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).

We also refer to your corresponence dated September 24, 2004 (serial # 080), regarding clarification of the minutes from the meeting held on August 4, 2004.

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

> Question 2: Does the FDA agree with the proposed timing for loading dose administration? We request inclusion of the additional clarification that the FDA response was in regard to the 300 mg LD of clopidogrel and the 60 mg loading dose of CS-747.

Agency response: The Agency agreed with the proposed timing for loading dose administration of clopidogrel and of CS-747. Regarding the clopidogrel 300 mg loading dose, we commented in our letter to you dated October 1, 2004 that the 300 mg loading dose for clopidogrel is acceptable and will be acceptable as a comparator even if 600 mg becomes an accepted loading dose. You will still need to make a case that the comparator is not worse than placebo in stented patients.

> Question 3: Does the FDA agree with the definition for treatment-related life-threatening bleeding to be used in the Phase 3 study? We provided the agency a revised definition of life-threatening bleeding during the meeting and agreement was reached. We would like to request that this definition be documented as part of the official record. The definition of life-threatening bleeding to be included in the registration protocol (H7T-MC-TAAL) is defined as any non-CABG-related TIMI major bleeding that is fatal OR leads to hypotension and requires treatment with intravenous inotropic agents OR requires surgical intervention for ongoing bleeding OR necessitates the transfusion of 4 or more units of blood over a 48-hour period OR any symptomatic intracranial hemorrhage.

Agency response: The Agency believes that there may be a misunderstanding regarding the discussion of life-threatening bleeding at the meeting. We believe we agreed that the specifics of your definition of life-threatening bleeding are reasonable and can be used for initial analyses of the data. We also noted at the meeting and recorded in the minutes that we are also concerned about CABG-related bleeding and will analyze it regardless of whether you include it in your definition. We remind you that safety evaluations are not limited to pre-specified definitions because unexpected, as well as projected, problems must be counted.

> Question 4: Does the FDA agree that the proposed duration of the Phase 3 study is adequate to register CS-747 with an indication for chronic therapy? The Agency's minutes state "The agency finds this question difficult to answer at this time. Six months seems acceptable for the period of treatment after the procedure, but what to say about continued use would depend upon how much clinical benefit is seen. This will be a review question." We would like to clarify that during the meeting, FDA confirmed that our proposed patient exposure would support chronic dosing. It was stated that the Division would inspect the

separation of the Kaplan-Meier survival curves over the duration of therapy. The drug would be indicated

This trial is designed to have a minimum treatment duration of 6 months for all patients, with a maximum treatment duration of 15 months. We understand the agency will review the totality of our safety and efficacy data to support labeling claims. We request that the official minutes be amended to state that the drug will be

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Agency response: The Agency believes that our minutes accurately summarize the major conclusion of our discussion on this point: The labeling recommendation regarding duration of therapy is a review question. As you note in your description of the meeting discussion, we will examine the data by such means as inspecting the separation of the Kaplan-Meier survival curves. Until we have reviewed the data thoroughly we can not commit to a statement that the drug will be indicated for

Question 5: Does FDA agree with the proposal of the availability of the CEC packets and classification forms during the NDA review if needed? Additionally, is it acceptable that an electronic database of routine management ECGs will not be available from the Phase 3 study? The Agency's minutes omit the discussion and response to the second portion of this question. During the meeting the Agency agreed that an electronic database of routine ECGs from the Phase 3 study is not required. We request that this be reflected in the official minutes.

Agency response: The Agency agreed that an electronic database of routine ECGs from the Phase 3 study is not required.

Question 4: Does the FDA agree with the proposed method for primary statistical analysis? The Agency's minutes do not include FDA's agreement that it is acceptable to use the Gehan-Wilcoxon test for the primary analysis. We request that this be reflected in the official minutes.

Agency response: The Agency agreed that it is acceptable to use the Gehan-Wilcoxon test for the primary analysis.

Question 5: Does the FDA agree with the proposal for testing all the secondary endpoints for labeling? The Agency's minutes state, "The sponsor is proposing to test each secondary endpoint at 0.05 level. Although some of the secondary endpoints are closely correlated, others are not. Multiplicity adjustment is needed to control the total alpha at 0.05 for all of the tests of the secondary endpoints." We request the minutes be amended to state the specific agreements regarding the secondary endpoints. We agreed the secondary endpoints of CV Death/MI/Stroke at 30 and 90 days and the secondary endpoint of All Cause Mortality/MI/Stroke at 12 months could be analyzed independently without alpha spending (each at alpha 0.05) and considered for labeling. However, the secondary endpoints CV Death/MI/Stroke/Re-hospitalization for cardiac ischemic events at 12 months, CV Death/MI/UTVR at 90 and 30 days should either be analyzed in either a hierarchical fashion or with a correction for multiplicity (alpha correction) to qualify for consideration in labeling.

Agency response: The Agency agreed that the secondary endpoints of CV Death/MI/ Stroke at 30 and 90 days and the secondary endpoint of All Cause Mortality/MI/Stroke at 12 months can be analyzed independently without alpha correction (each at alpha 0.05) if they are truly highly correlated with the primary endpoints, therefore can be considered for labeling. The secondary endpoints CV Death/MI/Stroke/Re-hospitalization for cardiac ischemic events at 12 months, CV Death/MI/UTVR at 90 and 30 days should either be analyzed in either a hierarchical fashion or with a correction for multiplicity (alpha correction) to qualify for consideration in labeling.

The Agency's minutes omit that we agreed it is acceptable to document how the secondary analyses will be handled in the Statistical Analysis Plan (SAP) and it is not necessary to specify this in the protocol. We request that this be included as part of the official record of the meeting.

Agency response: The Agency agreed that it is acceptable to document how the secondary analyses will be handled in the Statistical Analysis Plan (SAP) and it is not necessary to specify this in the protocol. The SAP must be submitted prior to any unblinding of the data (including "A vs. B" group results unblinding) and preferably prior to any substantial enrollment of patients or interim analyses.

The agency minutes state, "Dr. Temple suggested the sponsors look for biomarkers, including placental growth factor (PIGF) and soluble CD40 ligand as indicators for acute coronary syndrome and increased risk of cardiovascular events." We want to respond to this point that we will be banking blood samples from the Phase 3 study. The protocol does not include an analysis of either soluble CD40 ligand or placental growth factor. Biomarkers for analysis on the banked samples have not yet been finalized. However, banked samples go through a process of anonymization. Thus, we will not be able to link specific samples or biomarker results to study outcomes.

Agency response: The Agency acknowledges this statement but believes that much of the value of banking blood samples for biomarkers is lost if they can not be linked to study outcomes.

The Agency's minutes state ". . .that platelets return to normal after 72 hours to 5 days, adding that the drug effect is irreversible and last for the life of the platelet." We wish to clarify that the platelet inhibition effect is irreversible for the life of the platelet, but that aggregation (to ADP) returns to baseline over 3-5 days after stopping treatment as new platelets enter the circulation.

Agency response: The Agency acknowledges this clarification.

The Agency's minutes state "CS-747 is metabolized by CYP3A4 and there is controversial information in the literature for predicting the possible influence of CS-747 if any, on the pharmacokinetics of co-administered statins, some of which are also substrates for CYP3A4." We believe the agency intended to say "....there is controversial information in the literature for predicting the possible influence of clopidogrel..."

Agency response: The Agency acknowledges this correction.

If you have any questions, call Meg Pease-Fye, M.S., 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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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 63,449

Eli Lilly and Company
Attention: Elizabeth 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 and to your H7T-MC-TAAL protocol.

Under 21 CFR 312.32, you, (the holder of the IND) are required to report to the FDA, serious and unexpected adverse drug reactions as soon as possible but within 7 working days by telephone for death or life threatening experience, and in writing by 15 working days of learning of the event. Since the major endpoints of the H7T-MC-TAAL protocol include mortality, and the trial is designed to determine whether the frequency of such events is affected by treatment with CS-747 and clopidogrel, a treatment relationship cannot be excluded until the trial has been completed and the data analyzed. It is not reasonable, under the circumstance of the H7T-MC-TAAL trial, to expect to report to FDA of all mortality and serious morbidity events you will observe. Such reports are ordinarily requested to be certain that subjects' safety is being protected.

You have a Data Safety Monitoring Committee whose responsibility is to ensure the safety of the trial as it is ongoing. Consequently, as we have done for a variety of similar circumstances, the following outlines the requirements that fulfill your responsibilities under your IND:

As holder of the IND you are the person responsible for reporting serious and unexpected adverse reactions to the FDA.

The Data Safety Monitoring Committee should make all judgments with respect to what are serious and unexpected adverse drug reactions to report to you. Your 7 and 15 working day limits start upon your receipt of serious and unexpected adverse reaction information from the Safety Monitoring Committee. You have no obligation to us until the Safety Monitoring Committee reports an event to you.

We anticipate that the Data Safety Monitoring Committee will report events to you in a blinded (e.g., groups A and B) fashion. For purposes of reporting serious and unexpected adverse drug reactions, there is no need to unblind. As mortality and serious morbidity are endpoints in your trial, such events should not be considered "serious and unexpected." Certainly the Committee will have developed a means for ensuring that the trial is still able to continue morally and ethically. Neither you, nor the FDA, should play a role in their decision-making process.

What the Committee should report as "serious and unexpected" is somewhat more difficult to define. For the purposes of the H7T-MC-TAAL trial, the adverse events that should be reported to you are where the circumstances are such that your Committee thinks a treatment relationship cannot be excluded and/or when the frequency of such events has had a meaningful (another committee judgment) increase in incidence, including hepatic toxicity, bone marrow depression, or pancreatitis.

The blind need be broken only when a number of events or disproportion of events between treatment groups reaches a magnitude that could require an alteration in the trial design or in the discontinuation of the trial, as determined by the Data Safety Monitoring Committee.

Should you have any questions, please contact:

Ms. Meg Pease-Fye, M.S.
Regulatory Health Project Manager
Telephone: (301) 594-5327

Sincerely yours,

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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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:

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

We also refer to your August 18, 2004, request, serial number 079, for a special clinical protocol assessment, received August 19, 2004. The protocol is entitled, "A Comparison of CS-747 and Clopidogrel in Acute Coronary Syndrome Subjects who are to Undergo Percutaneous Coronary Intervention/TIMI-38."

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions.

1. During the September 20, 2002 meeting, FDA agreed that one large, well-controlled Phase 3 study in ACS patients with a superiority endpoint favoring CS-747 (LY640315) is acceptable for registration. Assuming a statistically significant result from TAAL, does FDA support the sponsor's intent to use this trial, as finalized in amendment B, as primary evidence of efficacy and safety for the registration of CS-747 in the treatment of patients with ACS who are to under go PCI?

Division response: Assuming CS-747 beats both the current regimen, robust statistical significance is demonstrated, and safety is acceptable, the Division agrees that results from this study will support registration of CS-747 in the targeted population.

2. In the October 2003 meeting, loading doses of the comparator (clopidogrel) were discussed. FDA encouraged the sponsor to include in the Special Protocol Assessment a formal request for agreement that 300 mg is the acceptable loading dose of clopidogrel and that it will be acceptable as a comparator for registration even if 600 mg becomes an accepted loading dose treatment option.

Division response: The 300 mg loading dose for clopidogrel is acceptable, and will be acceptable as a comparator even if 600 mg becomes an accepted loading dose. You will still need to make a case that the comparator is not worse than placebo in stented patients.

3. The sponsor requests formal confirmation of the agreement reached with the FDA during the August 4, 2004 meeting around the definitions of the primary endpoint and the primary statistical analysis using the Gehan-Wilcoxon test at a two-sided significance level of 0.05.

Division response: The primary endpoint definitions and the primary statistical analysis are acceptable. At a significance level of 0.05, we will consider the robustness of the efficacy and safety findings for approval.

4. The sponsor requests formal confirmation of the agreement reached during the August 4, 2004 meeting that FDA is in agreement that the secondary endpoints of CV Death/non-fatal MI/non-fatal Stroke at 30 and 90 days and the secondary endpoint of All Cause Mortality/non-fatal MI/non-fatal Stroke at 12 months will be analyzed independently without alpha spending (each at alpha 0.05) and considered for labeling, assuming a statistically significant result. However, the secondary endpoints of CV Death/non-fatal MI/non-fatal Stroke/Re-hospitalization for cardiac ischemic events at 12 months, and CV Death/non-fatal MI/UTVR at 90 and 30 days will be pre-specified in the Statistical Analysis Plan as to how they will be analyzed (either a hierarchical fashion or with a correction for multiplicity (alpha correction)). These will also qualify for consideration in labeling, assuming statistically significant results.

Division response: It is acceptable to test each of the secondary endpoints (CV death/nonfatal MI/nonfatal stroke at 30 and 90 days, all cause mortality/nonfatal MI/nonfatal stroke at 12 months) at the 0.05 level, assuming that they are highly correlated. However, what constitutes a high correlation needs to be defined in the protocol. The statistical analysis plan needs to have this information, and the alpha adjustment plan for the other secondary endpoints mentioned in the question. These analysis results will be considered for labeling.

5. In the October 2003 meeting, FDA requested the sponsor to ask for an exemption regarding SAE reporting in this SPA. In this study, the primary efficacy analysis is incidence of the composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. Secondary endpoints include all-cause death, re-hospitalization for cardiac ischemic events, urgent target coronary revascularization, non-CABG related TIMI major (including life-threatening bleeding) and minor bleeding. In order to avoid biasing the analysis and compromising the integrity of the study, we propose to maintain the blinding of the treatment codes for these events and to treat these as disease related and not subject to expedited reporting. Those primary, or secondary endpoints judged by the investigator or by Lilly as having a reasonable causal relation to study drug, and as being serious and unexpected for LY640315 (CS-747 or prasugrel) or comparator will be reported to FDA and other regulatory authorities as expedited safety reports. All unexpected serious adverse events that are not study endpoints will be reported in accordance with the standard pharmacovigilance guidance. In addition, a Lilly physician will review all reports of death received from all investigators in a timely fashion. Any death believed by the Lilly physician to be related to study drug and unexpected will be reported to the regulatory authorities in an expedited manner. It is important to note that this study is designed to have periodic safety reviews conducted by an independent Data Safety Monitoring Board. Does the FDA agree with the SAE reporting procedure outlined here and as detailed in the protocol?

Division response: A separate letter will be sent to you addressing these issues.

In addition, we have the following comments.

You should amend the protocol to include:

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).

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA*

Products"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at http://www.fda.gov/cder/guidance/index.htm. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, please call Meg Pease-Fye, M.S., 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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