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Subject:	**Minutes of a pre NDA Meeting w/FDA on May 30, 2007** **IND 63,449**
Date:	June 19, 2007
Pages including this sheet:	15

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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 NDA
Classification:	Type B
Meeting Date:	May 30, 2007
Preliminary Responses Sent:	May 29, 2007
Briefing Package Received:	May 1, 2007
Confirmation Date:	March 13, 2007
Meeting Request Date:	March 7, 2007
Meeting Chair:	Thomas Marciniak M.D.
Recorder:	Meg Pease-Fye, M.S.

List of Attendees:

Division of Cardiovascular and Renal Products

Thomas Marciniak, M.D.	Team Leader, Medical Officers
Karen Hicks, M.D.	Medical Officer
Elena Mishina, Ph.D.	Clinical Pharmacology and Biopharmaceutics
James Hung, Ph.D.	Director, Division of Biometrics I
Meg Pease-Fye, M.S.	Regulatory Health Project Manager

Eli Lilly

Cheryl Beal Anderson, Pharm.D.	US Regulatory Affairs
Norma Ascroft	US Regulatory Affairs
Elizabeth Bearby, Pharm.D.	US Regulatory Affairs
Eileen Brown, Ph.D.	Statistics
Javan Collins	Product Team Leader
William Macias, M.D., Ph.D.	Product Team Medical
Elena Moscarelli	Global Product Safety
Lan Ni	Pharmacokinetics
Jeff Riesmeyer, M.D.	Product Team Medical
Govinda Weerakkody, Ph.D.	Statistics

Daiichi Sankyo Co., Ltd:

Rich Cuprys, M.S.	Regulatory
Howard Hoffman, M.D.	Regulatory
Francis Plat	Clinical Development
Ching Hsu	Statistics
Masafumi Yokota	Japan Regulatory

Consultants:

Eugene Braunwald, M.D.	Clinical
Stephen Wiviott, M.D.	Clinical

BACKGROUND

Lilly is planning to stop collecting data for their pivotal study, H7T-MC-TAAL, TRITON-TIMI 38 (TAAL) for the NDA filing near the end of September 2007 and to target their submission at the end of 2007/early 2008. They requested this meeting to discuss requirements for successfully filing a NDA for prasugrel, and to obtain feedback on the content of the Common Technical Document (CTD) and electronic CTD (eCTD) format supporting registration. Lilly and Daiichi Sankyo also seek any insight and advice from the FDA that would lead to an efficient review of the application.

Eli Lilly and Company, Daiichi Sankyo, and the Thrombolysis In Myocardial Infarction (TIMI) Study Group have had several formal interactions with the FDA concerning prasugrel:

End of Phase 1 meeting in September 2002
Protocol Guidance meeting in October 2003
Special Protocol Assessment of the Carcinogenicity Protocols received on 24 July 2003
Special Protocol (TAAL) Assessment in October 2004
End of Phase 2A meeting in December 2004
End of Phase 2 meetings in August 2004, June 2006, and September 2006
Teleconference on Stent Thrombosis Data Requirements in December 2006 and February 2007

The sponsor submitted the Agency's minutes for reference in Appendix A of their briefing package.

Preliminary responses to the submitted questions were conveyed to the sponsor on May 29, 2007 and are reproduced below in *italics.*

DISCUSSION

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

Topic 1 - Non-Clinical

1. Does the FDA agree that the proposed non-clinical package is adequate for filing the NDA (Section 3.1.1)?

Preliminary Response

The content outline on preclinical studies looks adequate to file the NDA.

Meeting Discussion

There was no additional discussion concerning this topic.

Topic 2 - Biopharmaceuticals and Clinical Pharmacology

2. Does the FDA agree that the proposed clinical pharmacology package is adequate for filing the NDA (Section 3.2.1)?

Preliminary Response

The Division agrees.

Meeting Discussion

There was no additional discussion concerning this topic.

3. Does the FDA have any comments on the analysis plan (Appendix D) for the Phase 3, Study TAAL, PK data which, as previously agreed, includes direct measurement of only inactive metabolite concentrations (Section 3.2.2)?

Preliminary Response
The Division finds your analysis plan acceptable. The Division also has the following comments and questions:

1. *Given the proposed PD model (differential equation for P and E_{max} model for MPA), it seems that P=1 at baseline. Does that imply Kf=Kr?*

Meeting Discussion
Lilly pointed out that this was an error and the Division sent the responses pertaining to study TACJ, and they would like to discuss them here. It is correct that P=1 at baseline, and Kf=Kr is first order.

2. *Even though MPAm is defined as the MPA corresponding to maximum suppression of platelet aggregation, it is clear from the E_{max} model of MPA that even when P=0 (maximum suppression), MPA cannot reach MPAm unless PD50 is greatly less than 1. Is PD50 expected to be greatly less than 1?*

Meeting Discussion
Lilly stated that they expect the PD50 to be as high as 1.2.

3. *Is there any potential irreversible change to P at higher exposure level of Prasugrel that will invalidate the extrapolation from single dose to multiple dose?*

Meeting Discussion
Lilly noted that the PK/PD relationship is the same for both single and multiple doses. They expect the single dose to be predictive of the multiple dose in binding, metabolism, etc…

4. *Data sets and NONMEM code for population PK and PK/PD analysis should be submitted for review.*

Meeting Discussion
Lilly agreed and will submit them.

4. Does the FDA agree with the plan for early database lock for the PK subset of subjects in Study TAAL (Section 3.2.3)?

Preliminary Response
The Division agrees.

Meeting Discussion
There was no additional discussion concerning this topic.

Topic 3 - Clinically Significant Safety Events in TAAL

5. Does FDA agree with the list of Preferred Terms and central laboratory thresholds in Appendix F which prospectively identifies the clinically significant adverse events listed above? (Section 3.3.1)?

Preliminary Response

No, the Division does not agree.

Preferred Terms

1. *Please include QT prolongation and ECG observations of prolonged QT in the torsade de pointes SMQ.*
2. *Please perform an analysis using the angioedema SMQ.*
3. *Although the preferred terms listed in the Pre-NDA Briefing document are acceptable, the Division may ask the sponsor to perform additional analyses and queries using other terms or SMQs.*

Central Laboratory Thresholds

1. *Please perform two analyses for severe thrombocytopenia*
    a. *Platelet count < 50 x 10^9/L*
    b. *Platelet count < 100 x 10^9/L*
2. *Please perform two analyses for severe neutropenia:*
    a. *Absolute neutrophil count < 0.5 x 10^9/L*
    b. *Absolute neutrophil count < 1.0 x 10^9/L*
3. *Please perform two analyses for abnormal hepatic function:*
    a. *ALT value > 3 times the upper limit of normal*
    b. *ALT value > 3 times the upper limit of normal AND total bilirubin > 1.5 times the upper limit of normal*
4. *The Division may request additional analyses using different laboratory thresholds.*

Meeting Discussion

Lilly agreed to the terms above and clarified that the clinically significant events definition will include:

- Events adjudicated as TIMI major or TIMI minor
- SAE or abnormal laboratory values
    - Hematologic adverse event
    - Abnormal heparin function
    - Allergic reaction
    - Torsades de Points
- All events leading to discontinuation (serious or non-serious)

Topic 4 - Clinical Summary Documents

6. Substantial evidence of efficacy will be driven by Study TAAL as such, does the FDA agree with presenting data in the Clinical Summary of Efficacy from Study TAAL, TAAH, and TABL individually, noting that data from these studies will not be integrated (Section 3.4.1.1)?

Preliminary Response
Presenting the results separately by study without integration is acceptable.

Meeting Discussion
There was no additional discussion concerning this topic.

7. Does the FDA agree with the plan to organize safety data into the three databases as outlined (Section 3.4.1.2)?

Preliminary Response
Yes, the Division agrees.

Meeting Discussion
There was no additional discussion concerning this topic.

8. Does the FDA agree with the plan to present the analysis of the safety data in the Summary of Clinical Safety/Section 2.7.4 and 5.3.5.3 as described (Section 3.4.1.3)?

Preliminary Response
Yes, the Division agrees.

Meeting Discussion
There was no additional discussion concerning this topic.

9. Does the FDA agree with the proposed plan to provide safety data for ongoing and completed studies in the safety update (Section 3.4.1.4)?

Preliminary Response
In addition to what is proposed, the Division would like to receive any available late follow-up safety data from TAAL.

Meeting Discussion
Lilly stated that pending cases will be updated in the Safety Update to be submitted ~month 4 of the review cycle.

10. If upon review of the submission package, the FDA agrees with our request for a priority review, does the FDA wish to receive this update earlier than the fourth month of the review cycle (Section 3.4.1.4)?

Preliminary Response
No, thank you.

Meeting Discussion
There was no additional discussion concerning this topic.

Topic 5 - Data Set and Data Presentation

11. Does the FDA accept the Sponsors' process for submitting transport files and associated documentation (Section 3.5.1)?

Preliminary Response

It is not clear from your description of analysis datasets that you intend to provide all raw data transcribed from case report forms. These data are needed as well as datasets ready for analysis.

Meeting Discussion

The dataset will contain the raw data from the case report forms and derived variables and analysis datasets. Lilly will provide a map outlining shortcuts for the character limitation. Dr. Marciniak stated that he would like to see these raw data for events in addition to those for efficacy. Lilly will provide this information in the NDA submission. Dr. Marciniak requested multiple records for adverse events to include vitals, labs, etc...

12. Does the FDA accept sponsors' plan not to submit routine listings including baseline characteristics, adverse events, and concomitant medication as part of the Study TAAL CSR, given that the full analysis data sets for TAAL will be submitted (Section 3.5.1)?

Preliminary Response

Please submit PDF files of the routine listings.

Meeting Discussion

Lilly requested clarification of "routine listing" noting their intention to include a patient-by-patient listing (one patient per line). All the data in the CRF will be included in this listing, as well as a narrative. Further, Lilly will provide a preliminary template for the Division's consideration.

13. Does the FDA confirm there will be no restriction on dataset size, and that datasets greater than 100 MB need not be split (Section 3.5.2)?

Preliminary Response

Yes, the Division confirms there will be no restriction on dataset size. Please do not split datasets.

Meeting Discussion

There was no additional discussion concerning this topic.

Topic 6 - Case Report Forms, CEC Dossiers, Patient Narratives

14. Does the FDA agree that the plan for the inclusion of CRFs and CEC dossiers from the pivotal Study TAAL is adequate for submission (Section 3.6.1.1)?

Preliminary Response

No, the Division does not agree.

For TAAL:

1. *Please submit case report forms for*
    a. *all deaths*
    b. *all discontinuations due to adverse events (not just serious adverse events)*

c. *all serious adverse events*

regardless of whether or not the event is assessed as related or unrelated by either the investigator or sponsor.

2. *For all patients who died, for all patients who permanently discontinued study drug, and for all patients who experienced serious adverse events, the Division requests that all information collected from the study site be part of the case report form, not simply that information contained in documents labeled "CRF."*
3. *We also request case report forms for the following adverse events:*
   a. *All clinically significant serious bleeding*
   b. *All clinically significant thrombocytopenia (and not just severe thrombocytopenia)*
   c. *All clinically significant neutropenia (and not just severe neutropenia)*
   d. *All clinically significant abnormal hepatic function*
   e. *All clinically significant allergic reactions*
   f. *<u>All events</u> of Thrombotic Thrombocytopenic Purpura (TTP)*
   g. *<u>All events</u> of leukopenia/agranulocytosis*
   h. *<u>All events</u> of Pancytopenia/Aplastic Anemia*
   i. *<u>All events</u> of Thrombotic Thrombocytopenic Purpura (TTP)*
   j. *<u>All events</u> of Torsade de Pointes*
      i. *The Torsade de pointes case definition should also include terms reflecting QT prolongation and ECG observations of prolonged QT*
   k. *<u>All events</u> of angioedema (MedDRA SMQ)*
   l. *Please provide a summary listing of adverse events a through k by category*
4. *Please submit a summary listing of all serious adverse events*
5. *Please submit a summary listing of all discontinuations due to serious adverse events*
6. *Please submit a summary listing of all non-serious adverse events*
7. *Please submit a summary listing of all discontinuations due to non-serious adverse events*
8. *Case Report Forms for patients with adverse events (other than those requested above) should be available within 1 week of the Agency's request.*

<u>Meeting Discussion</u>

Lilly requested clarification as to what the Division meant by "summary listing" and Dr. Hicks noted that she is looking for separate PDF files listing all serious adverse events and all non-serious adverse events. Lilly should also indicate which serious adverse events or adverse events led to discontinuation. The PDF files should include patient ID, age, sex, SAE or adverse event, treatment group, etc. Lilly offered to submit a mock-up for consideration.

Additionally, the sponsor showed the following slides to demonstrate their intent for submitting Case Report Forms, Patient Narratives, and CEC Packets.

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They noted the 3 components:

- Core CRF (~74 pages)
- Endpoint CRF (11 to 9 pages)
- CEC Dossier (~10 to 40 pages)

Dr. Marciniak noted that sometimes the SAE reports and CEC packages are not included and the Division is interested in some form of consolidated CRF that has the raw data, SAE reports and, most importantly, the original comments from the investigator. He noted that often these comments provide pertinent data that should not be translated or omitted through editing. When Lilly offered to type the narrative from the adverse event form, Dr. Marciniak noted that copies of the original forms may be requested to verify the inclusion of the information that should have been collected. Further, the source documents should be in one location. He cited a recent refusal-to-file action due to narratives not in alignment with the CRF. Lilly offered to submit CIOMS report along with CRF and Dr. Marciniak agreed.

The Division also clarified that the Code of Federal Regulation states that this information should be submitted for all deaths and all patients who discontinue due to an adverse event, not just a serious adverse event. The narrative requirement comes from the ICH guidelines. Dr. Marciniak encouraged Lilly to be prepared to provide the serious adverse event report with accompanying full CRF within a week of request for any events of concern other than deaths or withdrawals identified by a reviewer. The Division noted their concern for the submission clock for a priority review when there is a large gap between when the information is requested and when it is submitted for review. The Division also requested, where possible, a machine readable version. Lilly noted that most are available only in paper, but would commit to turning around the request within one week.

15. Does the FDA require CEC dossiers for any additional endpoints sent for adjudication (Section 3.6.1.1)?

Preliminary Response
For TAAL, please submit all available CEC dossiers (and not just CEC dossiers for patients who died or permanently discontinued study drug as a result of a serious adverse event, regardless if the event was assessed as related by either the investigator or the Sponsors).

Meeting Discussion
Lilly stated that their CEC packets for suspected events are part of the CRF and believe them to be very comprehensive and produced the following slide:

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16. Does the Agency agree that the plan for the inclusion of patient narratives from the pivotal Study TAAL is adequate for submission (Section 3.6.1.2)?

Preliminary Response
No, the Division does not agree.

For TAAL:

1. *Please submit narratives for*
    a. *all deaths*
    b. *all discontinuations due to adverse events (not just serious adverse events)*
    c. *all serious adverse events*

    regardless of whether or not the event is assessed as related or unrelated by either the investigator or sponsor.
2. *We also request narratives for the following adverse events:*
    a. *All clinically significant serious bleeding*
    b. *All clinically significant thrombocytopenia (and not just severe thrombocytopenia)*
    c. *All clinically significant neutropenia (and not just severe neutropenia)*
    d. *All clinically significant abnormal hepatic function*
    e. *All clinically significant allergic reactions*
    f. *All events of Thrombotic Thrombocytopenic Purpura (TTP)*
    g. *All events of leukopenia/agranulocytosis*
    h. *All events of Pancytopenia/Aplastic Anemia*
    i. *All events of Thrombotic Thrombocytopenic Purpura (TTP)*

j. All events of Torsade de Pointes
i. The Torsade de pointes case definition should also include terms reflecting QT prolongation and ECG observations of prolonged QT
k. All events of angioedema (MedDRA SMQ)

3. Narratives for patients with adverse events (other than those requested above) should be available within 1 week of the Agency's request.

Meeting Discussion
There was no additional discussion concerning this topic.

Topic 7 - Proposed Labeling

17. Would the FDA comment on the proposed plan to present, in labeling, bleeding data from Study TAAL based on all adjudicated events in the all ACS population (combining subjects with UA, NSTEMI and STEMI) (Section 3.7.1)?

Preliminary Response
The Division has no comment at this time.

Meeting Discussion
There was no additional discussion concerning this topic.

18. In the prasugrel clinical development program, based on studies with an active comparator, it is difficult to identify non-hemorrhagic adverse reactions that may be product-specific. Under this scenario, would the FDA provide insight into the development of the adverse reactions section of the labeling (Section 3.7.1)?

Preliminary Response
The Division needs clarification on what you are considering to be non-hemorrhagic adverse reactions that may be product-specific. As such, the Division has no comment at this time.

Meeting Discussion
There was no additional discussion concerning this topic.

19. A patient package insert is not planned. Patient counseling information will be included in the physician's insert as warranted by the data. Does the FDA agree with this plan (Section 3.7.1)?

Preliminary Response
No, the Division does not agree. The Division recommends development of a patient package insert.

Meeting Discussion
Lilly asked if this is a class request since clopidogrel currently does not have a patient package insert. The Division is mainly concerned about patient compliance and potential effects. Lilly agreed to submit their draft by Day 60 of the review.