Topic 8 - Common Technical Document

20. Does the FDA agree that the Sponsors may submit the application in eCTD format with study reports in the legacy format (Section 3.8.1)?

Preliminary Response

Yes, the Division agrees.

Meeting Discussion

There was no additional discussion concerning this topic.

Topic 9 - Additional Discussion Topics

21. If a response has not been provided prior to the Pre-NDA meeting, can the FDA please provide an update on the trademark review (Serial Number 407)? Does the FDA agree with the proposal for submission of the study synopsis in lieu of final study reports for the studies conducted in Japan as outlined above (Serial Number 423) (Section 3.9)?

Preliminary Response

The Division is not able to comment on the status of the trademark review at this time. In regard to the study synopses, please clarify how many studies were conducted in Japan and list their titles.

Meeting Discussion

There was no additional discussion concerning this topic.

Additional Preliminary Comments

1. *Please submit the final version of the statistical analysis plan for TAAL as soon as possible for review.*

Meeting Discussion

Lilly noted that this has been submitted for review.

2. *For TAAL, please analyze all primary and major secondary efficacy endpoints as well as all major safety endpoints by age (≥ 75, < 75 years old), sex, and ethnicity.*

Meeting Discussion

Lilly agreed to incorporate these comments.

3. *In the TAAL Clinical Study Report, please analyze all excessive bleeding related to CABG by age, sex, weight, and renal function (Creatinine Clearance by Cockcroft-Gault Equation: < 30 ml/min, ≥ 30 and ≤ 60 ml/min, and > 60 ml/min) (See EOP2 8/4/2004 Minutes).*

Meeting Discussion

Lilly agreed to incorporate these comments.

4. *For TAAL, please analyze bleeding events by age (≥ 75, < 75 years old) , sex, weight, and renal function (Creatinine Clearance by Cockcroft-Gault Equation: < 30 ml/min, ≥ 30 and ≤ 60 ml/min, and > 60 ml/min).*

Meeting Discussion
Lilly agreed to incorporate these comments.

5. *Please analyze the primary and major secondary efficacy endpoints as well as major safety endpoints according to sex, troponin or CPK/MB positivity at baseline, and whether or not patients received GPIIb/IIIa inhibitors as part of their therapy.*

Meeting Discussion
Dr. Hicks cited the Boersma Meta-analysis and her concerns that women do not routinely receive as much benefit as men in the non ST-segment elevation myocardial infarction population. Lilly will consider and address this.

6. *For all patients in TAAL or TABY* who experience stent thrombosis:*
    a. *Please submit a folder entitled, "Stent Thrombosis"*
    b. *Within the Stent Thrombosis folder, there should be a separate folder for each patient who experienced stent thrombosis in either trial*
    c. *Within each patient folder, there should be a separate PDF file for each cardiac catheterization/PCI the patient underwent, so we can easily determine how many procedures the patient underwent during the course of the trial. Each PDF file should be labeled by patient name and date of procedure*
    d. *Please submit all available summary data for stent thrombosis (TRITON/TIMI 38 Registry data for TAAL and any similar data for TABY)*
    e. *Please provide subgroup analyses for stent thrombosis summary data by age, sex, and ethnicity.*

    **We realize that patients in TABY are predominantly going to be treated medically; however, circumstances may arise such that patients not initially taken to the cath lab may subsequently develop symptoms such that he or she is taken to the cath lab at some later point during the study. We would like to track stent thrombosis data on this population. Please record stent type, length, and diameter, whether or not intravascular ultrasound (IVUS) guidance was utilized, and if the stent was post-dilated (if so, what was the length and diameter of the balloon used, and how many atmospheres was the balloon inflated to for post-dilatation of the stent?) Please also record the other items to be followed in the TRITON TIMI 38 Registry and compliance, dates, and doses of dual antiplatelet therapy).*

Meeting Discussion
Lilly noted they will provide the requests made in *a*, *b*, and *c* above. Further, they can address the issues in *d* although they noted that no one in this registry will be on prasugrel. Dr. Hicks requested that Lilly send a summary with stent thrombosis broken down by age, gender and ethnicity. Lilly agreed.

The TIMI group will forward stent thrombosis information at 6-month intervals

7. *For Study TABY: Since there is still some question as to whether or not women may receive less benefit than men from the use of upstream GPIIb/IIIa inhibitors in the setting of ACS in which*

patients are not routinely referred for PCI, we ask the sponsor to consider prospectively randomizing male and female patients to GPIIb/IIIa inhibitor therapy and to record whether or not these patients had positive CPK/MBs or troponins at baseline.

Meeting Discussion
The Division recommended further discussion concerning stent thrombosis.

ACTION ITEMS
- Lilly will submit data sets and NONMEM code for population PK and PK/PD analysis for review
- Lilly will provide dataset containing the raw data from the case report forms and derived variables and analysis datasets for both events and efficacy
- Lilly will provide additional CRFs within one week from the time of the request by the Agency
- Lilly will submit a mock-up of summary listing for Division consideration
- Lilly agreed to submit their draft of the patient package insert by Day 60 of the NDA review

Date Minutes Drafted: June 6, 2007
Date Minutes Finalized: June 19, 2007

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

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

Reviewed:
T. Marciniak 6/19/07
K. Hicks 6/18/2007
E. Mishina 6.15.07
J. Hung 6.12.07

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/s/

Margaret Pease-Fye
6/19/2007 11:06:36 AM

Thomas Marciniak
6/19/2007 12:32:34 PM

www.lilly.com

Lilly

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.

Phone 317 276 2000

May 7, 2007

CORRESPONDENCE:
MINUTES FROM
TELECONFERENCE

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

RE: Prasugrel, Proposed Tradename EFFIENT, IND 63,449 (LY640315), Serial No.: 0438
Correspondence: April 25, 2007 Teleconference Minutes

Reference is made to the March 28, 2007 (serial number 425) submission containing background materials for a joint teleconference between Eli Lilly and Company and the Food and Drug Administration.

Attached are minutes taken by the sponsor for this teleconference. Agreement was reached that the information outlined in the CEC Stent Thrombosis adjudication case report form was adequate to provide the agency useful analyses about the events of stent thrombosis. Therefore, the need to calculate mean reference diameter and collect the angiogram films was agreed to not be necessary.

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

Sincerely,

ELI LILLY AND COMPANY

Elizabeth C. Bearby, Pharm.D.
Scientific Director
US Regulatory Affairs

Minutes

Teleconference on April 25th

FDA

- Meg Pease-Fye, CDER, Project Management
- Dr. Norman Stockbridge, CDER, DCRD, Division Director
- Dr. Thomas Marciniak, CDER, Medical Team Leader
- Dr. Karen Hicks, CDER, Medical Officer

TIMI

- Dr. Eugene Braunwald, Distinguished Hersey Professor of Medicine Harvard Medical School and TRITON TIMI-38 Study Chairman
- Dr. Stephen Wiviott, Cardiovascular Division, Brigham and Women's Hospital

Lilly

- Cheryl Beal Anderson, Director, US Regulatory Affairs
- Elizabeth Bearby, Scientific Director, US Regulatory Affairs
- William Macias, Medical Director, Prasugrel Team
- Jeffrey Riesmeyer, Medical Advisor, Prasugrel Team
- Govinda Weerakkody, Statistics Research Advisor, Prasugrel Team

Daiichi-Sankyo

- Ryszard Cuprys, Regulatory Executive Director
- Francis Plat, Vice President of Clinical Development

Summary of Discussion:

Elizabeth Bearby provided introductions and outlined the purpose of the meeting. Lilly, Daiichi-Sankyo and TIMI believe the concerns around Drug Eluting Stents and the reported events of late stent thrombosis are important. To that end, the sponsors instituted a process to adjudicate events of stent thrombosis in TRITON as well as study TABL (PRINCIPLE, an ongoing Phase 2 study). Additionally, we have supported the TIMI registry which follows the TRITON study and has been discussed with the agency.

Lilly is prepared to submit an application for prasugrel within the year. We need to understand what is necessary for the evaluation of the safety and efficacy of prasugrel and what additional data is needed by the Division to evaluate this important issue apart from the submission.

www.lilly.com

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

March 8, 2007

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

Correspondence

Re: IND 63,449: Prasugrel (CS-747, LY640315) **Serial No.: 0416**
February 27, 2007 Teleconference Meeting Minutes

Attached are the meeting minutes from a teleconference held on February 27, 2007 between individuals of Eli Lilly and Company, Daiichi-Sankyo, the TIMI Organization, and representatives of the Food and Drug Administration (FDA).

This teleconference was requested by the FDA to discuss the TIMI registry. Prior to the teleconference, slides and a copy of the registry were sent to Ms. Pease-Fye via email. These documents are also attached for reference.

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

Sincerely,

ELI LILLY AND COMPANY

Cheryl R. Anderson, for

Elizabeth C. Bearby, Pharm.D.
Scientific Director, US Regulatory Affairs

Teleconference: February 27, 2007

Participants:

Lilly:

Cheryl Beal Anderson, Director, US Regulatory Affairs
Elizabeth Bearby, Scientific Director, US Regulatory Affairs
Eileen Brown, Statistics Research Scientist, Prasugrel Team
William Macias, Medical Director, Prasugrel Team
Jeffrey Riesmeyer, Medical Advisor, Prasugrel Team
Govinda Weerakkody, Statistics Research Advisor, Prasugrel Team

Sankyo:

Rich Cuprys, Regulatory Executive Director
Jim Hanyok, Clinical
Laurent Kassalow, Staff Biostatistician
Francis Plat, Vice President of Clinical Development

TIMI:

Dr. Eugene Braunwald, Distinguished Hersey Professor of Medicine Harvard Medical School and TRITON TIMI-38 Study Chairman
Dr. Stephen Wiviott, Cardiovascular Division, Brigham and Women's Hospital

FDA

Meg Pease-Fye, CDER, Project Management
Norman Stockbridge, CDER, DCRD, Division Director
Karen Hick, CDER, Medical Officer
Bram Zuckerman, CDRH, Division Director
Andrew Farb, CDRH, Medical Officer

The teleconference started at 8:30 AM and lasted approximately 50 minutes. Below is a summary of the discussion and action steps forward.

Dr. Zuckerman opened the meeting by stating drug eluting stents (DES) are an important transforming technology. He acknowledged the TRITON – TIMI 38 study. He stated CDRH is looking at real world clinical data on how DES are performing and how to maximize the safety profile. He stated a subset within TRITON where the drug is being tested is important. He noted that the stent use in the trial is considered 'off-label' and stated that it is OK for a drug trial to do this. It allows them to better understand how DES are being used under real world conditions. He noted we should not consider all brands of DES to be the same.

We stated we collect brand of DES, stent length, location of stent placement, and other information, but not diameter except in cases of stent thrombosis. Based on scientific interest in stent thrombosis, in the TRITON TIMI 38 trial, stent thrombosis events will be adjudicated by the CEC. This adjudication process is an addition and the CEC case report form is currently being finalized.

Dr. Wiviott and Dr. Braunwald provided a summary of the registry and detailed that data would be available on a rolling basis. Dr. Hicks inquired about the definition of MI in subjects that experience spontaneous symptoms and in those undergoing CABG surgery. Dr. Wiviott stated the registry implemented the same definition of MI as in TRITON TIMI 38. Overall, FDA commented that the registry is worthwhile and important.

FDA made the following suggestions throughout the teleconference for consideration by the sponsors:

- Consider working with device manufacturers in future clinical trials of prasugrel. CDRH and CDER stated they would be willing to facilitate collaborative discussions if requested. **Lilly understands this important health interest and agrees that such collaboration is important. Further internal management discussion between Lilly, Daiichi-Sankyo and TIMI would be required before such a commitment could be made. Lilly will follow-up.**
- After completion of the TRITON-TIMI 38 trial, and after submission of prasugrel, consider collecting additional detailed clinical information for those patients who experience an event of stent thrombosis. Angiographic data may be needed if the above data suggest there is a high risk subset. Type of information, design, timing, and objective of this request were not agreed upon or fully discussed. It was agreed additional discussion could be arranged with FDA.
    - Dr. Hicks noted particular interest in bifurcation lesions, total stent length, diameter of stents, if thrombus was present, if stents were overlapping, if the patient received BMS, DES or both, use of bracytherapy, and if placement of the stent resulted in a sub-optimal result with under-expansion or edge dissection.
    - Dr. Farb noted the willingness to review these clinical elements to reduce the overall collection burden.
    - Dr. Hicks, working with Dr. Farb, is preparing a list of interested analyses and she will share this with us when available.

  Lilly's perspective is that TRITON is designed to assess safety and efficacy of prasugrel, albeit information relative to stents is important. Lilly plans to file the NDA Dec 2007. Lilly will seek a follow-up teleconference to discuss the request relative to the available information and planned analyses that will meet the Agency's need via Triton or the TIMI Registry.

- Suggested that we submit the Statistical Analysis Plan for the Registry to CDRH for their comment. Particularly if we are considering propensity scores as part of the evaluation.

  TIMI and Lilly appreciated the Agency's offer and will provide the draft SAP for comment.

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 Prasugrel (CS-747).

We also refer to your amendment dated November 22, 2006 (serial # 379), containing your responses to our letter dated December 19, 2006 concerning stent thrombosis and requested angiograms.

We would like to confirm in writing the discussion during the teleconference on December 22, 2006 between Dr. Marciniak and your staff and representatives from the TIMI group. Dr. Marciniak discussed the following:

1. Regarding your letter dated November 22, 2006 (Serial 379) responding to our letter dated November 9, 2006, Dr. Marciniak commented as follows:

    a. Regarding stent thrombosis, the data elements collected in the Case Report Forms are reasonable and the proposal to adjudicate cases of stent thrombosis is good. We do not believe that a summary report from the blinded dataset would be useful at this time. We expect that all of the data discussed on the stent thrombosis cases will be submitted with the NDA and that all data from the CRFs will be available in the SAS datasets.

    b. Regarding providing coronary angiograms, we believe that the reports of the angiograms should be adequate for initial review and we do not need to review either the reports or the actual angiograms now. You should submit the reports with the NDA and, if we judge that any review of actual angiograms is worthwhile, we will request specific angiograms then.

2. The proposal for the TIMI 38 Coronary Stent Registry is excellent. We do not have any recommendations for modifying your proposal at this time.

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

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/s/

Norman Stockbridge
1/3/2007 11:02:51 AM

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 prasugrel (CS-747).

We also refer to your amendment dated November 21, 2006 (serial # 378), containing your request for confirmation of statistical significance required for the TABY study (H7T-MC-TABY).

We have completed the clinical and statistical reviews of your submission and have the following comments and recommendations.

> A significance of $p<0.05$ in Study TABY (with a seven-day enrollment window) for superiority of prasugrel compared to clopidogrel would be sufficient for registration provided that Study TAAL also demonstrates a statistically significant benefit on its primary endpoint and you provide the evidence that clopidogrel is not adverse, *i.e.,* look for data in other settings to demonstrate clopidogrel's effect over time, as discussed at the September 22, 2006, meeting. If Study TAAL does not show a statistically significant benefit on its primary endpoint, then the results of Study TABY should be highly statistically significant to support approval based on Study TABY alone.

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

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/s/

Norman Stockbridge
12/19/2006 03:13:30 PM