

## Meeting Minutes

**Date:** 9 December 2004  
**Sponsor:** Lilly Research Laboratories  
**Subject:** CS-747 (LY640315)  
IND 63,449  
**Type of Meeting:** B

### FDA Participants:

Norman Stockbridge, M.D., Ph.D., HFD-110, Acting Director, Div. of Cardio-Renal Drug Products  
Thomas Marciniak M.D., HFD-110, Acting Deputy Division Dir., Div. of Cardio-Renal Drug Products  
Mehul Mehta, Ph.D., Director, HFD-860, Division of Pharmacological Evaluation I  
Patrick Marroum, Ph.D., HFD-860, Team Leader, Clinical Pharmacology/ Biopharmaceutics  
Elena Mishina, Ph.D., HFD-860, Clinical Pharmacology/ BioPharmaceutics  
Belay Tesfamariam, Ph.D., HFD-110, Pharmacologist  
Edward J. Fromm, R.Ph., Chief, Project Management Staff  
LCDR Cheryl Ann Borden, MSN, R.N., Regulatory Health Project manager

### Sponsor Participants:

Elizabeth Bearby, Pharm.D.	Regulatory Fellow, US Regulatory Affairs
John T. Brandt, M.D.	Medical Fellow II, Diagnostic and Experimental Medicine
Nagy Farid, Ph.D.	Research Advisor, Drug Disposition, Cardiovascular
Mendel Jansen	PK/PPK/PD Scientist (Pharmacokineticist)
Gwen Krivi, Ph.D.	Cardiovascular Platform Leader
Christopher Payne	Senior Research Scientist, EU Program Phase Medicine
Debasish Roychowdhury, MD	Director, US Regulatory Affairs
David Small, Ph.D.	Principal Research Scientist, Global PK/PD
Ying Grace Li,	Asst Senior Statistical Analyst, Program Phase
Kenneth Winters, MD	Medical Fellow, CS-747 Product Team
Bernhardt G Zeiher, MD	Medical Director, CS-747 Product Team

### Sankyo Pharma participants:

Daniel Salazar, Ph.D.	Executive Director, Clinical Pharmacology and Pharmacokinetics
Howard Hoffman, MD	Executive Director, Regulatory Affairs

**BACKGROUND:** Eli Lilly and Company (Lilly), Sankyo, and the Thrombolysis in Myocardial Infarction (TIMI) Study Group have had three previous meetings with the FDA; An end End-of-Phase 1 meeting on 20 September 2002, a Protocol Guidance Meeting on 16 October 2003, and an End-of-Phase 2 meeting on 4 August 2004. In addition, Lilly and Sankyo met with the Division on 21 October 2004 to discuss the Special Protocol Assessment (SPA) for the Phase 3 Study TAAL.

The current proposed indication for CS-747 is:

1

b(4)

This meeting was requested by the sponsor to discuss the overall biopharmaceutics and clinical pharmacology development strategy to support registration of CS-747 (LY640315) in the treatment of patients with acute coronary syndrome undergoing PCI.

**DISCUSSION POINTS:**

**Biopharmaceutics Registration Package and Clinical Pharmacology Study Plans**

**Question 1:** Does the Agency agree that the biopharmaceutics package proposed as outlined for CS-747 in Section 5 of this briefing document is sufficient for registration?

**Division response:** Yes.

**Question 2:** Does the FDA agree that the bootstrap analysis and covariate screen from Study TAAD in patients with stable atherosclerosis, as well as the intended analysis of exposure-response data from the Phase 3 study support the proposal that a pharmacokinetic study in elderly patients is not required for registration?

**Division response:** Yes.

**Question 3:** Does the FDA agree with the proposed design for the renal impairment study?

**Division response:** Yes.

**Question 4:** Does the FDA agree that the proposed plan to evaluate patients with moderate hepatic impairment is sufficient for registration?

**Division response:** Yes.

**Question 5:** Does the FDA agree that the proposed interaction study with atorvastatin is sufficient to support labeling regarding statin coadministration?

**Division response:** That is acceptable. Dr Stockbridge mentioned that, although a separate study is acceptable, there may be a sufficient number of subjects in the phase 3 trials who are on atorvastatin such that an interaction could be ruled out using sparse sampling.

**Question 6:** Does the FDA agree with the design of the definitive food effect study?

**Division response:** The design is acceptable. We do not think the sponsor needs to pursue another food effect study.

**Question 7:** Does the FDA agree with the sponsors' proposal to extrapolate the 60-mg dose results to the 10-mg maintenance dose using the PK/PD model?

**Division response:** Yes.

#### **Evaluation of Exposure in the Phase 3 Study**

**Question 8:** Does the FDA agree with the sponsors' plan to evaluate exposure of the active metabolite R-138727 in the Phase 3 Study TAAL in a subset of patients by collecting pharmacokinetic samples of the two inactive metabolites, R-119251 and R-106583, and predicting the exposure to the active metabolite R-138727?

The following slides were presented by the sponsor:

#### **PK Proposal for TAAL**

~1500 patients (750 on CS-747)

5 PK samples collected

- 2 in the acute phase
- 3 in the maintenance phase

Measure inactive metabolites R-119251 and R-106583 to predict the concentration of R-138727

A slide was presented by the sponsor depicting *Preliminary Correlations Between R-138727 and R-106583 / R-119251; All Data.*

**Division response:** This plan is acceptable.

**Question 9:** Does the Agency agree with the proposal to collect pharmacokinetic samples in patients who experience a Serious Adverse Event in the TAAL trial as outlined above?

**Division response:** Yes.

**Question 10:** Understanding a full discussion regarding the submission will be the subject of a future pre-NDA meeting, can the agency provide initial comments regarding the proposal outlined above?

The following clarification slide was presented by the sponsor:

Submission:

- Complete overall characterization and PK analysis of the inactive metabolites

- Complete analysis of pre-defined conventional covariates (for example: age, gender, race)

120 Day Safety Update or in Response to Questions

- Further analysis of data already provided – **No new data**
- Results based on additional evaluation of the relationship between exposure and specific safety and efficacy outcomes found to be clinically important in the Phase 3 study

**Division response:** The proposal is reasonable.

**Question 11:** Does FDA agree with the sponsor that the Special Protocol Assessment is considered finalized per the discussion at the 21 October 2004 meeting?

**Division response:** Yes.

**Proposal for the Thorough Clinical QT/QTc Study**

**Question 12:** Does the FDA agree with the proposed design and statistical analysis for the thorough clinical QT/QTc study?

Dr. Stockbridge requested clarification on whether the sponsor planned to collect PK data during the thorough QT study. The sponsor responded the PK time points will correlate to the ECGs. There will also be analysis of the concentration/QT relationships.

Dr. Stockbridge recommended that they do blood draws on baseline days at the same times as the PK sampling during the treatment days

**Division response:** The proposed design and statistical analysis are acceptable.

**Question 13:** Does the FDA agree that 80 mg of CS-747 is the appropriate dose to evaluate in this study?

**Division response:** Yes.

**Question 14:** Does the FDA agree that the entire proposed QT/QTc package is sufficient for registration?

**Division response:** Yes, the package looks entirely adequate.

**Pharmacodynamic (PD) Effect-Based Evaluation of Intrinsic and Extrinsic Factors**

**Question 15:** The sponsors request confirmation that change in platelet aggregation response is an appropriate way to assess the importance of changes in pharmacokinetic parameters.

**Division response:** We agree with this assessment.

**Question 16:** The sponsors request confirmation that a change of less than 10 percentage points in MPA is not considered clinically meaningful.

**Division response:** We agree with this assessment

**Question 17:** Does the FDA agree that an MPA-based assessment of pharmacokinetic effects, using a PK/PD model, is an appropriate way to interpret the clinical relevance of intrinsic and extrinsic factors on R-138727 pharmacokinetics?

**Division response:** The Division is in agreement. However, it is possible to make dosing adjustments based on exposure only.

**SUMMARY/ RECOMMENDATIONS:**

**Signature recorder :** (see appended electronic signature page)  
LCDR Cheryl Ann Borden, MSN, R.N.

**Concurrence, Chair:** (see appended electronic signature page)  
Norman Stockbridge, M.D., Ph.D.

**Draft:** 09 DEC 04    **Final:** 17 DEC 04

Routed:

EFromm: 12/10/04

BTesfamariam: 12/10/04

EMishina: 12/10/04

PMarroum: 12/9/04

MMehta: 12/13/04

TMarciniak: 12/14/04

NStockbridge: 12/17/04

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 63,449

Eli Lilly and Company  
Attention: Elizabeth C. Bearby, Pharm.D.  
Director, U.S. Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Dr. Bearby:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CS-747 (LY 640315).

We also refer to your amendment dated October 22, 2004 (serial # 084), containing your clarification of the responsibilities of the Data Monitoring Committee for the proposed Phase III trial (protocol H7T-MC-TAAL).

We have completed the clinical review of your submission and have agreed to the following:

1. Drug relatedness will be assessed by your clinical site investigator. The report may be upgraded if it is assessed as not drug related by the clinical site investigator to possibly drug related by Lilly's global product safety physician during a blinded review of the case.
2. The Division will receive some serious, unexpected, and possibly related adverse event reports in an unblinded fashion. This applies to CS-747 treated as well as patients treated with clopidogrel.

If you have any questions, please call Meg Pease-Fye, Regulatory Health Project Manager, at (301) 594-5327.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Acting Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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Norman Stockbridge  
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## Minutes of a Meeting

**Meeting Date:** October 21, 2004  
**Application:** IND 63,449  
CS-747 (LY640315)  
**Sponsor:** Eli Lilly  
**Type of Meeting:** A  
**Classification:** Guidance  
**Meeting Request:** October 7, 2004  
**Confirmation Faxed:** October 8, 2004  
**Mtg. Package Rec'd:** October 14, 2004

**Meeting Chair:** Thomas Marciniak, M.D.  
**Meeting Recorder:** Meg Pease-Fye, M.S.

### FDA Participants:

Thomas Marciniak, M.D., HFD-110, Acting Deputy, Division of Cardio-Renal Drug Products  
Mehul Mehta, Ph.D., Director, HFD-860, Division of Pharmacological Evaluation I  
Patrick Marroum, Ph.D., Team Leader, HFD-860, Clinical Pharmacology and Biopharmaceutics  
Jogarao Goburu, Ph.D., Team Leader, HFD-860, Pharmacometrics  
Elena Mishina, Ph.D., HFD-860, Clinical Pharmacology and Biopharmaceutics  
Meg Pease-Fye, M.S., HFD-110, Regulatory Health Project Manager

### Eli Lilly Participants:

Elizabeth Bearby, Pharm.D., Regulatory Fellow, U.S. Regulatory Affairs  
Nagy Farid, Ph.D., Research Advisor, Drug Disposition, Cardiovascular  
David Small, Ph.D., Principle Research Scientist, Global Pharmacokinetics/Pharmacodynamics  
Kenneth Winters, M.D., Medical Fellow, CS-747 Product Team  
Bernhardt Zeiher, M.D., Medical Director, CS-747 Product Team

### Sankyo Participants:

Daniel Salazar, Ph.D., Executive Director, Clinical Pharmacology and Pharmacokinetics  
Howard Hoffman, M.D., Executive Director, Regulatory Affairs

### Background:

This meeting was held to discuss Lilly's proposed Phase 3 study protocol, in particular, a relevant section of the Special Protocol response letter sent by the Division on October 1, 2004. The points in contention are the Agency recommendations to modify the protocol as follows:

1. Sparse blood sampling in a sufficient number of randomly selected patients to adequately characterize the following:
  - Exposure/response (efficacy and/or safety) relationship.
  - Various covariates that affect the exposure and or response to the drug.
2. A plasma sample should be collected for each subject who experiences a serious adverse event as close as possible to the occurrence of the event.
3. From each patient, 2-4 blood samples should be obtained randomly at each of the time intervals 0-4, 4-8, 8-16, and 16-24 hours post-dose at steady state. The last blood sampling may be scheduled immediately before the next dose (to measure the trough plasma concentrations).

Lilly intends to start this Phase 3 study in early November and is looking to reach an agreement with the Agency concerning the comments in the SPA response letter.

**Meeting:**

Lilly noted limitations to the collection of the data the Agency is requesting. Lilly's recent data show pharmacokinetic/pharmacodynamic results are based on studies that will be discussed more fully during the End of Phase 2A meeting scheduled for December 9, 2004. Briefly, the studies entail:

1. pharmacodynamics on inhibition of platelet aggregation
2. concomitant use of ketoconazole with CS-747 in healthy volunteers
3. concomitant aspirin use in patients with stable atherosclerosis

The proposed Phase 3 study will explore dose range, patient population, as well as loading and maintenance doses. The clinical endpoints are death, non-fatal MI and non-fatal stroke.

Dr. Marciniak explained that the Agency is looking for,

- characterization of the target population
- determination of any potential correlation with outcome events
- determination of any potential relationship between exposure and outcome

Lilly noted that, in terms of associated bleeding with CS-747, the loading dose is well tolerated. In the 30 day Phase 2 study of the maintenance dose, excess nose bleeds and GI bleeds were noted, so the Sponsor planned on using a lower (10 mg) dose for the Phase 3 study.

Lilly stated that they are trying to correlate the dose to the response and several sites had tried the described sampling but had encountered difficulties. The problem is that the active component in blood is not stable and it is necessary to derivatize it over the next 30 seconds after the blood draw. Not many centers are structured with the trained staff and equipment. Alternatively, they intend to pursue looking at an exposure/response relationship. Dr. Marciniak suggested trying to correlate drug levels with efficacy and with safety.

Dr. Gobburu noted that the issue does not pertain to PK and the covariates, but rather with patients with an increased or decreased concentration of drug, and whether or not these patients have adverse events. He noted his concern that there is only one dose being tested so having plasma samples would be helpful if the selected dose was wrong. Dr. Marroum noted that in the event that the tested dose is either ineffective or toxic, the plasma concentrations might help design future studies and would provide some explanation on the relationship between dose and effect. Lilly agreed, but argued that they had been unable to get meaningful data from samples taken from a number of patients, and was not assured about the validity of the data collected.

One problem Lilly noted was that transportation of a patient to the site for sample collection at the time of an event. Sampling must be relative to the event and not correspond to the dynamic effect. Dr. Gobburu suggested implementing procedures for blood chemistry, PK, and dosing in the protocol as a matter of course, with the understanding that these draws may get missed, but that these protocol violations would be the exception. The Division emphasized the importance of the sampling in terms of the long-term development of CS-747. Dr. Marroum asked, if the selected dose is not optimum, and an adjustment is necessary, how Lilly would determine the adjustment. Lilly responded that they would look at frequency of events, as they believe there is

no correlation between inhibition of platelet aggregation and bleeding events. They also believe that the loading and maintenance dose are better than the standard of care.

Dr. Goburu asked if any of the centers were equipped to do pharmacokinetic sampling. Lilly responded that, some are capable, but reiterated their concern about the numbers of samples needed in order to find meaningful data, adding that they are also concerned about having sufficient numbers. They believe that in order to determine a correlation between exposure and outcome, large numbers of patients are needed. Dr. Marroum noted the possibility of having too many factors, and still needing the type of data the Division is requesting. Lilly suggested that the one or two sites equipped to do PCI be the sites to perform the extensive sampling for PK/PD as a separate study. Dr. Marciniak acknowledged that this would be helpful and better than no data, adding that collecting these data can only help Lilly, and they would not be penalized. Lilly believes that the elective PCI population is more stable leading to more reliably performed sampling. Dr. Mehta suggested that Lilly start the separate PCI protocol and come back at a later date to discuss results/problems.

**Conclusions:**

1. The Agency believes that better characterization of PK/PD relationships are important for approval. Lilly will submit PK/PD data from the studies that have not yet been fully reported to the Agency prior to the December End of Phase 2A meeting. At that time, Lilly and the Agency will discuss then the adequacy of these data and the need for any additional studies.
2. Lilly will consider submitting for review a separate PCI protocol in efforts to collect the PK data requested by the Agency.

Date Minutes Drafted: October 28, 2004  
Date Minutes Finalized: November 4, 2004

Signature minutes preparer: \_\_\_\_\_  
Meg Pease-Fye, M.S.

Concurrence, Chair: \_\_\_\_\_  
Thomas Marciniak, M.D.

Reviewed:  
T. Marciniak 11/3/04  
P. Marroum 11/1/2004  
J. Goburu 11/1/2004  
E. Mishina 11/1/2004

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Thomas Marciniak  
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