MEETING MINUTES

MEETING DATE: March 1, 2000 **TIME:** 10:30 AM **LOCATION:** Conf. Rm. "G"

IND: 40,061

Meeting Request Submission Date: January 25, 2000
Briefing Document Submission Date: February 16, 2000
Additional Submission Dates: None

DRUG: MTA (MultiTargeted Antifolate, LY231514)

SPONSOR/APPLICANT: Lilly Research Laboratories

TYPE of MEETING:

1. End of Phase 2 (2nd meeting)
2. Proposed Indication: For the use of MTA in patients with mesothelioma.

FDA PARTICIPANTS:

Richard Pazdur, M.D. - Director, Division of Oncology Drug Products
James Krook, M.D. - FDA ODAC Member – pre-meetin only
John Johnson, M.D. - Medical Team Leader
Robert White, M.D. - Medical Officer
David Smith, Ph.D. - Statistical Team Leader
Doo Young Lee-Ham, Ph.D - Pharmacology/Toxicology Reviewer
Eric Duffy, Ph.D. – Chemistry Team Leader
Alvis Dunson -Project Manager

INDUSTRY PARTICIPANTS:

Gregory Brophy, Ph.D. – Director, North American Regulatory Affairs, Cancer
Axel Hanauske, M.D. – Medical Director, MTA Product Team
Clet Niyikiza, Ph.D. - Research Scientist, Statistician
Paolo Paoletti, M.D. – MTA Product Team Leader
James Rusthoven, M.D. - Clinical Research Physician
Brian Stuglik - MTA Product Team, Chief Operating Officer
John Worzalla - Senior Regulatory Reprensative
Paul A. Bunn, Jr., M.D. – Consultant, University of Colorado Health Science Center
Hilary Calvert, M.D. – Consultant, University of Newcastle, U.K.

TRIAL EXHIBIT 2102

MEETING OBJECTIVES:

To discuss changes of vitamin supplementation instituted for the ongoing mesothelioma registration trial.

QUESTIONS for DISCUSSION with FDA RESPONSE, and DECISIONS REACED:

Question 1a. Does the FDA agree that toxicity and mortality data support a programmatic intervention to improve patient safety in LY231514 trials and that daily low dose folic acid supplementation appropriately serves this purpose?

FDA RESPONSE: The addition of vitamins to the pivotal trial(s) is at Lilly's risk. We share your concerns about toxicity; your options include:

1. Temporarily closing the trial and conducting a new Phase 1 trial with MTA + vitamins.
2. Stop the current trial and open a trial using a new protocol and new dose.
3. Continue the current trial with the addition of vitamins and with a recalculated sample size to provide adequate power for comparisons.

- Lilly agrees to option #3.
- After approximately 150 patients are treated on the revised protocol with vitamin supplementation, a survival analyses will be done pooling the approximately 150 patients with vitamin supplementation with the approximately 150 patients without vitamin supplementation. Lilly will soon submit to FDA a prospective detailed plan for this analysis.

Question 1b. Does the FDA agree that a randomized trial comparing patients receiving LY231514 with and without vitamins is no longer feasible or advisable given the demonstrated toxicity risks to LY231514 patients?

FDA RESPONSE. See 1a.

Question 2. Do the proposed analyses of efficacy and safety described here for Study JMCH sufficiently address the impact of the folic acid supplementation intervention on the results of this trial such that the trial will qualify as a randomized, well-controlled trial for the mesothelioma and NSCLC indications?

FDA RESPONSE. We do not believe the proposed changes would allow us to adequately determine the benefit of adding vitamins to this trial. The proposed package for registering MTA is weakened by these changes. Tampering with the pivotal trials does not strengthen the case for well-controlled trials. There is no standard dose of vitamins administered to patients and we believe this is problematic. Please specify exact dose(s).

- Lilly will provide dosing information for each patient (i.e., patient diary, pill count).
- Lilly will provide a revised statistical plan before proceeding with this trial. Specifically, the plan should contain information with respect to interim analysis on survival, and the statistics tests proposed for analyzing vitamin supplementation. A Type I Error penalty is necessary if the trial should be stopped.

Question 3a. Does the agency support the replacement of vinorelbine with docetaxel as the comparator in the JMBQ study?

FDA RESPONSE. No. A new trial should be initiated and a new protocol should be submitted. Does the proposed sample size have sufficient power to demonstrate superiority of MTA over taxotere? The trial is too small to demonstrate equivalence.

Question 3b. Does the agency agree that these modification will allow Study JMBQ to continue to serve the role of a randomized, well-controlled trial in support of the mesothelioma and second-line NSCLC indications, as previously discussed in the End-of Phase II meeting in June of 1999?

FDA RESPONSE. We remind you that two trials in NSCLC will be required to obtain this claim. In addition, your eligibility in the lung cancer trial should be similar to the taxotere trial in order to gain approval based on equivalence.

- Taxotere is an acceptable comparator.
- Taxol prior therapy is acceptable with stratification.
- Patients who progress on prior therapy will be acceptable in the labeling.
- Sponsor will submit a proposal for 1st line NSCLC.
- FDA will get back to sponsor on the number of trials in NSCLC and no commitment is made at this meeting.

ADDITIONAL COMMENTS.

1. Your proposed clinical benefit response is not acceptable. At a mininum, you must use the Agency's Clinical Benefit Response table listed below for the mesothelioma trial. This table is also listed in the meeting minutes dated June 25, 1999. Please note that clinical benefit response alone, as measured in this study, will not be a basis for approval.

CLINICAL BENEFIT RESPONSE

	Pancreas ca GEMZAR	Mesothelioma MTA	**FDA Recommendations for Mesothelioma trial**
change in pain intensity	≥ 50% reduction	≥ 10 mm decrease on a 100 mm visual analog scale	**≥ 50% reduction**
change in analgesic consumption	≥ 50% reduction	≥ 30% reduction	**≥ 50% reduction**
change in performance status (Karnofsky)	≥ 20 point improvement	≥ 20 point improvement	≥ 20point improvement
weight change	≥ 7% increase	N/A	
Dyspnea		≥ 10 mm decrease on a 100 mm visual analog scale	**≥ 50% reduction**

2. More justification should be submitted than you have presently for the use of MTA + vitamins.

THE PROTOCOL—H3E-JMCH
2/14/99; serial #206

Revised Protocol Sections

page 3:

A rationale for the B12 injection has not been provided.

Protocol H3E-MC-JMCH (d)

Page 16: A rationale for the dose, timing, and schedule of administration of the vitamins has not been provided. What is the evidence that folate/B12 repletion will not stimulate tumor growth prior to the administration of chemotherapy?

Page 20: A creatinine clearance derived with urine collection and serum creatinine may achieve the goal of patient safety better than calculated creatinine clearance derived by formula and serum creatinine.

Page 30: Are leucovorin and thymidine rescue still necessary if vitamins are added to the protocol?

Page 38: In the Disease Status section, delete references to photographs of skin and oral lesions.

Page 51: Data Analysis Methods: there are no specifics for the evaluation of the impact of vitamins on efficacy endpoints.

Page 52: An intent-to-treat analysis should also be performed.

Page 54-56: Since the plan is to complete the accrual of patients to the pivotal trial, the rationale for the interim analysis is weak. Lilly may believe that evidence in their interim analysis may support early filing and stopping of the trial. The FDA is not convinced that clinical benefit response data will warrant early filing. The interim analysis for efficacy endpoints should be deleted. Alternatively, Lilly may accrue all the required patients and then perform an interim analysis of the first 75 patients per arm.

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