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Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

November 18, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncologic Drug Products, HFD-150
Attn: Ms. Linda McCollum, CSO
1451 Rockville Pike
Rockville, Maryland 20852-1448

IND # 40,061 - LY231514 **Serial No.: 137**
End-of-Phase 2 Meeting Minutes
Compound LY231514 (MTA, Multitargeted Antifolate)

Enclosed are Lilly's minutes for the End-of-Phase 2 meetings held on September 23 (Biopharmaceutics) and September 25 (Clinical) 1998 to discuss LY231514 with members of the Division of Oncologic Drug Products. We sincerely appreciate the willingness of the Division members to meet with us and to offer advice regarding the development of this investigational drug.

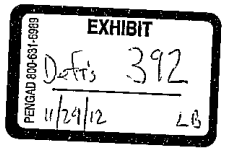
We respectfully request a copy of the Division's meeting minutes when they are available.

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



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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: December 31, 1999
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
November 18, 1998

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 _____ *(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 submission should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
137

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 CFR 312.7(d)

FOR FDA USE ONLY

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

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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 [21CFR 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

NA

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

Steven J. Nicol, 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	Gregory D Enos	
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	11/18/98

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

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DHHS Reports Clearance Officer
Paperwork Reduction Project 0910-0014
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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Please DO NOT RETURN this application to this address.

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LY231514 (MTA) End of Phase 2 Meeting with the FDA
Biopharmaceutics Issues – Wed. Sept. 23, 1998 at FDA

FDA Participants: Division of Oncology Drug Products
Robert White, M.D., Medical Reviewer
Atiq Rahman, Ph.D., Biopharm Team Leader
Liang Zhou, Ph.D., Chemistry Team Leader
Linda McCollum, Consumer Safety Officer
Lilly Participants:
Steven Hamburger, Ph.D., U.S. Regulatory Affairs
Robert D Johnson, Ph.D., Pharmacokineticist
Mary Pat Knadler, Ph.D., Drug Disposition
Clet Niyikiza, Ph.D., Statistician
David Seitz, M.D., Ph.D., Medical Advisor
Jackie Walling, Ph.D., Director of Science, MTA Team
John Worzalla, U.S. Regulatory Affairs
Lilly Consultant:
Sharyn Baker, Pharm.D., Cancer Therapy and Research Center, San Antonio Cancer Institute

Meeting Request Submission Date: July 13, 1998
Briefing Document Submission Date: July 29, 1998
Additional Submission Dates: Sept. 8, 1998

Meeting Minutes:

Issue 4: MTA and NSAIDS

The FDA showed the following acetate:
"MTA and NSAIDS – Currently the Phase 2 studies and all registration directed studies have excluded those patients who have a need for chronic administration of NSAIDS or aspirin. Do you agree that if this study shows no pharmacokinetic interaction that this will be sufficient evidence to take the course of action outlined, i.e., remove the exclusion criterion, and to prevent this exclusion from being part of the label?"

4A NO. The decision to remove exclusion criterion for Ibuprofen will depend on the outcome of the study. Depending on the PK parameter variability, sample size of the proposed interactions study may be inadequate to rule out absence of interaction between MTA and Ibuprofen. Please submit a detailed protocol for Agency Review.

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