



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 63,449

Eli Lilly and Company  
Attention: Peter Morrow  
Manager, U.S. Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Mr. Morrow:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for prasugrel (CS-747) 5-mg and 10-mg Tablets.

We also refer to your amendment, dated August 22, 2005 (serial # 183), containing briefing materials for a scheduled meeting.

We have completed the reviews of your submission and have the following comments and requests for additional information. Please note that these requests are not clinical hold issues. However, response to them is requested.

Chemistry:

- Since the 5-mg tablet is a different formulation than the 10-mg tablet and the container closure system is not yet known to be optimized in terms of protection aspects, it is expected that you will follow the ICH guidance registration provisions for placing the 5-mg tablet on stability (*i.e.*, see reference to the use of primary stability studies, p. 9). Please clarify how you intend to utilize the other referenced comparative studies that are intended to help support expiration date assignment of the 5-mg tablet.
- Please justify why it may be expected that there would be no differences between the degradation mechanisms and resultant degradation products for your proposed 5-mg tablet relative to the currently developed 10-mg tablet. Include clarifications relating to the extent to which there is similarity with respect to the manner that specific subject degradants of interest are in compliance with the ICH guidance provisions for both identification and qualification levels.
- Please justify why it is expected that the unit process manufacturing operations utilized for the 10-mg tablet are to be appropriate for the 5-mg tablet. Include understandings relating to the assessments of all critical manufacturing process variables in terms of their impact on drug product quality performance.
- Please explain how discerning is the dissolution rate procedure in terms of monitoring expected unwanted trending effects identified for critical control parameters. This will help in the interpretation of the outcome results of comparative studies.
- Please clarify how you intend to delineate analytically \_\_\_\_\_ effects in the planned storage-optional stability trials (*i.e.*, p. 24). For example, ratio effects can be calculated in comparative measurement of selected diagnostic peaks and variability limits utilized in assessment protocols.
- Please justify how you have harmonized the analytical methodologies used to monitor the stability of the 5-mg and 10-mg tablets. Include understandings relating to how these methodologies may have been initially optimized to allow for the discerning assessment for any unwanted trending effects.

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- Please justify why you do not utilize samples stored at accelerated conditions in your "In-Use" stability study since it would be expected that use of such an accelerated temperature would provide an opportunity to understand better any contributing temperature /heat impacting effects involved.

Clinical Pharmacology and Biopharmaceutics:

- This study will be adequate to characterize the relative bioavailability of the 5-mg tablet. The relative bioavailability study for the 5-mg tablet will not be sufficient to support the registration of the 5-mg dose strength. You will not use the 5-mg tablet in the pivotal clinical study; therefore, the effectiveness of this dose will not be assessed.

If you have any questions, please call:

Meg Pease-Fye, M.S.  
Regulatory Health Project Manager  
(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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/s/

Norman Stockbridge  
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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 (LY640315) 60 mg Tablets.

We also refer to your amendment dated July 6, 2005 (serial # 160), containing your proposal for an amendment options to the Phase 3 protocol H7T-MC-TAAL (TRITON-TIMI 38).

We have reviewed submission and have the following responses to your questions:

1. Does the Agency agree that it is acceptable for registration to amend the trial to change the loading dose of clopidogrel to include 600-mg by the choice of each individual clinical study site?

**Division comments:** The Division finds this acceptable.

2. Does the Agency agree that the primary efficacy analysis and key safety analysis for this amended design would be a comparison of prasugrel and the combined clopidogrel (300-mg and 600-mg loading dose/75-mg maintenance dose) treated?

**Division comments:** The Division agrees for the primary efficacy. For safety, both loading doses should be considered.

3. Does the Agency agree that statistical significance is not required for prasugrel versus clopidogrel subgroups (300/75-mg and 600/75-mg)?

**Division comments:** The Division agrees that statistical significance is not required for the subgroup.

4. Does the Agency accept the proposal to analyze the prasugrel safety data against the combined clopidogrel population?

**Division comments:** The Division agrees that this is acceptable.

5. Understanding that the labeling of prasugrel will depend on the clinical study results, does the Agency agree that the amendment proposal does not alter the targeted indication? Does the Agency agree that the clinical study section of the label would include the separate comparisons between prasugrel and the 300-mg and 600-mg doses and reflect the limitation of this comparison?

**Division comments:** You should submit your rationale for the inclusion of the 600-mg dose and the change in sample size in order to amend the specifications. A statistical analysis plan should be submitted and it should be clearly laid out how the assumptions have changed.

If you have any questions, please call:

Ms. Meg Pease-Fye, M.S.  
Regulatory Health Project Manager  
(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:** January 25, 2005  
**Application:** IND 63,449  
CS-747 (LY640315)  
**Sponsor:** Eli Lilly  
**Type of Meeting:** B  
**Classification:** End of Phase 2A - CMC  
**Meeting Request:** December 2, 2004  
**Confirmation Faxed:** December 15, 2004  
**Mtg. Package Received:** January, 2005

**Meeting Chair:** Kasturi Srinivasachar, Ph.D.  
**Meeting Recorder:** Meg Pease-Fye, M.S.

**FDA Participants:**

Kasturi Srinivasachar, Ph.D., Team Leader, Chemistry, HFD-810  
Stuart Zimmerman, Ph.D., Chemistry, HFD-810  
Raj Misra, Ph.D., Chemistry, HFD-810  
Belay Tesfamariam, Ph.D., HFD-110, Pharmacologist  
Meg Pease-Fye, M.S., HFD-110, Regulatory Health Project Manager

**Eli Lilly Participants:**

Sally Anliker, Ph.D., Manager, Regulatory Affairs – CMC  
Elizabeth Bearby, Pharm.D., Regulatory Fellow, U.S. Regulatory Affairs  
Mark Kryah, Manager, CMC Project Management  
Wayne Luke, Ph.D., Research Fellow, Chemical Process Development  
Dan Ness, D.V.M., Ph.D., Research Advisor, Toxicology - Cardiovascular Safety Assessment  
Neil Pearson, Research Scientist, Analytical Development - Drug Product  
Joerg Pfeifer, Ph.D., Principal Regulatory Scientist, Regulatory Affairs - CMC

**Sankyo Participants:**

Tomonori Konse, Ph.D., Group Director, Analytical and Quality Evaluation Research  
Laboratories  
Paulette F. Kosmoski, RAC, CQA, QMS-LA, Senior Director, CMC Regulatory Affairs

**Ube Participants:**

Takashi Kobayashi, Ph.D., Manager, Quality Control Group, Ube API & Intermediates Factory  
Shinji Takamura, Ph.D. Manager, API & Intermediates Business Unit  
Naoyuki Yokota, Principal Chemist, Process Chemistry Group, API Process Development Center

**Background:**

The objective of this meeting was to come to an agreement on CMC issues for the manufacturing process for CS-747. The proposed indication for CS-747 is for \_\_\_\_\_

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**Discussion Points:**

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**Question 2:** Does the Division agree with the design of the drug substance stability protocol for the primary stability batches?

**Division Response:** This is acceptable to the Division.

**Question 3.1:** Does the Division agree with the proposed control strategy for monitoring the purity of the drug product during the registration stability study?

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**Division Response:** The Division agrees with Lilly's approach to determining the degradant profile of the drug product although there is concern about the level and number of degradants. Lilly should continue to use methods in this regard.

**Question 3.2:** Does the Division agree with the design of the drug product stability protocol for the primary stability batches?

**Division Response:** The Division agrees.

**Question 4:** Does the Division agree to accept additional drug substance and drug product stability data during the NDA review period and agree that this does not constitute a major amendment necessitating an extension of the review clock?

**Division Response:** The Division agrees.

**Question 5:** Does the Division agree to the proposed impurities and degradation products qualification strategy?

**Discussion:** Dr. Tesfamariam asked about the difference in metabolites between animals and humans, noting that if the ratio is greater than the metabolites should be tested for toxicity. Lilly commented that there were no unique metabolites, that the metabolites seen in animals and in humans were the same.

**Division Response:** The Division agrees with the proposed qualification of impurities in drug substance and product (based on Q3A and Q3B).

It is recommended that metabolites accounting for plasma levels f the administered dose have safety testing performed as major metabolites. Appropriate studies for assessing metabolite safety include general toxicity testing (minimum 14 day animal study), genotoxicity (point mutation and chromosomal aberrations), embryo-fetal development assessment and carcinogenicity (case-by-case). Pharmacologically inactive metabolite does not preclude lack of potential toxicity.

Lilly is encouraged to identify any unique metabolite(s) and determine relative concentrations between animals used in non-clinical studies and humans to allow timely assessment of potential safety issues.

**Additional Issues:** Dr. Srinivasachar added that Lilly should determine particle size and include a test for this attribute with appropriate limits in the drug substance specifications.

**Conclusions:**

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- ——— degradation products should continue to be monitored and efforts should be made to minimize their formation
- Lilly will need to monitor metabolites for potential safety testing
- The Division agrees with Lilly's proposed drug substance and drug product stability protocols

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Date Minutes Drafted: January 27, 2005  
Date Minutes Finalized: February 16, 2005

Signature minutes preparer *{See appended electronic signature page}*  
Meg Pease-Fye, M.S.

Concurrence, Chair *{See appended electronic signature page}*  
Kasturi Srinivasachar, Ph.D.

Reviewed:  
K. Srinivasachar 2-15-05  
S. Zimmerman 1.27.05  
B. Tesfamariam 1/27/2005  
R. Misra 1/30/05

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/s/

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Margaret Pease-Fye  
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Kasturi Srinivasachar  
2/16/05 05:17:13 PM