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.

We also refer to your amendment dated July 12, 2006 (serial # 320), containing your request for clarification of the minutes from the meeting on June 20, 2006.

We have completed the review of your submission and have the following comments and clarifications.

Topic 1 – Proposed Indication and Study Design

Study TAAL (TRITON-TIMI 38) is an ongoing Phase 3 pivotal study in subjects presenting with acute coronary syndrome (ACS) and undergoing percutaneous coronary intervention (PCI). Study H7T-MC-TABY will be a Phase 3 pivotal trial in patients with acute coronary syndrome who are medically managed.

Sponsor's question: Can TABY be coupled with TAAL to argue for superiority of prasugrel over clopidogrel?

FDA Response:
Although TAAL and TABY have different designs and target populations, if both studies are successful ($p < .05$), a reasonable argument may be made for a superiority claim over clopidogrel.

Topic 2 – Study Population

Question 2A. Does the FDA agree that the proposed study population of moderate to high-risk ACS subjects, as defined in the meeting package and including a TIMI Risk score of ≥ 3, is appropriate to support the proposed indication?

FDA Response:
As previously stated, we agree that the proposed study population of moderate to high-risk ACS subjects, as defined in the meeting package and including a TIMI Risk score of ≥ 3 is appropriate to support the proposed indication. STEMI patients who are medically treated may be included in TABY. Additionally, using an alternative enrichment strategy to the TIMI risk score may be acceptable.

Topic 3 – Enrollment Window
FDA Response:
We agree with the following paragraph:

"It was noted that patients in the CURE study were not randomized to begin study drug at different times (that is, clopidogrel vs. placebo on a background of ASA was assessed with study drug initiated in the first 24 hours after the index ACS event); thus, the beneficial effects of clopidogrel seen in the CURE study during follow-up are based on initiation of treatment within the first 24 hours. This leaves uncertainty as to whether or not clopidogrel would be effective if started later."

Topic 4 – Study Treatments

Question 4B. Does the FDA agree that the proposed study treatments are appropriate: prasugrel (60 mg loading dose, 10 mg maintenance dose), compared with clopidogrel (300 mg loading dose, 75 mg maintenance dose), both coadministered with aspirin?

FDA Response:
Dr. Stockbridge stated this dose seemed to be appropriate, but he recommended studying more than one dose in Phase 3 to determine what dose optimizes benefit and minimizes bleeding.

Topic 8 – Desire Claims Concerning Inhibition of Platelet Aggregation
FDA Response:

We have reviewed the Target Product Profile (TPP) and are in agreement with the proposed indications and usage if H7T-MC-TAAL and H7T-MC-TABY support these indications. The statements regarding the inhibition of platelet aggregation (IPA) are considered review issues. If you can demonstrate a plausible association between IPA and the primary endpoint (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), incorporation of these exploratory findings in labeling may be possible.

Other Clarifications:

1. In the patients who receive glycoprotein IIb/IIIa inhibitors upstream, we recommend analyzing the primary endpoint by gender according to therapy received. We also recommend examining 30-day death and/or myocardial infarction by gender, stratified by whether or not patients received glycoprotein IIb/IIIa inhibitors upstream.

2. **Safety Data**
   The FDA requests the following safety data:

   Patient Narratives:
   a. For all patients who died
   b. For all serious adverse events, regardless of whether or not they are assessed as related by either the investigator or sponsor
   c. For all events of serious bleeding, thrombocytopenia/thrombotic thrombocytopenic purpura, neutropenia/agranulocytosis, aplastic anemia/pancytopenia, allergic reactions, and Torsade de Pointe
   d. For all discontinuations due to serious adverse events

For all discontinuations due to non-serious adverse events, a listing is acceptable

Case Report Forms
a. For all patients who died
b. For all patients who permanently discontinued study drug due to a serious adverse event, regardless of whether or not the event is assessed as related or unrelated by either the investigator or sponsor
c. For all patients who died and for all patients who permanently discontinued study drug, the FDA requests that all information collected from the study site be part of the case report form, not simply that information contained in documents labeled "CRF."

CEC Dossiers

a. For all patients who died
b. For all adjudicated patients who permanently discontinued the trial (since the sponsor has informed us that not all patients who discontinue the trial will be adjudicated)
c. For all other patients, CEC dossiers should be available within approximately 1 week of the Agency's request.

If you have any questions, please call:

Meg Pease-Fye, M.S.
Regulatory Health Project Manager
(301) 796 -1130

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge
8/30/2006 05:35:43 PM

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION

WHITE OAK COMPLEX
10903 NEW HAMPSHIRE AVE
BLDG. 22
SILVER SPRING, MD 20993

US Mail address:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Transmitted via e-mail to:	Peter Morrow
Sponsor:	Eli Lilly
Phone:	**317.277.9382**
Subject:	**Minutes from a Meeting** **IND 763449 (6.20.06)**
Date:	June 28, 2006
Pages including this sheet:	15

From:	**Meg Pease-Fye, M.S.**
Phone:	**301-796-1130**
Fax:	**301-796-9838**
E-mail:	**meg.peasefye@fda.hhs.gov**

Please note that you are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

PreIND Meeting with Eli Lilly

Application Number:	IND 63,449
Sponsor:	Eli Lilly
Drug:	Prasugrel (CS-747)
Type of Meeting:	Pre-Phase 3
Classification:	Type B
Meeting Date:	June 20, 2006
Preliminary Responses Sent:	June 19, 2006
Briefing Package Received:	May 26, 2006
Confirmation Date:	May 4, 2006
Meeting Request Date:	May 3, 2006
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Recorder:	Meg Pease-Fye, M.S.

List of Attendees:

Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Thomas Marciniak, M.D.	Team Leader, Medical Officer
Karen Hicks, M.D.	Medical Officer
Elena Mishina, Ph.D.	Clinical Pharmacology/Biopharmaceutics
James Hung, Ph.D.	Director, Division of Biometrics I
Meg Pease-Fye, M.S.	Regulatory Health Project Manager

Eli Lilly

Elizabeth Bearby, Pharm.D.	Regulatory Fellow, US Regulatory Affairs
Eileen Brown, Ph.D.	Principal Research Scientist, Statistics
William Macias, M.D., Ph.D.	Senior Medical Director, Prasugrel Global Brand Development Team
Peter Morrow, M.Sc.	Manager, US Regulatory Affairs
J. Anthony Ware, M.D.	Vice President, Prasugrel Global Brand Development Leader
Kenneth Winters, M.D.	Medical Fellow, Prasugrel Global Brand Development Team

Daiichi Sankyo Co., Ltd:

Howard Hoffman, M.D.	Vice President, Regulatory Affairs
Rich Cuprys, M.S.	Executive Director, Regulatory Affairs
Francis Plat, M.D.	Vice President, Clinical Development - Cardiovascular
Laurent Kassalow, M.S.	Staff Biostatistician

Consultant:

[redacted] b(4)

BACKGROUND

This meeting is to discuss the design of the proposed Phase 3 study, "A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome (ACS) Subjects who are Managed Medically" (H7T-MC-

TABY). The TABY study will be the second Phase 3 study of prasugrel and is designed to complement the ongoing TRITON-TIMI 38 study (H7T-MC-TAAL), which compares prasugrel and clopidogrel in ACS patients undergoing Percutaneous Coronary Intervention (PCI). The TABY study will exclude patients scheduled for procedural or surgical intervention, enrolling only ACS patients whose principal therapy is intended to be pharmacological or those who will be managed medically.

Preliminary responses to the submitted questions were conveyed to the sponsor on June 19, 2006 and are reproduced below in *italics.*

MEETING

After introductions, Lilly gave a brief introduction outlining the background of study development and the stages of study completion. All agreed to go directly to outstanding issues not addressed in the preliminary responses.

Question 1. Does FDA agree that one pivotal Phase 3 study (Study TABY), as described in this briefing document, is acceptable for determining the safety and efficacy of prasugrel for the proposed indication of "Prasugrel, co-administered with aspirin, is indicated for the reduction of atherothrombotic events in patients with recent acute coronary syndrome undergoing medical management?"

Preliminary Response

The Division agrees that one pivotal Phase 3 study (Study TABY), is acceptable for determining the safety and efficacy of prasugrel for the proposed indication; however, Lilly would not receive a claim of superiority against clopidogrel but only a claim of superiority against placebo. For a superiority claim against clopidogrel, prasugrel needs to beat clopidogrel in two trials or at a much lower p-value.

Meeting Discussion

Lilly requested clarification of superiority trials versus non-inferiority trials in terms of labeling and getting claims. Dr. Stockbridge explained that if a comparison is made to a drug that is known to work and beats it, we have much more confidence that the study drug beats placebo than we have that the superiority over the comparator can be replicated. The results of the trial are described in the label, including the name of the active comparator, as well as the decision-making process behind the claim. A second trial beating the active comparator would be necessary to show superiority, but one study with a suitably low p-value might be adequate. When asked about a p-value, Dr. Stockbridge explained that replication in distinct centers has value not reflected in the p-values, but, nevertheless, we expect a p-value for a single trial to be <0.01. Lilly asked, for example, how a p-value < 0.00125 would be described in the label. Dr. Stockbridge assured them that if the Agency were giving a claim of superiority to a drug, the label would clearly state it; however, the new drug needs to beat the approved regimen and in addition to having a specific claim attributable to the comparator product, the active comparator must have an approved indication in the target population. Dr. Hung added that, p-value aside, the active comparator should also be the most efficacious approved regimen.

Lilly is considering coupling the proposed trial to their on-going trial. Since both studies have different target populations and are not designed similarly, Dr. Stockbridge noted that both trials should be nominally related, citing the example of losartan versus atenolol. Lilly cited the draft guidance about evidence of indication which says is a drug can be proved effective in two populations or two vascular beds; in their case, one trial is in PCI patients and the proposed trial in ACS patients not going to PCI. If the two trials are performed and both are significant, an indication would be given for both. This led to

discussion about loading doses: currently clopidogrel is approved for a 300-mg loading dose but a study looking at a 600-mg loading dose is ongoing. In previous discussions (October 16, 2003) with the Agency, Lilly was discouraged from using the higher loading dose. Lilly's is concerned that, if the 600-mg loading dose is found to be more effective than the 300-mg loading dose, it will negatively impact their trial. Dr. Stockbridge still agreed with the earlier statements made by the Agency, noting that it is always possible that the results will show no added benefit to the 600-mg loading dose and that the 600-mg loading dose regimen will not get approved; if Lilly were to have gone forward with the higher loading dose as the comparative dose, they would be comparing their drug against the wrong regimen.

Question 2A. Does the FDA agree that the proposed study population of moderate to high-risk ACS subjects, as defined on page 12 of the briefing package, including a TIMI Risk score of > 3, is appropriate to support the proposed indication?

Preliminary Response
The Division agrees.

Meeting Discussion
There was no additional discussion about this topic.

Question 2B. Does the FDA agree that the proposed age limit of >60 years is an appropriate means of enriching the study population?

Preliminary Response
The Division agrees.

Meeting Discussion
Lilly noted their concerns about:

- Not including the STEMI population
- Keeping the risk definitions simple so that all sites can achieve consistent results
- Taking the TIMI risk score out to 42 days

Dr. Marciniak added his concern about deviating from the known effects of clopidogrel.

Question 3A. Does the FDA agree with the proposed enrollment window or up 14 days post-ACS event and that this constitutes a recent ACS population as stated in the indication?

Question 3B. Provided that there is evidence of a treatment benefit of prasugrel over clopidogrel throughout the treatment period, does the FDA agree that the results could be generalized to support the initiation of prasugrel therapy beyond the 14-day enrollment window (up to 35 days for example)?

Question 3C. Does the FDA agree that a 35-day enrollment window would also support the proposed indication of "recent ACS" and would constitute a valid trial design?

Preliminary Response
*The Division does **not** agree with the proposed enrollment window of up to 14 days post-ACS (acute coronary syndrome) event. Clopidogrel is effective if administered within 24 hours of ACS but it does not*

appear to be effective if administered later. The longer the enrollment window, the less confidence the Division has that clopidogrel is effective.

Meeting Discussion

Lilly presented several slides (see attached) of data from the CURE study (Clopidogrel in Unstable angina to prevent Recurrent Events), showing:

- aspirin plus clopidogrel in NSTEMI ACS patients over time (months of follow-up) against CV Death, MI or Stroke
- long-term results by treatment, again, over time (days of follow up) against CV Death, MI or Stroke
- benefit of clopidogrel therapy at various time intervals (weeks and months against proportion of being event-free)

Lilly argued that relative risk effect was consistent over time in the CURE study, introducing their rationale for using dual anti-platelet therapies. The patients in the CURE study were not randomized to begin therapy at different times, and the effect of clopidogrel is known to be within the first 24 hours. Lilly is considering looking at effect out to 30 days and after 30 days. Using data from the CREDO study (Clopidogrel for the Reduction of Events During Observation) and CRUSADE study, Lilly presented their outline for dual anti-platelet use for uncertain long-term medical management. Dr. Stockbridge noted that there are two questions that Lilly will need to answer:

1. When do the events happen?
2. When does clopidogrel offer benefit?

A potential hurdle Lilly may encounter during enrollment is what to do if enrollment is initiated past when clopidogrel is known to work. In this scenario, there can be no claim of beating clopidogrel. Lilly noted that the CURE study treated patients medically and then the patients were followed out to a year; the CHARISMA study showed a potential benefit but there was a large gap between the increase in event rate with early treatment and increased risk. Dr. Stockbridge suggested Lilly should make a persuasive case that clopidogrel adds benefit in the weeks after an event, keeping in mind that if the Division is unable to interpret the trial as a positive-controlled trial, then we may think of it like a placebo-controlled trial. Lilly may need to stick to a narrower window of enrollment. Dr. Stockbridge suggested Lilly try to understand the effects of late enrollment as an exploratory endpoint and base further decisions on a more familiar window. Lilly asked if they could enroll patients at the time of the index event in the hospital and the Division agreed, but still suggested Lilly submit their argument that clopidogrel works with late initiation. Dr. Hicks suggested starting immediately with hospitalization when a patient presents with ACS, since discharge summaries may not be accurate or available. She added that it is important to separate out the timeframes and to study both groups, with strict enrollment criteria in order to get clear results. Lilly asked if it were acceptable to recruit and randomize during the in-patient stay if it will not delay initiation of therapy, adding that if a patient comes in already on clopidogrel, they would re-load the patient and randomize. Dr. Stockbridge responded that this would be acceptable but warned Lilly to name and be very specific as to their targeted time frame. Lilly stated that this will be based on when the majority of the patients can get enrolled. Dr. Stockbridge suggested a further conversation after Lilly submits their arguments to determine how long a window that clopidogrel can establish effectiveness.

Question 4A. Does the FDA agree that the proposed study treatments are appropriate: prasugrel (60 mg loading dose, 10 mg maintenance dose), compared with clopidogrel (300 mg loading dose, 75 mg maintenance dose), both co-administered with aspirin?

Preliminary Response
The doses of medications chosen for a particular study are up to the sponsor. It is uncertain at this time whether or not a 60 mg loading dose of prasugrel followed by a 10-mg maintenance dose is appropriate.

Meeting Discussion
Dr. Stockbridge reiterated that Lilly should be prepared to take more than one dose into Phase 3. Dr. Hicks requested that the data be stratified by gender, and by age $\geq$ 70 years.

Question 4B. Does the FDA agree that the proposed doses of the comparator clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) will support registration of prasugrel even if the standard of care in this group expands to include higher doses of clopidogrel?

Preliminary Response
We do not believe this is an issue, because this study is not the basis for a comparative claim against clopidogrel.

Meeting Discussion
There was no additional discussion about this topic.

Question 4C. Does the FDA agree that subjects who have received a previous loading dose with clopidogrel should receive an additional loading dose upon enrollment in this study?

Preliminary Response
The Division agrees.

Meeting Discussion
There was no additional discussion about this topic.

Question 4D. Does the FDA agree that the proposed daily low-dose aspirin (75-162 mg) regimen is appropriate?

Preliminary Response
The Division agrees.

Meeting Discussion
There was no additional discussion about this topic.

Question 5A. Does the FDA agree with the definition of each individual component of the primary endpoint?

Preliminary Response
Yes, we agree with all definitions except that stated for the troponin. Please refer to page 961 of The Joint European Society of Cardiology/American College of Cardiology Committee document entitled, "Myocardial Infarction Redefined—A Consensus Document of The Joint European Society of

Cardiology/American College of Cardiology Committee for the Re-definition of Myocardial Infarction (JACC, 36(3):959-969, 2000). As stated in this document,

> *"An increased value for cardiac troponin should be defined as a measurement exceeding the 99th percentile of a reference control group. Reference values must be determined in each laboratory by studies using specific assays with appropriate quality control, as reported in peer-reviewed journals. Acceptable imprecision (coefficient of variation) at the 99th percentile for each assay should be defined as ≤ 10%. Each individual laboratory should confirm the range of reference values in their specific setting."*

Meeting Discussion
Lilly noted that they plan to deal with adjudication of events in the charter and not in the protocol.

Question 5B. Does the FDA agree with the primary endpoint of CV death, non-fatal MI, and non-fatal stroke?

Preliminary Response
The Division agrees.

Meeting Discussion
There was no additional discussion about this topic.

Question 5C. Does the FBA agree with the proposed definition of the quadruple endpoint?

Preliminary Response
Yes, but please see Point 2 under other comments and clarify why you have chosen the particular definition.

Meeting Discussion
There was no additional discussion about this topic.

Question 5D. Does the FDA agree that if both the triple and quadruple endpoints are positive, it would be appropriate to add the results to the indication statement in the label?

Preliminary Response
The Division agrees.

Meeting Discussion
There was no additional discussion about this topic.

Question 5E. Would the FDA endorse the use of the quadruple composite endpoint described in the preceding questions as either the primary endpoint or (in conjunction with the triple composite) as a co-primary endpoint for proposed study TABY?