

Minutes of a Meeting

Meeting Date: August 4, 2004
Application: IND 63,449
CS-747 (LY640315)
Sponsor: Eli Lilly
Type of Meeting: B
Classification: End of Phase 2
Meeting Request: March 23, 2004
Confirmation Faxed: March 23, 2004
Mtg. Package Rec'd: July 16, 2004

Meeting Chair: Robert Temple, M.D.
Meeting Recorder: Meg Pease-Fye, M.S.

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation I
Thomas Marciniak, M.D., HFD-110, Acting Deputy, Division of Cardio-Renal Drug Products
Abraham Karkowsky, M.D., Ph.D., HFD-110, Team Leader, Medical Officer
Mehul Desai, M.D., HFD-110, Medical Officer
Salma Lemtouni, M.D., M.P.H., HFD-110, Medical Officer
Albert Defelice, Ph.D., HFD-110, Team Leader, Pharmacology
Belay Tesfamariam, Ph.D., HFD-110, Pharmacologist
Elena Mishina, Ph.D., HFD-860, Clinical Pharmacology and Biopharmaceutics
James Hung, Ph.D., HFD-710, Team Leader, Statistics
Charles Le, Ph.D., HFD-710, Statistics
Meg Pease-Fye, M.S., HFD-110, Regulatory Health Project Manager

Eli Lilly Participants:

Mark Barbato, Product Platform Leader
Elizabeth Bearby, Pharm.D., Regulatory Fellow
John Brandt, M.D., Medical Advisor, Clinical Diagnostic Medicine
Leslie Carter, Pharm.D., Director, Global Regulatory Affairs
Nagy Farid, Ph.D., Research Advisor, ADME
Daniel Ness, Ph.D., Principal Research Investigator, Toxicology
Jeff Riesmeyer, M.D., Clinical Research Physician
Holger Schilske, MD, Cardiovascular Medical Director
Kenneth Winters, MD, Medical Fellow
Govinda Weerakkody, PhD, Principal Research Scientist, Statistics
Bernie Zeiher, MD, Director, Critical Care Medical

Sankyo Participants:

Howard Hoffman, MD, Executive Director Regulatory Affairs
Laurent Kassalow, Ph.D, Staff Biostatistician
Jeff Warmke, Ph.D, Senior Director, Global Project Management

Consultants:

Dr. Elliot Antman, MD
Dr. Eugene Braunwald, MD
Dr. Steve Wirriott, M.D.

Background:

This meeting is to discuss the proposed Phase 3 registration study design, statistical analysis plans, and planning and registration issues for this CS-747. The proposed indication is:

┌

b(4)

└

The sponsors had two previous meetings with FDA; an End-of-Phase 1 meeting on September 20, 2002, and a Protocol Guidance Meeting on October 16, 2003. The following conclusions were reached:

September 20, 2002

- The non-clinical safety pharmacology and toxicology testing strategy is acceptable to support clinical development and registration of CS-747.
- One large, well-controlled Phase 3 study in patients with ACS is acceptable with a superiority endpoint.
- The composite primary efficacy endpoint (death from CV causes, nonfatal MI, and nonfatal stroke) is acceptable for a superiority trial.
- An adequate assessment will be made of any potential effect on QT interval.

October 16, 2003

- A single pivotal study with $p < 0.05$ is acceptable for registration provided it is a superiority study against active control. FDA cautioned the sponsors against stopping the study for efficacy following an interim analysis.
- The sponsors will submit the registration protocol under a Special Protocol Assessment.
- The sponsors will have additional discussions around the clinical pharmacology package.

Meeting:

Discussion Point #1 Dose Selection

1. Does the FDA agree with the proposed CS-747 doses for the Phase 3 study?

Agency Response: Based on the data from previous studies, the sponsor proposed a loading dose of 60 mg and a maintenance dose of 10 mg of CS-747 HCL salt to use in the pivotal Phase 3 study. The Agency agrees with the choice of the dose.

Discussion Point # 2 Phase 3 Study

1. Does the FDA agree that clopidogrel is the appropriate comparator for the proposed patient population in the Phase 3 study?

Agency response: Yes. The study design will seek to show superiority.

2. Does the FDA agree with the proposed timing for loading dose administration?

Agency response: This is acceptable to Agency.

3. Does the FDA agree with the definition for treatment-related life-threatening bleeding to be used in the Phase 3 study?

Agency response: The sponsors clarified the definition as including “major bleeding” and “intracranial hemorrhage.” Dr. Temple asked how excessive bleeding related to coronary artery by-pass graft (CABG) would be handled. The sponsors noted that these events would be tracked but are not part of the primary endpoint. The Division noted its interest in seeing this data.

4. Does the FDA agree that the proposed duration of the Phase 3 study is adequate to register CS-747 with an indication for chronic therapy?

Agency response: The Agency finds this question difficult to answer at this time. Six months seems acceptable for the period after the procedure, but what to say about continued use would depend upon how much clinical benefit is seen. This will be a review question.

5. Does FDA agree with the proposal of the availability of the CEC packets and classification forms during the NDA review if needed? Additionally, is it acceptable that an electronic database of routine management ECGs will not be available from the Phase 3 study?

Agency response: The Agency wants to see samples of clinical events, including case report forms, as well as source documents. Specifically, deaths, discontinuations and all bleeding events should be considered. The sponsors agreed to make this information available.

6. Does the FDA agree with the definitions of each component of the primary endpoint: CV death, nonfatal MI, and nonfatal stroke?

Agency response: The Agency agrees.

Discussion Point # 3 Statistical Analysis Proposal for Phase 3

1. Does the FDA agree with the proposal to conduct the statistical analysis using the primary composite triple endpoint in the UA/NSTEMI population? If the result of this analysis demonstrates superiority, does the FDA agree with the proposal to then test the composite triple endpoint in the entire ACS population?

Agency response: The Agency agrees, but with one caveat: if the results for the first group are so they drive the second analysis, this will not be sufficient to support the broader claim.

2. If the statistical analysis using the primary composite triple endpoint in the UA/NSTEMI population demonstrates superiority but the analysis on the entire population does not, it is the intention of the sponsors to submit the study for registration based on the result of demonstrated superiority for the primary analysis for the UA/NSTEMI population. Does FDA agree that this would be an acceptable strategy?

Agency response: The Agency agrees.

3. Does the FDA agree with the proposal for patient stratification at randomization?

Agency response: The Agency finds this acceptable.

4. Does the FDA agree with the proposed method for primary statistical analysis?

Agency response: Dr. Hung suggested that the confidence interval for the hazard ratio be generated over time if the hazard ratio is not constant over time. In response to a question from Dr. Temple, the sponsors noted their intent to retain blood samples. Dr. Temple suggested the sponsors look for biomarkers, including placental growth factor (PIGF) and soluble CD40 ligand as indicators for acute coronary syndrome and increased risk of cardiovascular events.

5. Does the FDA agree with the proposal for testing all the secondary endpoints for labeling?

Agency response: The Sponsor is proposing to test each secondary endpoint at 0.05 level. Although some of the secondary endpoints are closely correlated, others are not. Multiplicity adjustment is needed to control the total alpha at 0.05 for all the tests of the secondary endpoints.

6. Does the FDA agree with the proposed patient population designated for the safety and efficacy analyses?

Agency response: The Agency agrees.

Discussion Point #4 Data Monitoring Committee

1. Does the FDA agree with the planned DMC interim review intervals and objectives?

Agency response: The Agency agrees.

2. Does the FDA agree with the proposed stopping rules for safety?

Agency response: The Agency agrees.

3. Does the FDA agree with the proposed stopping rule for futility?

Agency response: The Agency agrees.

4. Does the FDA agree with the proposed stopping rule for overwhelming efficacy?

Agency response The Agency agrees with the updated interim analysis plan for overwhelming efficacy.

5. Does the FDA agree that using the data analysis group internal to a contract research organization is acceptable for preparing analyses for data monitoring committee review in lieu of an external statistician?

Agency response: The Agency agrees.

Discussion Point #5 Pediatric Study Waiver Request

1. Lilly and Sankyo have not and do not intend to conduct studies with CS-747 in a pediatric population as the drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients. Does the FDA agree to grant a pediatric study waiver for CS-747 at the time of NDA submission?

Agency response: The Agency agrees.

Discussion Point #6 Submission Considerations

1. If the Phase 3 registration study meets its stated objectives and demonstrates a favorable risk-benefit profile, would the CS-747 NDA be considered for priority review?

Agency response: The Agency will give this consideration.

Action Items:

1. The sponsors will request a separate End-of-Phase 2 meeting to discuss the large number of CMC topics to be addressed. They will also request an End-of-Phase 2A meeting with the Biopharmaceutics Division to discuss proposed studies.
2. The sponsors will conduct a clinical QT/QTc study, the design of which will be discussed at the EOP2A meeting. ECGs will be electronically captured in this study and will be part of the NDA submission.
3. The sponsors will submit data on clinical events, including death, discontinuation and major bleeding events.

Other Discussion Points

1. In response to a question from Dr. Temple, the sponsors noted that platelets return to normal after 72 hours to 5 days, adding that the drug effect is irreversible and lasts for the life of the platelet. Dr. DeFelice asked if animal antigenicity studies detected any autoantibodies being raised to platelets if the drug is covalently bound to them. The sponsors have not seen thrombocytopenic effects and are trying to raise antibodies to metabolite(s), which may be on the platelet surface, as an assay for the metabolite(s)

2. CS-747 is metabolized by CYP3A4, and there is controversial information in the literature for predicting the possible influence of CS-747, if any, on the pharmacokinetics of co-administered statins, some of which are also substrates for CYP3A4. The Agency recommended studying the interaction between CS-747 and statins, and the sponsor proposed to study the atorvastatin-CS-747 drug-drug interaction.
3. Dr. Temple noted that the Agency is particularly interested in drug effects for the elderly (over 75 years of age) and women.

Conclusions:

1. The proposed doses are acceptable
2. The statistical plan for the Phase 3 study is acceptable
3. The data monitoring plan is acceptable
4. The Agency agrees that a pediatric waiver request is appropriate

Date Minutes Drafted: August 6, 2004
Date Minutes Finalized: August 30, 2004

Signature minutes preparer: _____
Meg Pease-Fye, M.S.

Concurrence, Chair: _____
Robert Temple, M.D.

Reviewed:
R. Temple 8/25/04
T. Marciniak 8/24/04
A. Karkowsky 8/15/04
S. Lemtouni 8/22/04
A. Defelice 8/10/04
B. Tesfamariam 8/10/04
E. Mishina 8/10/04
J. Hung 8/13/04
C. Le 8/11/04

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

/s/

Robert Temple
9/1/04 07:35:13 PM

Executive CAC

Date of Meeting : July 22, 2003

Committee: David Jacobson-Kram, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Abigal Jacobs, Ph.D., HFD-540, Member
C. Joseph Sun, Ph.D., HFD-570, Alternate member
Albert DeFelice, Ph.D., HFD-110
Belay Tesfamariam, Ph.D., HFD-110, Presenting Reviewer

Author of Minutes: Belay Tesfamariam

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review

The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following section E of the 'Guidance for Industry, Providing Regulatory Submission in Electronic Format, New Drug Application.'

IND number: 63,449
Drug name: CS-747 (LY 640315)
Sponsor: Eli Lilly & Co., Indianapolis, IN

Background: CS-747 is a member of thienopyridine class of antiplatelet agents. It is an inhibitor of ADP-induced platelet aggregation by direct inhibition of ADP binding to its receptor. CS-747 is a prodrug that is de-esterified to form an active metabolite that irreversibly inhibits P2Y₁₂ ADP receptor and thus prolong bleeding time. Bleeding is a potential risk that may be expected with CS-747 due to the mechanism of action of inhibition of platelet aggregation.

Rat Carcinogenicity Study Protocol and Dose Selection:

The dose selection was based on changes observed in repeated oral administration of CS-747 at doses of 0, 10, 30, 100, or 300 mg/kg/day for 3- and 6-month study in Fisher 344 rat (n=10-15). At 100 mg/kg, body weight gain was decreased by 17 % and 19% in males and females, respectively. Prothrombin times and activated partial thromboplastin times (APTT) were prolonged in rats receiving ≥ 100 mg/kg. Slight anemic tendencies in the group treated with ≥ 100 mg/kg and slight increases of reticulocyte ratio in female rats treated with 300 mg/kg were observed. Prothrombin and activated partial thromboplastin times were prolonged rats treated with ≥ 100 mg/kg, and fibrinogen levels were increased in the 300 mg/kg group. Histopathological examination revealed hypertrophy of the hepatocytes in the ≥ 30 mg/kg group. These changes are consistent with enzyme induction. The maximal tolerated dose (MTD) is estimated to be 100 mg/kg/day. The AUC₀₋₂₄ of the active metabolite (R-138727) at the MTD is about 189-fold higher than that projected in human plasma levels.

The sponsor proposes a 2-year carcinogenicity study with CS-747 HCl in the Fischer 344 rat at oral doses of 0, 10, 30, and 100 mg/kg/day (n=55/sex/group). The vehicle to solubilize CS-747 is 0.5 % w/v tragacanth solution. Animals in the control group will receive the vehicle (0.5% w/v tragacanth solution).

Executive CAC recommendations and Conclusions:

The Committee concurred with the proposed doses of 0, 10, 30, 100 mg/kg/day, based on MTD (decrease in body weight) and a variety of toxicities, including irreversible inhibitor of platelet function and thus prolong bleeding time.

Mouse Carcinogenicity Study Protocol and Dose Selection:

The dose selection was based on changes observed in repeated oral administration of CS-747 at doses of 0, 100, 300, or 1000 mg/kg/day for 3-month study in Crj:B6C3F1 mice (n=10). Doses of 1000 mg/kg/day caused decrease body weight gain by 46 to 62%. In the 300-mg/kg group, the primary effects were suppression of body weight gain by 16 and 28% in males and females, respectively, increased liver weight, and hypertrophy of the centrilobular hepatocytes. Doses of 100 mg/kg/day did not cause overt toxicity, although increased liver weight was observed. Hematology revealed decrease in red blood cell count, hemoglobin, hematocrit and MCHC and increase in reticulocyte ratio and MCV in the 1000 mg/kg group. The MTD is estimated to be 300 mg/kg/day. The AUC₀₋₂₄ of the active metabolite (R-138727) and primary human inactive metabolite (R-106583) at the MTD were > 265-fold higher than that projected in human plasma levels.

The sponsor proposes a 2-year carcinogenicity study with CS-747 HCl in Crj:B6C3F₁ mice at oral dose of 0, 30, 100 and 300 mg/kg/day (n=55/sex/group). Organs and tissues of all animals will be fixed with phosphate buffered formalin for histopathology examination. Representative examples of normal and abnormal findings will be photographed when drug-related changes are observed.

Executive CAC recommendations and Conclusions:

The Committee concurred with the proposed doses of 0, 30, 100, 300 mg/kg/day, based on decrease in body weight gain at three months and decrease in RBC count at 300 mg/kg/day. It was also noted that the active metabolite exposure ratio is quite high (about 200:1).

If the sponsor plans histological evaluation of tissues from only control and high dose treatment groups, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:

- (a) for any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups

- Co) for an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, they will also need to look at the next lower dose group

- (c) for an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma etc.; see McConnell et al, JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level,

- (d) for an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

- /Division File, HFD-110
- /Team leader, HFD-110
- /Reviewer, HFD-110
- /CSCO/PM, HFD-110
- /ASeifried, HFD-024

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

/s/

David Jacobson-Kram
7/24/03 10:24:48 AM

Minutes of a Meeting between Eli Lilly and Company, and the FDA

Date: October 16, 2003
Sponsor: Eli Lilly
Subject: IND 63,449
CS-747, Phase 3 Clinical Trial Design
Type of Meeting: B
Briefing materials received: September 25, 2003

FDA Participants:

Robert Temple, M.D., Director, Office of Drug Evaluation I
Douglas C. Throckmorton, M.D., Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D., Deputy, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D., Medical Team Leader, HFD-110
Shari Targum, M.D., Medical Officer, HFD-110
Elena Mishina, Ph.D., Clinical Pharmacology and Biopharmaceutics, HFD-860
James Hung, Ph.D., Team Leader, Biostatistics, HFD-710
Belay Tesfamariam, Ph.D., Pharmacologist, HFD-110
Edward Fromm, Regulatory Health Project Manager, HFD-110
Meg Pease-Fye, Regulatory Health Project Manager, HFD-110

Eli Lilly Participants:

Leslie Carter, Pharm.D., Regulatory Affairs
Elizabeth Bearby, Pharm.D., Director, Regulatory Affairs
Jen Stotka, M.D., Executive Director, Regulatory Affairs
Ken Winters, M.D., Medical Advisor
Jeff Riesmeyer, M.D., Clinical Research Physician
Holger Schilske, M.D., Executive Director, Medical
Govinda Weeakkody, Ph.D., Statistician
Jamie Croaning, Project Management
John Brandt, M.D., Laboratory Medicine

Sankyo Participants

Bruce Behounek, M.D., Sr. Director, Clinical
Jeff Warmke, Ph.D., Project Management

Consultant

Dr. Eugene Braunwald, M.D., TIMI Group

Background:

Eli Lilly requested this meeting to discuss preliminary Phase 3 clinical study design for CS-747 (LY640315) for treatment of patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). The Sponsor is requesting guidance with design elements such as population, study power and primary endpoints.

Meeting:

Lilly told the Division that they intend to request an End of Phase 2 meeting in Spring, 2004. They began with a brief summary of the status of their clinical development. They are currently testing their CS-747 against clopidogrel. Both clopidogrel and CS-747 are thienopyridine class of antiplatelet agents, and CS-747 is currently being tested using the salt form (CS-747 HCl), not the base form. They believe the salt form PK data will go forward to their Phase 3 trials, as its absorption appears unaffected by pH. The Sponsor noted that they want to test three hypotheses in the on-going trial:

1. CS-747 will achieve higher platelet inhibition than clopidogrel
2. CS-747 gives a more consistent response with less effect on increased vascular resistance
3. CS-747 may get to a higher, more consistent level of platelet inhibition more quickly

Lilly believes that CS-747 has a unique metabolic pathway that will enable it to accomplish the above goals.

In the planned phase 3 trial, it is expected that many patients entering the study will already be on clopidogrel. Lilly plans on using pre-treatment loading for patients who aren't already on clopidogrel; those who come to the study on clopidogrel won't get a loading dose. Patients will be randomized as soon as the investigators decide to either treat at the time of PCI or pre-treat, stratifying by pre-treatment or no pre-treatment. Dr. Braunwald explained that this study is looking at a comparison of two thienopyridines across a broad range of patients who:

- Go to the cardiac cath lab and have a PCI
- Go to the cardiac cath lab, but do not need a PCI, or
- Do not go to the cath lab

All patients eventually move to the out-patient phase of the trial with a one year follow-up during which the patients continue on the study drug. Dr. Temple clarified that if the patient does not go to the cath lab as planned, the patient would not be entered into the study but would be followed. The inclusion criteria are unstable angina, non-ST elevation MI (NSTEMI), or ST elevation MI (STEMI).

Dr. Throckmorton noted that the Sponsor would be seeking a claim for acute coronary syndrome (ACS) if the trial is successful, but that including the STEMI (ST-segment elevation myocardial infarction) population was unusual for ACS (*e.g.*, GP IIb-IIIa pathways). We would need to have a conversation on how to describe the population in the trial, if it is ultimately successful. He also noted that the comparator drug also did not have a claim in stented patients, and that the sponsor would need to be able to make a case that the comparator was not worse than placebo, based on whatever data they could obtain, in this population. The population with ST-segment elevations, for instance, would be an important population to understand the benefits of clopidogrel in, as we're not aware of lots of studies in that population with this drug.

Dr. Temple asked the Sponsor if they were considering a non-inferiority trial. The sponsor responded that, no, they were designing a superiority study with either the triple or quadruple endpoints and they would not include salvage or rescue angioplasty patients. They also noted that they would also exclude patients currently taking thrombolytic agents.

Dr. Targum asked for clarification concerning their definition for enzymatic MI, specifically in terms of cardiac troponin measurement. The Sponsor replied that troponin would be measured when the patient exhibited symptoms, and not as a routine guide.

Questions:

1. The Sponsor has proposed that this single superiority study with an active comparator (clopidogrel) would provide clinical evidence of effectiveness that is adequate for registration.

Population: Moderate to high risk ACS patients for whom invasive therapy is intended, including patients presenting with unstable angina, NSTEMI, and STEMI.

Comparator: clopidogrel tablets

Stratification: study drug pre-treatment (administering a loading dose of study drug 3 to 24 hours prior to PCI) versus no pre-treatment (administering a loading dose during the PCI).

Is the FDA in agreement with the study design?

FDA response: the design, as described, is acceptable. The robustness of the data will determine its overall adequacy for registration.

2. Does the FDA agree with the inclusion of patients previously on clopidogrel (capped at 20% of total study population) and the plan that these patients would be randomized directly to maintenance therapy without reloading of study drug?

FDA response: In general, in the United States, most patients will already be taking clopidogrel. Dr. Throckmorton said that the planned enrollment is acceptable.

3. The following composite endpoints are candidates for invasive management with PCI (with 1 year follow-up).

Triple endpoint: a composite of all-cause mortality, new nonfatal MI, or nonfatal stroke

Quadruple endpoint: a composite of all-cause mortality, new nonfatal MI, nonfatal stroke or ischemia-driven coronary revascularization.

Would the FDA agree to registration on superiority using co-primary endpoints by achieving either one of the two composite endpoints?

FDA response: The Sponsor acknowledged that they intend to achieve one or two endpoints and discontinue the patient. Broadly, the coronary vascularization is defined either as being mechanical or pharmacological. Dr. Throckmorton asked about the definition of ischemia-driven revascularization. Dr. Braunwald responded that the patient presents with symptoms of increased ischemia leading to revascularization, and believes it may extend to other arteries as there may be an effect on other lesions. Dr. Throckmorton agreed that the co-primary endpoints were acceptable. It's critical to continue to follow patients after they experience a non-fatal component of the endpoint.

4. Does the FDA agree with the proposed methodology for the efficacy analysis?