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Lilly

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Indianapolis, Indiana 46285
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Phone 317 276 2000

November 14, 2007

Correspondence

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: IND 63,449: Prasugrel (CS-747, LY640315) Serial No. 0504
Prasugrel Pharmacogenomics Data Submission: Summary of FDA Meetings and Agreements

We are herewith submitting minutes from two meetings between the sponsors and the Food and Drug Administration (FDA) regarding pharmacogenetic data for prasugrel which has been under investigation for reduction of atherothrombotic events in patients with acute coronary syndromes managed by percutaneous coronary intervention. Additionally, we are summarizing a teleconference discussion between Ms. Meg Pease-Fye and Elizabeth Bearby via teleconference which provides agreement between FDA and the sponsor how the anonymized and non-anonymized pharmacogenomic datasets will be submitted the Agency to support the New Drug Application for prasugrel.

September 13, 2007 IPRG Face to Face Meeting

A joint meeting with the IPRG (Interdisciplinary Pharmacogenomics Review Group) was held September 13, 2007. The purpose of this meeting was to review exploratory pharmacogenomics data for prasugrel. Minutes from this meeting are enclosed. As a result of this meeting, the sponsors agreed to arrange a call with the Division to discuss submission of anonymized datasets with the eCTD.

October 3, 2007 Teleconference with Division of Cardio-Renal Drug Products

A joint teleconference with the Division of Cardio-Renal Drug Products on October 3, 2007 was held. The purpose of this call was to understand how the pharmacogenomic data for prasugrel would be submitted and how anonymity of patient genetic information will be maintained thereafter at the FDA. The sponsor minutes from this discussion are enclosed. As a result of this teleconference, the Division agreed to provide its response to the sponsor's proposal afterwards.

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November 8, 2007

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Products
5901-B Ammendale Road
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Teleconference Minutes

Re: Prasugrel, Proposed Tradename EFFIENT, IND 63,449 (LY640315)
Serial No.: 0503

Lilly has captured key elements of the teleconference discussion on November 3, 2007 between Lilly, Daiichi Sankyo and FDA regarding the Japanese datasets from several clinical pharmacology studies. Please refer to Serial No. 0444 and No. 0489 regarding previous communications surrounding these studies.

Participants:

Lilly:

Cheryl Beal Anderson, Director, US Regulatory Affairs
Norma Ascroft, Scientific Director, US Regulatory Affairs
Elizabeth Bearby, Scientific Director, US Regulatory Affairs
William Macias, Medical Director, Prasugrel Team
Lan Ni, Head – Global Pharmacokinetics

Daiich Sankyo:

Rich Cuprys, Regulatory, Executive Director, Regulatory Affairs
Manini Patel, Associate Director, Regulatory Affairs
Go Saito, Associate Director , Project Management
Shashank Rohatagi, Executive. Director, Clinical Pharmacology

FDA:

Meg Pease-Fye, CDER, Project Management
Karen Hicks, CDER, Medical Officer
Elena Mishina, CDER,
Thomas Marciniak, CDER, Acting Deputy Division Director

The studies discussed were non-IND studies conducted in Japan by Daiichi Sankyo and were intended to be submitted with the NDA as informational but were not designed to be directly supportive studies to the application.

FDA indicated, because of the fair number of patients enrolled across these studies and their concern for the potential of the Asian population to have a more pronounced affect, they wished for the full clinical study reports and datasets to be submitted with the application. Additionally, half of the subjects were smokers.

Lilly stated in terms of the 1A2 affects on smoking, a conclusion has been made that we do not believe 1A2 is involved in the metabolism of prasugrel.

The conclusion of the teleconference was that for the phase I and II non-IND studies conducted in Japan that will be submitted in the application, full translated datasets and the full reports will be included for FDA to conduct their analysis.

Lilly requested whether the datasets could be submitted with the Patient Package Insert and withdrawal of consent information requested by FDA at Day 60 (post submission), as previously agreed upon by FDA. Dr. Hicks and Ms. Pease-Fye responded they would need all information at the time of initial submission based on the enforcement of FDA's new initiative to require full information at the time of an applicant's submission. Dr. Marciniak was agreeable to the proposal to submit later, however, acknowledged this initiative. FDA agreed to follow-up at the Division level for confirmation of whether these specific items would be required at the time of initial submission.

In a post meeting note November 2, 2007 sent to Elizabeth Bearby, Lilly Regulatory, from Meg Pease-Fye, she stated that *all* information, including the previously agreed PPI and withdrawal of consent follow-up information would be required at the time of submission.

Lilly and Daiichi Sankyo would like to thank FDA for responding to this but would like to point out the change of FDA's direction from previously agreed commitments as documented in the pre-NDA meeting (May 30, 2007) minutes.

Thank you for your continued assistance. Please call me at (317) 277-2308 if you require any additional information or if there are any questions. Alternatively, you may contact Dr. Elizabeth Bearby at (317) 276-1203, Mr. Peter Morrow at (317) 277-9382 or Dr. Cheryl Beal Anderson, Director, U.S. Regulatory Affairs, at (317) 651-9826.

Sincerely,
ELI LILLY AND COMPANY

for Norma K. Ascroft, PharmD
Scientific Director, US Regulatory Affairs

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 prasugrel.

We also refer to your September 13, 2007, request, serial number 478, for a special clinical protocol assessment, received September 14, 2007. The protocol is entitled, "A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome (ACS) Subjects with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) Who are Medically Managed – the TRILOGY ACS Study."

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

1. Does the Division agree with the revised enrollment period of seven days from index ACS event to subject randomization?

Please note that a five-day period had been previously proposed and was accepted by the Division. In the interim, through contact with prospective study sites, it has been determined that lengthening this period will better accommodate international medical practice. In certain regions, more than 5 days from presentation of the ACS event are needed for the diagnostic procedures sometimes necessary (*e.g.* coronary angiography) to make a reasonably certain decision for a medical management strategy. A seven-day enrollment window will therefore increase the number of available study subjects.

Division Response: The Division agrees with the revised enrollment period of seven days from the index event.

2. Does the Division agree with the following addition to the list of enrichment criteria ("high-risk features") that may qualify a subject for Study TABY (five such features are described in the protocol and a subject must possess at least one of these to qualify):

"Prior evidence of peripheral vascular disease or cerebrovascular disease including at least one of the following: prior ischemic stroke, prior lower extremity amputation, or prior surgical or percutaneous revascularization of a carotid, iliac, or femoral artery"?

Division Response: The Division agrees as long as the trial is a superiority design. Non-inferiority will not be an option for TABY since the regiment of clopidogrel in the trial is different from the ones approved.

3. Does the Division agree with the safety evaluations provided for in section 6.3 of Protocol TABY, and in particular with the items listed below?

a. The bleeding endpoints described in section 6.3.1.1.

Division Response: The Division agrees.

b. The exclusion of the clinical outcomes of death, MI, stroke, and rehospitalization for recurrent UA from serious adverse event reporting, except in circumstances where the investigator believes the event may have been caused by study drug (see section 6.3.2.1).

Division Response: The Division agrees.

c. The 30-day limit on adverse event collection for subjects who permanently discontinue study drug prior to study completion. Such subjects will remain in the study for efficacy and safety endpoint analyses. After 30 days, only serious adverse events thought related to study drug or a study procedure will be reported.

Division Response: The Division agrees; however, we recommend that you carefully document the date of drug discontinuation.

4. Does the Division agree with the following aspects of the Clinical Evaluation Committee (CEC) Charter:

a. The definitions of the safety and efficacy endpoints that will be adjudicated by the CEC (see sections 5 and 6 of the CEC Charter), and

Division Response: The Division agrees.

b. The documentation that must be presented to the CEC for adjudication of an event (please see section 4.3 of the CEC Charter)?

Division Response: The Division agrees. The documentation presented to the CEC must be submitted as part of the case report forms for the cases specified by regulation (deaths, discontinuations for adverse events) as well as any other cases requested by Division reviewers.

5. Does the Division agree with the updated Target Product Profile?

Division Response: The Division agrees as long as TAAL and TABY studies support the proposed indications; however, two proposals in the TPP remain problematic:

**(1) A global superiority claim to clopidogrel, *i.e.*, _____ b(4)
_____ ' will be difficult. One issue is that your study designs are not identical to those with which clopidogrel was studied, so even if you win in TAAL and TABY, we do not know whether clopidogrel would be superior to prasugrel in the context in which clopidogrel was studied. Another issue is how to weight differences in efficacy against differences in adverse events. We may consider bringing the prasugrel studies to an advisory committee meeting for recommendations on a superiority claim.**

**(2) The statements regarding inhibition of platelet aggregation (IPA) must reflect what was pre-specified and what was demonstrated. That _____ b(4)
_____ will be very**

difficult to prove. Any claims for IPA would be supported best by defining secondary endpoints based on initial IPA results and with preservation of an overall alpha of 0.05 for TABY. Any specific IPA claim must be supported by two studies.

In addition to the specific questions posed above, you asked that the Division provide formal confirmation of the following agreements reached during the previous regulatory interactions concerning Protocol TABY:

1. Study TABY, as designed, can support the proposed indication,

Division Response: The Division agrees.

2. Study TABY, provided the results are sufficiently compelling, can support a claim of therapeutic superiority of prasugrel over the studied clopidogrel regimen,

Division Response: Please see response to Question 5 above.

3. The primary endpoint, a composite of time to first occurrence of cardiovascular death, myocardial infarction, or stroke, is appropriate,

Division Response: The Division agrees.

4. Analysis of the primary endpoint by a stratified two-sided log-rank test at a significance level of 0.05 is appropriate, with stratification consisting of three levels based on a subject's clopidogrel status within 24 hours following presentation of the ACS event.

Division Response: The Division agrees.

5. The study population, defined by the entry criteria in protocol sections 4.1 and 4.2, is acceptable, including

a. Disease diagnostic criteria for non-ST-segment myocardial infarction (NSTEMI),

Division Response: The Division agrees.

b. Disease diagnostic criteria for unstable angina (UA), c. Enrichment criteria,

Division Response: The Division agrees.

6. The study treatments are acceptable, including

a. The administration of a loading dose to only those subjects who, on study entry, are either naive to clopidogrel or deemed not to be at steady state,

Division Response: The Division agrees.

b. The greater-than-12-month treatment with both prasugrel and clopidogrel is appropriate.

Division Response: The Division agrees.

In addition, we have the following comments.

Submit your statistical analysis plan as soon as possible.

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
(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
10/19/2007 11:28:36 AM

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
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Transmitted via e-mail:	Elizabeth Bearby, Pharm.D.
Company Name:	Eli Lilly
Phone:	(317) 276-1203
Subject:	**Preliminary Reponses to 7.13.07 Meeting with FDA re: TABY IND 63,449**
Date:	July 10, 2007
Pages including this sheet:	5

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

IND 63,449
Prasugrel (CS-747)
Eli Lilly
Preliminary Responses
July 10 2007

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for ***July 13, 2006 at 9:30am*** *between* ***Eli Lilly*** *and the Division of Cardiovascular and Renal Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (please contact Ms. Meg Pease-Fye), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to* ***your development plan, the purpose of the meeting or to the questions*** *(based on our responses herein), we may not be prepared to discuss or to reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, please contact Ms. Meg Pease-Fye to discuss the possibility of including these for discussion at the meeting.*

DISCUSSION

Question 1: Does the Division agree that one pivotal Phase 3 study (Study TABY), as revised, is acceptable for determining the safety and efficacy of prasugrel for the following proposed indication:

b(4)

Preliminary Response

The Division agrees. TABY, as revised, is acceptable for supporting the proposed indication.

Question 2: Does the Division agree that the revised inclusion criteria define a study population that supports the proposed indication?

Preliminary Response

The Division agrees. The revised inclusion criteria are acceptable.

Question 3: Does the Division agree with the proposed study treatments (dose and duration)? Moreover, does the Division agree that clopidogrel is the appropriate control treatment beyond 12 months (up to a possible maximum of 30 months)?

Preliminary Response
The Division agrees. The proposed study treatment dose and duration are acceptable, including treatment beyond 12 months.

Question 4: Does the Division agree that Study TABY, as revised, would support a claim of superiority for prasugrel over the active control, clopidogrel, in the target indication, provided that the results are sufficiently compelling (robust statistical significance [p<.01], internal consistency across subgroups, and acceptable overall risk/benefit profile)?

We ask the Division to consider the following when answering this question:

- The estimated proportion of clopidogrel-naïve subjects entering the study compared with the proportion expected to enter while receiving commercial clopidogrel.
- The definition of the onset date of the UA/NSTEMI index event compared with the definition used in the CURE study.
- The use of clopidogrel as the active comparator beyond 12 months and up to a possible maximum of 30 months.

Preliminary Response
The Division agrees. TABY could support a claim of superiority for prasugrel over the clopidogrel regimen used if the results are sufficiently compelling.

Question 5: What comments does the Division have on the Targeted Product Profile, considering in particular the points listed below?

- Based on the sponsor's reading of the FDA's Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format, the description of Study TABY in labeling should be quite detailed. We propose that this should include a presentation of the primary endpoint results identifying the active control by name, including a figure depicting the Kaplan-Meier time to event analysis.
- To what extent would comparative data versus clopidogrel (that is, survival claims, tables/figures/listings) be presented in labeling should the p-value be >.01 and p<.05 (assuming consistency across subgroups and an acceptable overall risk/benefit profile)?
- What would be the most appropriate means for presenting in labeling (that is, survival curves, tables/figures/listings, and wording in the Clinical Trial section) the ability to substitute clopidogrel with prasugrel within 5 days of an UA/NSTEMI event in order to improve long-term outcomes for medically managed subjects?

Preliminary Response
The general nature of the proposals for the Targeted Product Profile seems reasonable, although it is too early to comment upon many specific details without results; however, the statement [redacted] is not justified by the hypothesized marginal b(4)

superiority of prasugrel over clopidogrel. We suspect it should have read, "[redacted]" b(4)

Question 6: Does the Division agree that no PK data is needed from the TABY study in order to support the proposed indication?

Preliminary Response
The Division agrees that no PK data are needed from TABY.

Additional Preliminary Comments

1. Page 25: Although patients are initially to be managed medically, if they ultimately undergo CABG during the course of the study, we are also interested in CABG related bleeding.

2. We recommend that CPK, CK-MB, **AND** troponin I or T be checked in each patient.

3. You do not appear to be spending alpha on components of the composite end points, and we think that is acceptable; however, a claim based on a component of the composite end point would require a very low p-value if it were not part of the alpha-conserving analytic plan. We would certainly want to show the components separately, even if you did not declare them formal end points. We strongly recommend that you faithfully follow subjects after they experience the nonfatal end point events. Your statistical analysis plan must address the issue of how subjects who cannot be followed up for each component endpoint would be handled in statistical analysis of the composite.

4. All the analyses to be conducted in a subset of study subjects using IPA are exploratory only because:
   - no alpha adjustments are proposed
   - time-dependent covariate adjustment analysis is known to be difficult to interpret
   - missing data handling is always problematic and depends on the assumptions made, even though MMRM might be better than other imputation method is accounting for bias

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
7/10/2007 08:03:30 AM