FDA response: Dr. Hung responded that, overall, the concept was acceptable. Dr. Hung asked for clarification of the α, explaining that since there were two endpoints, the α needs to be divided for each endpoint by taking into consideration that the two endpoints have three overlapping components and can be substantially correlated. The Sponsor further clarified their plan of combining the tests of the two endpoints to produce a global p-value that is to be compared with the overall α for showing a statistically significant treatment effect. Dr. Hung acknowledged that this may be a more statistically efficient way to show treatment effect based on the two endpoints, but raised the concern that, clinically, the result of such a combined global test would be difficult to interpret. It would also be difficult to write a label. There needs to be a plan for testing each of the two endpoints are the combined test achieves statistical significance.

Dr. Throckmorton added that he did not think it was in the company's best interests to stop the trial for interim analyses as there are good reasons for having a substantial sample size. First, there will be only one trial. Second, they also need to evaluate the safety of CS 747. The Sponsor noted that the two interim analyses planned are only for safety, although there may be one later for futility. Dr. Throckmorton noted that if the trial is stopped, all records from the DSMB will need to be submitted to the Division, and such stopping should only occur for clear outcomes (*e.g.*, death, MI).

5. Does the FDA recommend that the Sponsor consider loading doses greater than 300 mg of clopidogrel?

FDA response: The Sponsor intends to use 375 mg of clopidogrel in the trial (300 mg loading dose followed by a 75 mg maintenance dose). They noted that there are recent medical literature references referring to using 600 mg loading dose regimens and are concerned that they may reach the end of their trial and find that the 300 mg loading dose is no longer the standard of care for this indication. Dr. Throckmorton noted that 75 and 300 mg were acceptable, but did not wish to encourage a high loading dose. Further, clopidogrel does not have an indication for PCI.

Dr. Throckmorton asked if patients with drug eluting stents were included in the trial and the Sponsor replied that they would be and would collect data on observations.

6. Does the FDA agree with this proposal for monitoring serious adverse events?

FDA response: Dr. Throckmorton notes that primary and secondary outcomes were to be reported only if they were considered to be drug-related. He noted that when the sponsor sends in the phase 3 trial design as part of a Special Protocol Request, we can comment further on their proposal for monitoring serious adverse events.

7. Does the FDA agree that this pre- specified secondary endpoint, if met, could be included in final labeling?

FDA response: Please see previous discussion.

8. Does the FDA deem the proposed indication acceptable?

FDA response: The indication is compatible with our labels from other clinical settings. Dr. Throckmorton cautioned against using the term "atherothrombotic" as it is not well understood as an indication, and it mixes two processes that the average physician may not clearly distinguish.

Dr. Throckmorton also added a comment that he would like to see hospital events more clearly defined.

The Agency recommended discussing the ADME and PK/PD issues with the clinical pharmacology staff in a separate meeting.

Signature minutes preparer: _____
Meg Pease-Fye

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

Drafted: 10.19.03 Finalized: 11.04.03
RD:

Temple	11.03.03
Throckmorton	10.29.03
Stockbridge	10.28.03
Marciniak	10.28.03
Targum	10.24.03
Mishina	10.22.03
Hung	10.24.03
Tesfamariam	10.20.03
Fromm	10.27.03

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/s/

Robert Temple
11/7/03 05:57:21 PM

Meeting Minutes

Sponsor:	Eli Lilly and Company
Applications:	IND 63,449
Meeting was originally scheduled for August 13, 2002.	
Date Sponsor requested date change: June 24, 2002	
Date Meeting Confirmed:	July 11, 2002
Meeting Date:	September 20, 2002
Type:	EOP1
Classification:	B

Meeting Chair:	Douglas C. Throckmorton, M.D.
Meeting Recorder:	Zelda McDonald
External Participant Lead:	Leslie D. Carter, Pharm. D.

FDA Participants:

Douglas C. Throckmorton, M.D.	Director, HFD-110
Norman Stockbridge, M.D.	Team Leader, Medical, HFD-110
Shari Targum, M.D.	Medical Officer, HFD-110
Belay Tesfamarium, Ph.D.	Pharmacologist, HFD-110
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
Patrick Marroum, Ph.D.	Team Leader, Clinical Pharmacology Biopharmaceutics, HFD-860
Valeria Freidlin, Ph.D.	Statistician, HFD-710
Elena Mishina, Ph.D.	Pharmacokineticist, HFD-860
Zelda McDonald	RHPM, HFD-110

Eli Lilly:

Bruce Behounek, M.D.	Senior Director, Clinical Research (Sankyo)
John Brandt, M.D.	Medical Advisor, laboratory Medicine (Lilly)
Elizabeth Sloan, Pharm. D.	Director, Regulatory Affairs (Lilly)
Leslie Carter, Pharm. D.	Senior Regulatory Research Scientist (Lilly)
Paul Eisenberg, M.D.	Vice President, Internal Medicine (Lilly)
Nagy Farid, Ph.D.	Senior Research Scientist, Drug Disposition (Lilly)
James Molt, Ph.D.	Vice President, Regulatory Affairs (Sankyo)
Daniel Ness, D.V.M., Ph.D.	Research Scientist, Toxicology (Lilly)
Stanley Sorgen	Program Leader (Lilly)
Govinda Weerakkody, Ph.D.	Research Scientist, Statistics (Lilly)
Kenneth Winter, M.D.	Senior Clinical Research Physician (Lilly)
Elliott Antman, M.D.	Consultant, TIMI Group

Background

CS-747 (LY640315), an adenosine diphosphate (ADP) receptor antagonist, is a potent inhibitor of ADP-mediated platelet aggregation. CS-747 is being investigated as a therapeutic agent for the secondary prevention of thrombotic cardiovascular events I patients presenting with acute coronary syndromes (ACS), such as non-ST-segment elevation myocardial infarction or unstable angina. CS-747 may also prove to be effective in the prevention of cardiovascular complications in patients with ischemic stroke or peripheral arterial disease.

CS-747 was discovered and developed by Sankyo Co. Ltd., which sponsored all preclinical investigations and five completed Phase 1 studies in healthy subjects in the United Kingdom. CS-747 is a co-developed project between Sankyo and Eli Lilly and Co. (Lilly-Sankyo). Lilly-Sankyo has sponsored four completed Phase 1 studies I healthy subjects in the Netherlands and the United States. Lilly-Sankyo began another Phase 1 study in the US in July 2002. A total of 148 healthy subjects have received CS-747 in completed studies as of July31, 2002. Lilly-Sankyo requested this meeting to discuss the Phase 2 development plan and strategy for Phase 3.

Meeting:
After introductions and an overview of their program, the following questions were addressed:

#1. Dr. Throckmorton stated that the first question regarding the preclinical, pharm/tox testing strategy is acceptable with one exception. He asked how much Lilly-Sankyo knew about the effects of CS-747 on cytochrome P450. Lilly-Sankyo stated that they were presently testing the potential for CS-747 to interact with CYP enzymes glutathione transferases and whether it is a PGP substrate or inhibitor.
Dr. Throckmorton asked Lilly-Sankyo to discuss the data with the Division when it became available.
Dr. Throckmorton stated that the Division would need adequate assessment of the potential for an effect of CS-747 on the QT interval. This could be done as part of the initial clinical studies, and could be obtained from normal volunteers. Whether or not there is an effect will drive the need for additional studies. If Lilly-Sankyo knows there is a 3A4 interaction, they would need to state whether an interaction study was done with ketoconizole.

The Division had looked at the Guidance and found that mass balance, pH interaction and renal interaction would need to be addressed. Lilly-Sankyo stated that they had done a mass balance study and found that CS-747 is 65 – 70% excreted in the urine. They are in the process of doing the pH interaction and renal impairment studies.

#2. With regard to the proposed Phase 1b study, Dr. Throckmorton stated use of inhibition of platelet aggregation as a primary endpoint, although possibly helpful, would not support an efficacy claim because it is only a rough correlate for clinical benefit.

#3. Lilly-Sankyo proposed a Phase 2 study to demonstrate that the more potent inhibition of platelet aggregation and greater prolongation of bleeding time achieved with CS-747 do not result in unacceptable rates of bleeding complications. Dr. Throckmorton suggested that the primary endpoint be an efficacy endpoint instead of a safety endpoint so that the alpha would be spent on MACE with a potential to support clinical efficacy noting that the data could be pooled if pre-specified up front. Lilly-Sankyo asked if it were possible to have co-primary endpoints. Dr. Throckmorton said a statistical penalty would be paid with co-primary endpoints, therefore, he did not think it would be in Lilly-Sankyo's best interest to spend alpha on bleeding as an endpoint. Lilly-Sankyo would have to decide whether to do a safety study or a study large enough to obtain information on efficacy. He also pointed out that Lilly-Sankyo should pre-specify the order of testing the secondary endpoints, i.e., stop if lose on the first one. Dr. Throckmorton agreed that patients undergoing either planned or urgent coronary stenting are an acceptable population for the proposed study. He encouraged Lilly-Sankyo to maximize the data they could get from such a population.

#4. Dr. Throckmorton agreed with the use of clopidogrel as the comparator for the proposed Phase 2 study, however, the Division has concerns about reporting rates and interpretability when part of a study is unblinded. Dr. Stockbridge asked how hard it would be to double dummy.
Lilly-Sankyo stated that they had thought about that but wanted to see the PK/PD data before deciding. If there is significant impairment of clopidogrel effect in the early hours, then they may consider blinding the study.

Lilly-Sankyo's questions 5 and 6 were addressed in the above responses.

Lilly-Sankyo had the following questions so as to provide guidance on their Phase 3 program that is currently under development. They will finalize the Phase 3 plan and submit it for discussion at a future End-of-Phase 2 meeting.

#7. Does the FDA agree that one large, well-controlled Phase 3 study in patients with acute coronary syndromes (ACS) is acceptable for NDA submission and approval? Does the FDA agree with the proposed study population and treatment duration planned for this study?

Dr. Throckmorton stated that Lilly-Sankyo is proposing a superiority study with a roll-back to non-inferiority if superiority is not established. He cautioned that although the proposal is viable, the Division will have difficulty interpreting a non-inferiority study. He noted that there will be an additional burden with the study, as proposed, since the margins are to be set for the active comparator. The Division will be asked to accept a non-inferiority margin based on a point estimate from a single study where the effect size is variable. That makes it harder to say that the correct margin has been chosen. It would be preferable to do a superiority trial or an add-on study, and at some point, Lilly-Sankyo would need to provide an argument as to why either is not a viable alternative. Lilly-Sankyo would also need to make a case for doing only one study, especially if it is a non-inferiority study. Up front, the standards for a non-inferiority study would have to be fairly broad. It is not impossible to do such study, and the Agency does realize that sometimes there is a need to look at other ways of studying a drug.

Lilly-Sankyo asked if they were too narrowly focussed and whether they should be looking at other disease states such as stroke and hi-risk vascular disease. Dr. Throckmorton stated that it may be easier to do a superiority trial against placebo, but he could not think of a population where such a trial could easily be mounted (perhaps ESRD?). If another trial was done and a benefit shown, he was not sure how it would fair since the study would have drawn on shared disease states. Lilly-Sankyo would have to make a case for doing a trial like HOPE.

#8. Does the FDA agree that the safety data from the proposed Phase 2 coronary stent study will be sufficient to allow inclusion of patients undergoing coronary stent implantation in the Phase 3 ACS study and to allow these patients to remain on blinded study drug (that is, either CS-747 or clopidogrel)?

Dr. Throckmorton agreed but asked if the patients would be rolled-over into the larger trial. Lilly-Sankyo stated that they had not planned to roll-over those patients, instead the patients in the Phase 3 study would continue on study drug, blinded, if the Phase 2 safety data are favorable. Dr. Throckmorton stated that the Division favors long-term follow-up and suggested that the patients from the Phase 2 study stay blinded and be rolled-over into the Phase 3 study to increase

the power of the study. Lilly-Sankyo stated that it would not be feasible since the study drug in the Phase 2 study will be a base, but the Phase 3 study drug will be the salt.

#9. Does the FDA agree with the proposed composite primary efficacy endpoint of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke?

Dr. Throckmorton stated that the proposal does not address adverse safety events. If there is more bleeding than with clopidogrel, there would be no point in submitting an application. Alternatively, an endpoint could be devised that captures bleeding and clinical benefit in the same endpoint. He recommended that Lilly-Sankyo submit a request for a special protocol assessment so as to obtain specific written comments and recommendations from the Division on the protocol.

Question 10 was address in the response to question 7.

#11. Does the FDA agree that the current plan for Phase 2 and Phase 3 supports the wording in the proposed indication if the proposed primary endpoints are achieved?

This question was not discussed since the data from the trials, if successful, will determine the labeling.

#12. Dr. Throckmorton stated that Lilly-Sankyo's question 12 regarding metabolites is very complicated. Dr. Throckmorton acknowledged that there is no information on active metabolites for clopidogrel, however, the Guidance states that if there are active enantiomers, an effort needs to be made to follow their plasma levels. He recommended that Lilly-Sankyo make a proposal that would collect that information in an at-risk sub-population. Lilly-Sankyo stated that they had done HPLC and mass spectrometry on the four enantiomers and were trying to determine the ratio, however, there seems to be conversion over time. Dr. Marroum suggested that Lilly-Sankyo look at ratios of the 40 mg dose (or some other single dose that is high enough to give measurable levels or a loading dose) in the at risk population and make inferences. The Division is not looking for full exploration of the PK. Evidence of different kinetics in a diseased population, if there is any, would be useful to have. Lilly-Sankyo stated that they were planning to take samples during the loading dose phase and look at the over-all ratios of the four enantiomers in the phase 1b study. If they can, they will include, the 40 and 60 mg loading doses. Lilly-Sankyo stated they would submit that data to the Division before starting the next phase. The Agency recommended that Lilly-Sankyo assess whether CS-747 is a potential inducer or inhibitor of CYP450 in vitro, and whether it is a substrate or inhibitor of PGP. Lilly-Sankyo was encouraged to obtain sparse plasma samples for population PK and PK/PD assessment in the future clinical studies in the target patient population.

Signature minutes preparer: _____

Concurrence, Chair: _____

Drafted 9/25/02 Finaled 10/2/02

RD:

Throckmorton	10/2/02
Stockbridge	10/2/02
Targum	10/1/02
Tesfamariam	10/1/02
Mishina	9/30/02
Hung	10/1/02
Freidlin	10/1/02
Marroum	9/26/02

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

/s/

Zelda McDonald
10/8/02 11:04:20 AM
CSO
Dr. Throckmorton signed-off on these minutes on 10/7/02 and they were faxed to the sponsor on 10/8/02.