

Preliminary Response

A consensus view did not emerge in our preliminary discussions. This will need further discussion at the meeting.

Meeting Discussion

As far as the quadruple endpoint is concerned, the Division is anticipating a problem knowing what clopidogrel does with it. If prasugrel beats clopidogrel, the reviewer(s) do not have faith that clopidogrel would have won in a placebo-controlled trial, and we may think of it more like we would a placebo-controlled study. Dr. Stockbridge suggested spending α on a triple endpoint.

Question 5F. Does the FDA agree with the proposed statistical analyses (p value for two-sided log-rank test) of the primary endpoint?

Preliminary Response

The Division agrees.

Meeting Discussion

There was no additional discussion about this topic.

Question 5G. Does the FDA agree with the proposed statistical analyses, including an alpha adjustment in the case of co-primary endpoints?

Preliminary Response

Please refer to the response for Question 5E.

Meeting Discussion

There was no additional discussion about this topic.

Question 6A. Does the FDA agree that determining the study duration using the total accumulated event rate, the 15-month median duration of therapy, and minimum follow-up of 3 months for all subjects is acceptable?

Preliminary Response

The Division agrees.

Meeting Discussion

There was no additional discussion about this topic.

Question 7A. Does the FDA agree that the proposed interim safety monitoring plan for the Phase 3 Study is acceptable?

Preliminary Response

The Division agrees.

Meeting Discussion

There was no additional discussion about this topic.

Question 7B. Does the FDA agree with the proposed interim analysis plan for efficacy, in which an O'Brien-Fleming type of stopping rule would be employed at the second and third interim analyses?

Preliminary Response

The Division agrees. In addition, the secondary endpoint should be tested at the same alpha as the primary endpoint.

Meeting Discussion

Dr. Stockbridge noted that with respect to the secondary endpoint, Lilly will encounter the same problem with either the long window of enrollment or the quadruple endpoint.

Question 8A. Does the FDA agree that the specific inhibition of platelet aggregation (IPA)-related objectives described above (and summarized below) are appropriate and sufficient for establishing the clinical relevance of IPA in this study:

- (i) Correlation of IPA with study outcomes
- (ii) Comparison of IPA between treatment groups
- (iii) Comparison of variability in IPA between treatment groups
- (iv) Interaction between baseline IPA and treatment effect in subjects entering on clopidogrel?

Preliminary Response

Please pre-specify which measurement and endpoint will be correlated. Please also consider studying the comparison of inhibition of platelet aggregation (IPA) by gender and treatment, and correlate with outcome. These data could provide a hypothesis to explain any difference in the treatment arms, but it would not be conclusive.

Meeting Discussion

Dr. Stockbridge noted that although the Division is very interested in the results of this study, the problem remains that it is difficult to validate a surrogate with a trial, even one with 2 drugs. It is difficult to determine how to describe results particularly if the study is not a superiority trial; if we are not sure it beats clopidogrel, we'd be reluctant to add unvalidated surrogate information. Lilly asked about proposing some level of IPA, in addition to death, MI and stroke, to see if there was a correlation with outcome and level of anti-platelet effect achieved. Dr. Stockbridge was both interested and enthusiastic about this approach, but still could not guarantee a labeling claim, especially in the absence of conclusive superiority.

Lilly asked for the Division's comments about the Target Product Profile in their briefing package. Dr. Stockbridge noted that superiority is achieved by controlled level of inhibition. Dr. Hicks requested Lilly keep in mind the following:

- upstream use of tirofiban, eptifibatide, or other GP IIb/IIIa inhibitors
- measuring baseline and post-study troponin levels
- enrolling women
- IPA analysis by gender

Dr. Marciniak added that Lilly should ensure that the IPA hypothesis is clear in the secondary analysis plan. Dr. Stockbridge suggested Lilly see if they can find a difference in variability for prasugrel and clopidogrel, adding that suppose for prasugrel it is 10% variability versus 9% for clopidogrel.

Dr. Mishina asked for clarification as to how the IPA would be analyzed. Lilly noted that they intend to pool the results, use IPA to time-to-primary endpoint and use as a secondary comparison between the treatment groups and intra-subject variability in a mixed model and fit for variance/co-variance. Dr. Mishina requested results by gender and Lilly agreed.

Question 8B. Does the FDA agree that the specific IPA objectives above, if fulfilled, should be included in the Clinical Studies section of the US Prescribing Information?

Preliminary Response

At this point, the Division is not sure what will be included in labeling, but we are enthusiastic about you studying points (i) through (iv) listed under 8A, as well as the comparison of inhibition of platelet aggregation by gender and treatment.

Meeting Discussion

There was no additional discussion about this topic.

Question 8C. Does the FDA agree that in order to achieve the IPA objectives listed above, and support inclusion in labeling, it would be sufficient collect IPA data in a large subset (approximately 1/3) of subjects?

Preliminary Response

The Division agrees.

Meeting Discussion

There was no additional discussion about this topic.

Question 8D: In order to achieve the desired label claims noted above, would the agency agree that is acceptable to collect these data only in those countries where the device has been granted marketing authorization?

Preliminary Response

We do not expect these data will support a labeling claim. As an exploratory end point, we are not concerned about how widely you implement it.

Meeting Discussion

There was no additional discussion about this topic.

Question 9A. Does FDA agree to the proposed plan to provide case report forms and patient narratives in the NDA and the sNDA submissions?

Preliminary Response

In addition to case report forms for 1) all patients who died and 2) for all patients who permanently discontinued study drug due to a serious adverse event, the Division requests all CEC dossiers for subjects who died or permanently discontinued the trial.

Meeting Discussion

Lilly noted that patients who discontinue the trial are not adjudicated. Dr. Stockbridge stated that this was acceptable but made it clear that for patients who do get adjudicated, Lilly should submit the same documents to the Division that are submitted to the committee. Data collection documentation needs to be comprehensive. Dr. Marciniak noted that the Division has recently encountered problems in this area with other products and encouraged Lilly to read the guidance.

Additional Preliminary Comments

1. It is important to note that unstable angina may or may not involve ST-T wave changes (Please see ACC/AHA 2002 Guideline for the Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction, page 5).
2. Please clarify why you have chosen the following definition for unstable angina, as it differs from the high risk definition for unstable angina described on page 11 of the ACC/AHA 2002 Guidelines:

“UA is defined as a history of chest discomfort or ischemic symptoms of ≥ 30 minutes duration at rest with persistent or transient ST-segment deviation ≥ 1 mm in one or more electrocardiogram (ECG) leads without elevation of creatine kinase myocardial bands (CK-MB), troponin T, or troponin I.”

According to the 2002 ACC/AHA Guidelines, high risk patients with unstable angina have had prolonged ongoing (> 20 minutes) of rest pain and transient ST-segment changes > 0.05 mV.

3. Troponins are not mentioned in the Clinical Laboratory Tests described on page 76 of the submission. Please also consider checking placental growth factor.
4. Please collect IPA data at the time of serious adverse events.

Additional Discussion during Face to Face Meeting

Dr. Marciniak referenced Lilly's statement in the briefing package about blinding and advised that access to the randomization tables should be limited to one individual, adding that recent events in the Division have shown that sponsors amend the statistical analysis plan just prior to unblinding and suggested Lilly submit any changes to the plan before accumulating a large amount of data.

ACTION ITEMS

Lilly should submit the following

- arguments that clopidogrel adds benefit in the weeks after an event
- further explore the effects of late enrollment as an endpoint and base further decisions on a more familiar window
- their argument that clopidogrel works with late initiation

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 6.25.06
T. Marciniak 6.24.06
K. Hicks 6.23.06
E. Mishina 6.26.06
J. Hung 6.26.06

Attached:
Slides

2 Page(s) Withheld

 X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

 Personal Privacy (b6)

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

/s/

Margaret Pease-Fye
6/28/2006 07:56:01 AM

Norman Stockbridge
6/29/2006 08:14:07 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Docket Number 2005N-0262

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

JUN 16 2006

Dear Dr. Pfeiffer:

We acknowledge the receipt of your April 24, 2006, submission to Docket Number 2005N-0262, "Submission of Chemistry, Manufacturing and Controls (CMC) Information in a New Drug Application (NDA) Under the New Pharmaceutical Quality Assessment System; Notice of Pilot Program." You request that your upcoming NDA for prasugrel tablets, which is indicated for the reduction of atherothrombotic events in patients with acute coronary syndromes (IND 63,449) and expected to be submitted in early 2007, be accepted into this program. We also refer to our meeting on March 30, 2006, where you presented your rationale for why the prasugrel upcoming NDA should be considered for acceptance into the CMC pilot program.

Your NDA for prasugrel tablets has been accepted into this pilot program. As a participant in the program, you are expected to include in your NDA an expanded Pharmaceutical Development section and critical CMC information that appropriately demonstrate product knowledge and process understanding of the drug substance and drug product using QbD principles and science-based approaches. In addition, a more comprehensive Quality Overall Summary (cQOS) summarizing all critical CMC elements, along with an evaluation and assessment of those elements, is expected. We remind you that this pilot program only affects the CMC section of the NDA. Existing regulations and requirements for the submission of a NDA will not be waived, suspended, or modified for purposes of this pilot program, e.g., full submission requirements, fileability. The clinical divisions, Office of Compliance and FDA field investigators are aware of your participation in this program, and we will be working closely with them.

We look forward to working with you on this pilot. Please contact Amy Bertha, Regulatory Project Manager, at (301) 796-1647, when you are ready to discuss in more detail the scientific information and QbD approach you plan on submitting under this program.

Sincerely,

Moheb Nasr
Director
Office of New Drug Quality Assessment
Office of Pharmaceutical Sciences
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

JUN 16 2006

Dear Dr. Pfeiffer:

We refer to the meeting between representatives of your firm and the FDA on March 30, 2006. The purpose of the meeting was for you to present Lilly's proposal for the upcoming Prasugrel NDA to be considered for acceptance into 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,

A handwritten signature in black ink, appearing to read "Amy Bertha".

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

Enclosure

MEMORANDUM OF MEETING MINUTES

JUN 16 2006

MEETING DATE: March 30, 2006
TIME: 11:00 am- 12:00 pm
LOCATION: Food and Drug Administration, White Oak Room 1417
DRUG NAME: Prasugrel Tablets
MEETING CHAIR: Moheb Nasr
MEETING RECORDER: Amy Bertha

FDA ATTENDEES:

OFFICE OF NEW DRUG QUALITY ASSESSMENT

Moheb Nasr, Director
Chi-wan Chen, Deputy Directory
Guirag Poochikian, Associate Director Regulatory Policy
Rik Lostritto, Director, Division of Pre-Marketing Assessment III
Eric Duffy, Director, Division of Post-Marketing Evaluation
Michael Folkendt, Supervisory Project Manager
Amy Bertha, Regulatory Health Project Manager

OFFICE OF COMPLIANCE

Division of Manufacturing and Product Quality
Albinus D'Sa, Compliance Officer via telephone

EXTERNAL CONSTITUENT ATTENDEES:

John Towns, Director, Regulatory Affairs CMC
Sally Anliker, Manager, Regulatory Affairs CMC
Joerg Pfeifer, Regulatory Advisor Regulatory Affairs CMC
Mark Kryah, Manager, CMC Project Management
Elizabeth Bearby, Regulatory Fellow, US Regulatory Affairs
Paulette Kosmoski, Senior Director, Regulatory Affairs - CMC, Sankyo Pharma Development
Frank Sprecher, Senior Director, Operation Planning & Management, Sankyo Pharma Development

BACKGROUND:

The Federal Notice [Docket Number 2005N-0262] entitled "Submission of Chemistry, Manufacturing, and Controls Information in a New Drug Application Under the New Pharmaceutical Quality Assessment System" was published on July 14, 2005. Lilly requested a meeting with the FDA to discuss a candidate for acceptance into this pilot program.

THE MEETING:

After Moheb Nasr's opening comments, Chi-wan Chen provided information of some process related aspects of the pilot program. After listening to Lilly's presentation, FDA will decide whether the project meets the criteria of the pilot. If accepted into the program, a second meeting for a more detailed scientific discussion with the CMC review team will take place. Additionally, FDA mentioned that Lilly should begin thinking about the possibility of a regulatory agreement.

Lilly presented the slides that are attached to these minutes. During the presentation clarification questions were asked and discussions followed. Some highlights have been captured below.

In reference to Slide 3, Lilly clarified that the drug product used in Phase 1 and 2 clinical trials was the free base and that used in Phase 3 clinical trials was the HCL salt. In reference to Slide 6, Lilly noted that their NDA target submission date was May 2007, which would pass the March 30, 2007 dead line mentioned in the Federal Notice. Lilly is targeting, however, to pre-submit the CMC portion of the NDA earlier than May 2007. FDA assured Lilly that the timing of the submission could be discussed.

In reference to Slide 12, FDA asked for clarification on what was meant by _____
Lilly clarified that _____ % was referring to the percentage of impurity clearance.

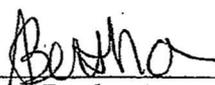
b(4)

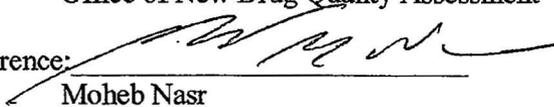
In reference to Slides 21 & 22, FDA pointed out the potential formation of toxic impurities that can be generated from _____ of the drug substance. Lilly acknowledged it was a concern, although in their opinion not a major one. Early study results indicate that the _____ products are not a concern; however Lilly is monitoring the formation of _____ products. Additionally, Lilly has not yet seen any safety issues related to clinical use. They do acknowledge the possible cumulative effect of a large number of small amounts of each impurity. Lilly is taking a proactive approach by exploring whether the impurities have similar structures, and therefore creating an additive effect.

b(4)

FDA asked Lilly if they had considered impurity formation in the context of patient use, i.e. once the drug product has been given to the patient for use at home. Lilly replied that they are in the process of generating this information. FDA also asked how Lilly was planning on packaging the bulk drug substance due to its moisture sensitivity. Lilly replied that currently the drug substance is being packaged in _____. Additionally, FDA asked what kind of strategy they had for controlling moisture in the manufacturing facilities. Lilly replied that currently the facilities have _____, but they are continuing to investigate the issue.

b(4)

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

Chair Concurrence: 
Moheb Nasr
Director
Office of New Drug Quality Assessment

Minutes of a Meeting

Meeting Date: November 4, 2005
Application: IND 63,449
CS-747 (LY640315)
Sponsor: Eli Lilly
Type of Meeting: FDA Request

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

FDA Participants:

Thomas Marciniak, M.D., Team Leader, Medical Officers, Division of Cardiovascular and Renal Products
Patrick Marroum, Ph.D., Team Leader, Clinical Pharmacology and Biopharmaceutics
Elena Mishina, Ph.D., Clinical Pharmacology and Biopharmaceutics
Meg Pease-Fye, M.S., HFD-110, Regulatory Health Project Manager

Eli Lilly Participants:

Peter Morrow, M.Sc., Manager, U.S. Regulatory Affairs
Joerg Pfeifer, Ph.D., Associate Director, Regulatory Affairs, Chemistry, Manufacturing and Controls
Cheryl Anderson, Pharm.D., Director, U.S. Regulatory Affairs
Mark Kryah, Manager, Development Project Management
David Small, Ph.D., Principal Research Scientist, Pharmacokinetics
Ken Winters, M.D., Medical Fellow II, Prasugrel Development Team

Sankyo Participants:

Howard Hoffman, M.D., Executive Director, Regulatory Affairs
Dan Salazar, Ph.D., Executive Director, Clinical Pharmacology and Pharmacokinetics
Paulette Kosmoski, Senior Director, Regulatory Affairs, Chemistry, Manufacturing and Controls

Background:

The proposed indication for CS-747 is : _____

_____ An End of Phase 2 meeting was held with the Agency on August 8, 2004 and a CMC only End of Phase 2 meeting was held on January 25, 2005. The objective of this meeting was to come to an agreement on issues surrounding the proposed 5 mg dose strength tablet.

b(4)

Discussion Points:

Lilly clarified that it sees the 5 mg dose : _____ At a previous meeting, the Agency noted the possibility of exposure-based dosage adjustment. When a specific dose is not studied during an efficacy trial, dosage adjustment for a special population (e.g. renal or hepatic impairment, elderly, low weight) may be based on PK data.. If Lilly pursues dosage adjustment

b(4)

in a special population, it may be acceptable provided the exposure for the lower dose in the special population is comparable to the exposure for the higher dose in the general population.

Lilly asked if the label could reflect that specific sub-groups should start at the lower dose. Dr. Marroum responded that this would be appropriate only if exposure in these populations is predictable and the 5 mg strength is effective then the Agency can approve the 5 mg dose for special population dose adjustment.

Conclusions:

- The 5 mg tablet cannot be registered for general use since it will not be used in the pivotal study; however, during NDA review the Division may recommend its use for dose adjustment for a particular subgroup of patients.
- Lilly does not intend to _____
- The FDA cited renal or hepatic impairment as the most likely situation for PK-based dose adjustment, provided exposure with the lower strength (5 mg) was comparable to exposure at the higher strength (10 mg). Elderly or low-weight patients would be other possibilities.

b(4)

Date Minutes Drafted: November 15, 2005
Date Minutes Finalized:

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

Concurrence, Chair *{See appended electronic signature page}*
Thomas Marciniak, M.D.

Reviewed:

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

/s/

Margaret Pease-Fye
11/23/2005 09:39:47 AM

Thomas Marciniak
11/23/2005 12:42:34 PM