 μg to 600 μg is acceptable if option #1 is not available. 3.) A dose of folic acid between 350 μg and 1000 μg is acceptable only if neither option #1 or option #2 is available." Given the global nature of our registration trial and the eventual global availability of LY231514, Lilly feels that the dose of folic acid must be recommended as a range of acceptable doses. From our research it is clear that low-dose folic acid is available in a wide variety of preparations and doses worldwide and folic acid would not be available in some countries if the specified dose was other than that available in that country.

Lilly would like to make the clarification that it is only tracking supplemental doses of folic acid, and it is not attempting to track folic acid that is ingested through the food of patients.

For Response to Question 3b:

Lilly proposes that the Consensus agreement to question 3a should read: Patients with any prior chemotherapy regimen other than one containing taxotere would be potentially eligible.

Patients who progress on prior therapy will be acceptable in the labeling if Lilly excludes such patients from the trial.

Lilly will make a proposal for a study in 1st line NSCLC with LY231514 in combination after completion of the appropriate phase 2 study.

Also please note that in response to Question 3b, Lilly made a number of comments concerning supporting trials in our recent IND submission (serial no. 212 on March 8, 2000).

DODP provided at the March 1 meeting "Additional Comments" and also the DODP responses and questions on protocol amendment H3E-MC-JMCH(d) (protocol amendment JMCH(d) was submitted to the IND as serial no. 206 on

February 14, 2000). Discussions on the "Additional Comments" and the JMCH(d) protocol were held at the March 1 meeting, but these discussions were not captured in the minutes. The latter part of Attachment 1 provides Lilly responses to the questions and comments raised in these two additional DODP documents. Attachment 2 that is enclosed contains the specific Lilly response to the Clinical Benefit Response table that was discussed at the meeting. Attachment 2 also contains the Lilly response providing the detailed statistical plan for the analysis of the impact of vitamins in the mesothelioma trial JMCH. DODP requested this analysis in their response to Questions 1a and 2 at the March 1 meeting, and this was agreed to by Lilly.

We again thank the Division of Oncology Drug Products for their assistance in the development of LY231514. Please call Mr. John Worzalla at (317) 276-5052 or me at (317) 277-3799 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

Enclosures (2)
Attachment 1 – Lilly version of March 1 meeting minutes
Attachment 2 – Lilly response regarding Clinical Benefit Response and the statistical analysis of the effects of vitamins for trial JMCH

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

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: September 30, 2002.
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
ELI LILLY AND COMPANY

2. DATE OF SUBMISSION
March 20, 2000

3. ADDRESS *(Number, Street, City, State and Zip Code)*
Lilly Corporate Center
Indianapolis, IN 46285

4. TELEPHONE NUMBER *(Include Area Code)*
317) 276-2000

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Compound LY231514 Disodium (MTA)

6. IND NUMBER *(If previously assigned)*
IND 40,061

7. INDICATION(S) *(Covered by this submission)*
Cancer

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER NA *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.
NA

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
2 1 6

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*
☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☒ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

FORM FDA 1571 (10/99) PREVIOUS EDITION IS OBSOLETE. PAGE 1 OF 2

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12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☐ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☒ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☒ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

James Rusthoven, M.D.

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Same as #14 Above

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Gregory T. Brophy, Ph.D., Director U.S. Regulatory Affairs		
18. ADDRESS *(Number, Street, City, State and Zip Code)*	**19. TELEPHONE NUMBER** *(Include Area Code)*	**20. DATE**
Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285	(317) 277-3799	3/20/2000

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
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Rockville, MD 20852-1448

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CDER (HFD-94)
5516 Nicholson Lane
Kensington, MD 20895

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