



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 63,449

Eli Lilly and Company  
Attention: Joerg Pfeiffer, Regulatory Advisor  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Dear Dr. Pfeiffer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for prasugrel tablets.

We refer to the meeting between representatives of your firm and the FDA on November 20, 2006. The purpose of this science focused meeting was to brief the CMC review team on the quality by design aspects of the drug development for this product. Lilly's upcoming NDA for prasugrel tablets is part of the CMC pilot program.

The official minutes of the above meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1647.

Sincerely,

*{See appended electronic signature page}*

Amy Bertha  
Regulatory Health Project Manager  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** November 20, 2006  
**TIME:** 1:00 pm – 2:30 pm  
**LOCATION:** Food and Drug Administration, White Oak Room 1419  
**APPLICATION:** IND 63,449  
**DRUG NAME:** Prasugrel Tablets  
**TYPE OF MEETING:** Type C  
**MEETING CHAIR:** Moheb Nasr  
**MEETING RECORDER:** Amy Bertha

### **FDA ATTENDEES:**

#### OFFICE OF NEW DRUG QUALITY ASSESSMENT

Moheb Nasr, Director  
Chi-wan Chen, Deputy Director  
Ramesh Sood, Branch Chief, Division of Pre-Marketing Assessment I  
Kasturi Srinvaschar, Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment I  
Zhengfang Ge, Chemist, Division of Pre-Marketing Assessment II  
Michael Folkendt, Supervisory Project Manager  
Amy Bertha, Regulatory Health Project Manager

#### OFFICE OF COMPLIANCE

Division of Manufacturing and Product Quality  
Anthony Charity, Compliance Officer

### **EXTERNAL CONSTITUENT ATTENDEES: Eli Lilly and Company**

John Towns, Director, Regulatory Affairs CMC  
Sally Anliker, Manager, Regulatory Affairs CMC  
Suntara Cahya, Senior Research Scientist, Statistics  
Patrick Jansen, Research Scientist, Degradation Research  
Marty Kral, Research Advisor, Formulation Development  
Wayne Luke, Research Fellow, Chemical Process Development  
Neil Pearson, Senior Research Scientist, Analytical Development  
Jim Rybka, Principal Research Scientist, Analytical Development  
Gregg Tharp, Research Advisor, Manufacturing Science and Technology  
Joerg Pfeifer, Regulatory Advisor Regulatory Affairs CMC  
Mark Kryah, Manager, CMC Project Management  
Paulette Kosmoski, Senior Director, Regulatory Affairs - CMC, Daiichi Sankyo  
Takashi Kobayashi, Manager, Quality Control Group, Ube  
Masaru Moritomo, Assistant Manager, Pharmaceuticals Development Department, Ube  
Shinji Takamura, Manager, API & Intermediate Business Unit, Ube  
Naoyuki Yokota, Principal Chemist, Process Chemistry Group, Ube

**BACKGROUND:**

This meeting is a follow-up to the March 30, 2006, meeting regarding participation in the CMC pilot program for prasugrel tablets (IND 63, 449). Lilly's upcoming NDA for prasugrel tablets was accepted into the CMC pilot program on June 16, 2006 and is expected to be submitted in 2007. The meeting was requested on October 31, 2006 and granted on November 6, 2006. The purpose of this meeting is to brief the review team on the quality-by-design (QbD) aspects of the drug development for this product. The briefing package dated November 7, 2006 was received on November 8, 2006. On November 17, 2006 FDA called Lilly and requested that Lilly revise their presentation (submitted in the November 7, 2006 briefing package) to include more science-focused information on the quality by design aspects of both the drug substance and drug product, and less information on the format and content of the NDA submission. Lilly agreed to revise their presentation.

**THE MEETING:**

FDA introduced the members of the CMC review team that will be responsible for reviewing the upcoming prasugrel NDA: Zhengfang Ge and Kasturi Srinivasachar. Anthony Charity from the Office of Compliance was also present at the meeting and is part of the larger review/inspection team. As the NDA submission date draws near, a field investigator will be identified and will also become part of the review/inspection team. Amy Bertha will be the CMC contact from the FDA for this pilot NDA.

Lilly's revised slide presentation and back-up slides are attached to these minutes. FDA thanked Lilly for their flexibility in accommodating FDA's request to revise the slide presentation in such a short notice. During the presentation clarification questions were asked and discussions followed. Some highlights have been captured below.

Lilly plans on pre-submitting the CMC section of the upcoming NDA for prasugrel in the Spring of 2007.

In reference to slide 7, FDA asked \_\_\_\_\_

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**CLOSING REMARKS:**

FDA remarked that a pre-NDA meeting could be scheduled to discuss "traditional" CMC issues. In general concerning the format and content of the NDA, it is challenging for FDA to comment on how much Quality by Design information should be included in the NDA and/or how the information should be presented. FDA encourages Lilly to use any format they deem appropriate and to provide relevant scientific data that is well organized and summarized, as appropriate.

FDA mentioned the CMC regulatory agreement and informed Lilly that FDA would not be able to approve any agreement at this time due to lack of a regulatory pathway. However, FDA is interested in pursuing the concept of a regulatory agreement, recommends that Lilly propose an agreement and informs Lilly that discussions on the regulatory agreement can continue post-approval.

Minutes Preparer: *{See appended electronic signature page}*

Amy Bertha  
Regulatory Health Project Manager  
Office of New Drug Quality Assessment

Chair Concurrence: *{See appended electronic signature page}*

Moheb Nasr  
Director  
Office of New Drug Quality Assessment

17 Page(s) Withheld

X Trade Secret / Confidential (b4)

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       Draft Labeling (b5)

       Deliberative Process (b5)

       Personal Privacy (b6)

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/s/

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Chi Wan Chen  
12/19/2006 04:02:11 PM  
for Moheb Nasr

**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

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FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266**

**Transmitted via e-mail to:** Peter Morrow

**Sponsor:** Eli Lilly

**Phone:** 317.277.9382

**Subject:** Minutes from a Meeting  
IND 63,449 (9.22.06)

**Date:** October 10, 2006

**Pages including this sheet:** 11

**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.

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:** September 22, 2006  
**Preliminary Responses Sent:** September 21, 2006  
**Briefing Package Received:** August 29, 2006  
**Confirmation Date:** July 14, 2006  
**Meeting Request Date:** July 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
Ellis Unger, M.D.	Deputy Director
Thomas Marciniak, M.D.	Team Leader, Medical Officers
Karen Hicks, M.D.	Medical Officer
Salma Lemtouni, M.D., M.P.H.	Medical Officer
James Hung, Ph.D.	Director, Division of Biometrics I
Edward Fromm, R.Ph.	Chief, Project Management Staff
Meg Pease-Fye, M.S.	Regulatory Health Project Manager

Eli Lilly

Cheryl Anderson, Pharm.D.	US Regulatory Affairs
Elizabeth Bearby, Pharm.D.	US Regulatory Affairs
Eileen Brown, Ph.D.	Principal Research Scientist, Statistics
Javan Collins	Product Team Leader
William Macias, M.D., Ph.D.	Medical Director
Peter Morrow, M.Sc.	US Regulatory Affairs
J. Anthony Ware, M.D.	Cardiovascular Platform Leader
Kenneth Winters, M.D.	Clinical Research Fellow
Jeff Riesmeyer, M.D.	Clinical Research Fellow

Daiichi Sankyo Co., Ltd:

Rich Cuprys, M.S.	Global Regulatory Affairs
Howard Hoffman, M.D.	Global Regulatory Affairs
Laurent Kassalow, M.S.	Staff Biostatistician
Helene Petitjean, M.D.	Clinical Research Physician

Consultant:

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## **BACKGROUND**

This meeting is a follow up meeting to the June 20, 2006 meeting that met to discuss the design for 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 outstanding issues that remain are:

- Agreement on the enrollment window for Study TABY
- Agreement on protocol modifications made since the June 20th meeting
- Agreement on the planned geographical distribution of subject enrollment in Study TABY, and in particular on the target proportion of patients from North American study centers
- Resolution of the differences in understanding from the June 20, 2006 meeting as reflected in Eli Lilly and Company's correspondence dated July 12, 2006, Serial No. 320
- Agreement on the proposal and format for Patient Narratives. These narratives will ultimately be submitted in the final study reports for Study TABY and the ongoing Study H7T-MC-TAAL (TAAL/TRITON TIMI 38)
- Agreement on the documentation of patient follow-up at the end of the TRITON Study and Agency feedback on the follow-up of patients in Study 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 percutaneous or surgical coronary intervention, enrolling ACS patients whose principal therapy is intended to be pharmacological or those who will be managed medically only.

Preliminary responses to the submitted questions were conveyed to the sponsor on September 21, 2006 and are reproduced below in *italics*.

## **DISCUSSION**

After introductions, all agreed to go directly to outstanding issues not addressed in the preliminary responses.

**Question 1A. Does the FDA agree that the 7-day enrollment window is appropriate for the proposed registration study comparing prasugrel and clopidogrel in medically-managed NSTEMI ACS patients?**

### **Preliminary Response**

*The Division agrees that a 7-day enrollment window is appropriate for a study to gain registration of prasugrel; however, we will not grant a superiority claim for prasugrel over clopidogrel on the basis of a clinical trial (or trials) with a 7-day enrollment window. To gain a superiority claim, prasugrel would have to be tested against the most efficacious regimen of clopidogrel, administered within the time frame wherein clopidogrel is known to be effective, i.e., within 24 hours. At this time, it is unclear whether or not clopidogrel would be effective if started later than 24 hours into the index ACS event. (See also response to 1B, below.)*

**Meeting Discussion**

There was no additional discussion on this point.

**Question 1B. Does the FDA agree that, provided the study results meet the necessary regulatory requirements as discussed during the June 20th meeting, the study data would support a claim of superiority over clopidogrel in labeling?**

**Preliminary Response**

*See response to 1A. In order for prasugrel to gain a superiority claim over clopidogrel, prasugrel would have to be tested within the time frame we know clopidogrel to be effective (i.e. within 24 hours). Please note that for patients with ACS in CURE, CLARITY-TIMI-28, and COMMIT, clopidogrel was given in the acute phase, i.e., within 24 hours after the symptom onset. At this time, it is unclear whether or not clopidogrel would be effective if started later than 24 hours after symptom onset.*

*In order to gain a superiority claim for prasugrel over clopidogrel, we suggest that subjects should have non-ST-segment-elevation acute coronary syndrome, and be randomized in the Emergency Department or within 24 hours of hospitalization. Subjects should receive concomitant aspirin.*

*The data would need to demonstrate that prasugrel (plus aspirin) significantly decreases the composite triple endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, relative to clopidogrel (plus aspirin).*

*In general, the evidentiary standard for a superiority claim is similar to the standard for approval of a new product. Thus, if you achieve  $p$ -value  $< 0.01$  in a single trial comparing prasugrel to the most efficacious regimen of clopidogrel, administered within 24 hours after the onset of symptoms, it may be possible to gain a superiority claim for prasugrel over clopidogrel. Similarly, if you achieve a  $p$ -value  $< 0.05$  in two trials, a superiority claim over clopidogrel could be possible. If both TAAL and TABY, which have different designs and target populations, are successful ( $p < 0.05$ ), you may be able to make a reasonable argument for a superiority claim over clopidogrel.*

**Meeting Discussion**

Lilly asked if they could get a superiority claim against clopidogrel if both TAAL and TABY studies came in at  $p < 0.05$  using the 7-day enrollment window. Dr. Stockbridge was clear that prasugrel **could not** get a superiority claim if prasugrel beat the comparator drug in a setting where it was not known if the comparator drug worked. Lilly's argument was that the elderly are not studied as a cohort and are not managed acutely. Lilly is concerned with their ability to randomize patients in the emergency room. Although the Division was sympathetic and recognized their interest in this type of study, clopidogrel is currently not approved for a 7-day setting, so the study as proposed would be an unfair comparison between prasugrel and clopidogrel. The Division was unable to advise Lilly on how to go forward in a study if it is unclear how the comparator works in an untried setting; there is a higher threshold for a superiority claim as opposed to beating placebo which only proves the presence of some activity.

Lilly asked if, hypothetically, both their TRITON and TABY trials were positive, would they suffice as the two trials needed for registration. Dr. Stockbridge responded that the Division would be more comfortable with approval if one could be confident that clopidogrel was not adverse. The 7-day time window should be studied to see if relative risk can be preserved. Dr. Stockbridge suggested Lilly look for data in other settings to demonstrate clopidogrel's effect over time and although the Division understands Lilly's predicament, we are unable to advise them on how to get a superiority claim from

their proposed trial. Lilly countered that they may lose patients they want to enroll by limiting enrollment to a 24-hour window. Dr. Stockbridge stated that the study is not sufficiently powered to tell if it will work in a narrower window and although Lilly may be able to show a statistically significant interaction at the time of enrollment, the margin cannot be ruled out because the study is not powered to detect it. When asked if there were analyses that could be tried, Dr. Stockbridge stated that early enrollment is not equal to late enrollment since there are other confounding factors.

**Question 2.A. During the June 20th meeting with the FDA, the FDA agreed that it was acceptable to include STEMI patients in this study; however, based on input from the CHMP, this patient population has been removed from the study. Does the FDA agree that exclusion of STEMI patients is acceptable and that evaluation in that patient group is not necessary to support registration with this study?**

**Preliminary Response**

*The Division agrees that exclusion of STEMI patients is acceptable and that evaluation in that patient group is not necessary to support registration with this study.*

**Meeting Discussion**

There was no additional discussion on this point.

**Question 2.B. The FDA previously mentioned that many different types of risk enrichment strategies can be implemented. Does the FDA agree with the revised enrichment strategy that incorporates modified GRACE criteria?**

**Preliminary Response**

*The Division agrees with the revised enrichment strategy that incorporates modified GRACE criteria.*

**Meeting Discussion**

There was no additional discussion on this point.

**Question 2.C. Does the FDA agree with the proposed 6-month minimum subject follow-up duration and 18-month median follow-up (increased from 3 and 15 months, respectively)?**

**Preliminary Response**

*The Division agrees.*

**Meeting Discussion**

There was no additional discussion on this point.

**Question 2.D. Does the FDA agree with the requirement that at least 350 (of the 851 total) primary endpoint events occur after 3 months of treatment?**

**Preliminary Response**

*The Division agrees.*

**Meeting Discussion**

There was no additional discussion on this point.

**Question 2.E. Does the FDA agree with the proposal for randomization and study drug loading dose administration in subjects entering the study having received a loading dose of clopidogrel?**

**Preliminary Response**

*The Division agrees with the proposal for randomization and study drug loading dose administration in subjects entering the study having received a loading dose of clopidogrel; however, the Division strongly discourages a large recruitment of patients initially treated with clopidogrel.*

**Meeting Discussion**

When Lilly asked for clarification as to what the Division means by "large" Dr. Hicks asked several targeted questions about their trial specifics. Although the initial protocol for TAAL/TRITON TIMI 38 proposed limiting patients on clopidogrel to less than 20% of the study population, the sponsor subsequently decided to enroll clopidogrel-naïve patients only. After some discussion, Lilly was told that they still need to prove there is not an effect of the loading dose, particularly a difference in loading dose in the clopidogrel cohort. Dr. Hicks added that if Lilly intends to prove superiority, having a clopidogrel-naïve patient population to begin with is optimal.

**Question 3. Does the FDA have any objections with the planned distribution of study sites and subject enrollment, and in particular with the planned proportion of 16% of subjects in North America (14% in the US)?**

**Preliminary Response**

*Although we encourage you to enroll a greater proportion of subjects from the United States, the Division does not object to the planned distribution of study sites, subject enrollment, and in particular, the planned proportion of 16% of subjects in North America (14% in the US).*

**Meeting Discussion**

Lilly noted they intend to increase the number of patients enrolled in the U.S. centers. Dr. Hicks recommended an increase in the proportion of US subjects from 14% to 25-30%, but she stated the Division had no objections to Lilly's revised plan.

**Question 4. Does the FDA agree with the proposed clarifications to the meeting minutes suggested in the July 12, 2006 request?**

**Preliminary Response**

*Please see the Division responses in the letter to you dated August 30, 2006. The Division plans to clarify our requests for patient narratives, case report forms, and CEC dossiers pending an e-mail communication from Elizabeth Bearby, which will discuss the adverse events to be adjudicated by the CEC and the adverse events for which CEC dossiers will be available, as per the protocol.*

**Meeting Discussion**

Dr. Stockbridge stated that the events that increasing the dose will cause are not as important as the events that prasugrel is trying to prevent, adding his concern that Lilly is over-valuing bleeding events.

Although the Division is still discussing what it will request in terms of patient narratives, case report forms, and CEC dossiers, the Division reviewed the Clinical Endpoint Committee Charter. The Division requested a totality of information collected and adjudicated by the CEC, including:

- CABG-related bleeding events
- All communication between the study site and sponsor
- All communication between the study site and DMC
- Patient information including:
  - Autopsy information
  - Information stating whether or not the patient went for cardiac catheterization, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) during the course of the study
  - Information about the stent a patient received (bare metal versus drug eluting stent, type of drug eluting stent, length, and diameter) to better evaluate stent thrombosis

The Division recommended that the two members of the CEC review events independently, and not jointly, and that their independent assessments be recorded and tracked. Additionally, should any patients undergo percutaneous or surgical intervention during the course of the study, it was recommended that the coronary anatomy picture describing lesion location be updated to reflect whether or not left main coronary artery disease was ostial, mid, or terminal. Dr. Hicks stated that since terminal left main disease often involves the ostial left anterior descending and left circumflex coronary arteries, the risk of a percutaneous procedure is increased. Dr. Hicks also recommended that adjudication be performed by practicing, board-certified cardiologists.

**Question 5. Is the agency in agreement with the information being collected in the revised CRF for the final close-out visit (that is conducted via telephone contact)?**

**Preliminary Response**

*No, the Division is not in agreement with the information being collected in the revised case report form (CRF) for the final close-out visit (that is conducted via telephone contact). The Division strongly recommends that specific cardiac ischemic events (e.g., unstable angina, non STEMI, ventricular dysrhythmia) and cerebrovascular events (e.g., intracranial hemorrhage, ischemic stroke, transient ischemic attack) be queried and recorded in the revised CRF for the close-out visit. We suggest that the CRF provide a listing of events, so that the investigator may check the appropriate box. Additionally, the Division recommends that the hospital name and location be indicated, and that a free text section be available on the form for the investigator to record pertinent information discussed with the patient telephonically.*

**Meeting Discussion**

The Division requested that two additional headings be added to the form (cardiac ischemia and cerebrovascular ischemia). Lilly noted that the form will be updated to make the terms consistent.

**Question 6A. Does the FDA agree that the minimum standard follow-up procedures are adequate to document the due diligence of study sites in securing subject follow-up?**

**Question 6B. Does the FDA agree with the classification of subjects who are lost to follow-up?**

**Question 6C. Does the FDA agree with the proposed censoring method for subjects who are lost to follow-up?**

**Question 6D. Does the FDA have any specific expectations for analyses of subjects who are lost to follow-up?**

**Preliminary Response**

*The Division agrees with the classification of subjects and the proposed censoring method for subjects who are lost to follow-up; however, patients lost to follow-up should be a rare occurrence in this study. The Division cautions that if substantial numbers of subjects are lost to follow-up, the study results may be difficult to interpret.*

*Analyses of subjects who are lost to follow-up should include "worst case scenarios," i.e., subjects randomized to prasugrel are presumed to have experienced an event, whereas subjects randomized to clopidogrel are presumed to be event-free.*

**Meeting Discussion**

There was no additional discussion on this point.

**Question 7. Does FDA agree with the proposal to provide the Patient Narratives in a format combining information from the clinical trial database plus the CIOMS report from our safety reporting database? Does FDA have any comments on the automated summary in Briefing Document?**

**Preliminary Response**

*In general, there will be confusion if laboratory values or concomitant medications are different between the locked clinical trial database and the CIOMS report. Please comment on how we would be able to resolve these discrepancies and clarify whether or not laboratory times and dates could be included in the reports.*

*In the Patient Narrative we request the following additional information:*

- *Admission date and time*
- *Date and time of coronary angiogram, if performed. If a coronary angiogram was not performed, that information should be stated in the narrative.*
- *Date and time of first, and if applicable, last dose of study drug*
- *Dates and times of all troponin results*
- *Dates and times of ALL laboratory results*
- *Description of 12-lead ECG and Chest X-Ray Results*

**Meeting Discussion**

Dr. Hicks noted that dates and times of cardiac enzymes are important to track, both before and after procedures. It is also important to know the time a cardiac procedure was performed, so it can be determined whether or not there was an elevation in cardiac enzymes before or after the procedure. Lilly noted that they perform chest X-rays but the reports are not routinely collected unless there is a serious adverse event. Dr. Hicks stated that congestive heart failure puts these patients into a higher risk category, so patient history, ECG, chest X-rays, medications, etc. are key components that should be included in the automated summary, if possible, and would help the review go faster.

**ADDITIONAL PRELIMINARY COMMENTS**

1. At the time of hospitalization/randomization, we recommend troponin and CPK/MB be performed at all study sites, if possible.

**Meeting Discussion**

Lilly stated that in the new American College of Cardiology Guidelines, the definition of myocardial infarction will be changed and the collection of CK-MB information will no longer be recommended. Nevertheless, Dr. Hicks advised Lilly to collect both troponin and CPK-MB results at all sites where these measurements are routinely performed.

2. We recommend measuring inhibition of platelet aggregation as close as possible to the time of adverse events (bleeding, nonfatal myocardial infarction, nonfatal stroke).

**Meeting Discussion**

This will be mandated at the index hospitals able to perform this measurement..

3. We recommend an aspirin dose between 75 and 100 mg. We do not believe the aspirin dose should be left to the discretion of the investigator.

**Meeting Discussion**

Lilly is aiming for the lower aspirin dose, particularly since the CURE study showed there was less bleeding at the lower doses. Particularly the lower doses will be used for the 900 mg loading doses of clopidogrel; however, if clinically indicated a higher aspirin dose may be used.

4. We recommend 12-lead ECGs be obtained on admission/at randomization, post intervention, at discharge, at 30 days, and at 3, 6, 12, 18, 24, and 30 months, as well as at end-of-study. (The Study Visit Schedule was not provided in the Draft Protocol, so we do not know the current schedule of the proposed ECGs.)

**Meeting Discussion**

Lilly will submit the Study Visit Schedule and further discussions will take place if necessary.

5. Please forward to us the Data Monitoring Committee (DMC) Charter and describe the qualifications of the individuals comprising the DMC.

**Meeting Discussion**

Lilly will submit this prior to study commencement.

6. Once randomized, it is possible for hospitalized patients to undergo coronary arteriography with revascularization, or medical management alone. It will be important to examine the study endpoints for these sub-groups.

**Meeting Discussion**

Lilly finds this acceptable. The Division also requested data showing loss to follow-up versus withdrawal of consent.

**CONCLUSION**

The Division encouraged Lilly to submit an SPA with specific questions.

**ACTION ITEMS**

- Lilly agreed to submit all communication between the study site and CEC to the Division
- Lilly will submit the Study Visit Schedule for review
- Lilly will submit the Data Monitoring Committee (DMC) Charter and describe the qualifications of the individuals comprising the DMC

Date Minutes Drafted:           October 4, 2006  
Date Minutes Finalized:        October 10, 2006

Recorder:                        *{See appended electronic signature page}*  
                                      Meg Pease-Fye, M.S.

Chair Concurrence:           *{See appended electronic signature page}*  
                                      Norman Stockbridge, M.D., Ph.D.

Reviewed:  
N. Stockbridge                10/10/06  
E. Unger                        10.06.06  
T. Marciniak                 10/6/06  
K. Hicks                        10/6/06  
J. Hung                         10-5-2006  
E. Fromm                       10/6/06

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/s/

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Norman Stockbridge  
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