

1 didn't understand the third one though. You will have to say  
2 that in plainer English.

3 DR. FLEMING: The third is that if you don't count  
4 death as an endpoint and you are looking at a time-to-event  
5 analysis on time to MI, those people are still in your  
6 analysis post their death. You are imputing, in essence, the  
7 time to their MI by the time to MI of other people who were  
8 free of MI at the time this person died but didn't die --

9 DR. LIPICKY: Okay, I retract my statement.

10 [Laughter]

11 DR. PACKER: We are making progress! Yes, Tom?

12 DR. FLEMING: Let me just largely concur with much  
13 of the rest of what has been said. As you can tell from this  
14 comment, I do believe death should be part of the endpoint.  
15 I do believe MI should be part of the endpoint. I have also  
16 been intrigued by the PURSUIT data and believe that there is  
17 a role for a CEC, but I believe that role of the CEC is, in  
18 essence, particularly in an unblinded trial, to get rid of  
19 the bias due to unblinding and, secondly, blinded or not, to  
20 achieve standardization.

21 What I think it isn't there for is to change the  
22 bar, and I think Rob has given some insights that I didn't  
23 have about maybe why the bar was changed so profoundly  
24 leading to a doubling of the number of events. It was  
25 intriguing there that those additional events that came in

1 were lesser associated with death, subsequent death, and  
2 were lesser impacted by the intervention.

3 My belief is endpoints ought to be clinically  
4 relevant. So, I am swayed to favor those that are  
5 investigator-detected. I am encouraged, Rob, by your point  
6 that when you had gone back to analyze the data what you  
7 found is that essentially those with 2- to 3-fold elevations  
8 -- if you had used that instead you would have come in  
9 concurrence. My belief on all of this then is that in  
10 essence should be investigator-driven assessment tweaked,  
11 but not profoundly changed by a standardized overview by the  
12 CEC.

13 The other comment I would make, for reasons we  
14 have discussed this morning, is I would prefer this death/MI  
15 endpoint to be assessed at 30 days.

16 DR. DIMARCO: Tom, that only reviews positives,  
17 not negatives.

18 DR. THADANI: No, no.

19 DR. FLEMING: Not necessarily, you know, you could  
20 achieve much of what you wish by reviewing the positives but  
21 you could, in fact, look at enzyme-based reviews but, as Rob  
22 was pointing out, not triggering any elevation to look at  
23 the case but significant elevation to look at the case.

24 DR. SEIGEL: Another perspective on the issue of  
25 investigator-determined versus CEC-determined endpoints is

1 to the extent that the rates may vary differently, as has  
2 happened on at least one occasion, even if the investigator-  
3 determined rate is perhaps the better measure of ultimate  
4 outcome and more clinically meaningful and, therefore,  
5 perhaps even more appropriate in the context of that trial,  
6 in the context of the discussion today we should also think  
7 about the implications of using the effect size in that  
8 trial for planning other trials, whether active control or  
9 not.

10           Let me point out that if the effect size that you  
11 are measuring is not one by precept criteria for an MI but  
12 by an investigator's judgment, unless you have all the same  
13 investigators with all the same judgment in your future  
14 trials, given that we see different effect sizes, depending  
15 on who calls the MI, it will add another very difficult  
16 variable to deal with in determining how to do an active-  
17 controlled trial, or even how to size any future trial. So  
18 that is an important point of variability that needs to be  
19 addressed.

20           I think on the issue of how different assessments  
21 correlate with outcomes, it ought to be noted that at least  
22 in some of these trials, I think the trials in question,  
23 often the investigator sends in the case report form in  
24 which he says whether or not there is an MI not at the time  
25 of the MI but after some period of time, such as at the end

1 of 30 days, at which point of time he may be aware as to  
2 whether the patient later died or had arrhythmias and that  
3 may influence his decision as to an infarct. So, that is  
4 something to think about.

5           Finally, I do want to get back to that question of  
6 inclusion of death. While I agree with everything that Tom  
7 said and I think it would be highly problematic to exclude,  
8 and unacceptable from my point of view, to exclude death,  
9 there is one thing Ray said which I think is important to  
10 note, and that is that we shouldn't be requiring a trend in  
11 the right direction if, in fact, we expect to have 8 deaths  
12 in each arm and if, in fact, we expect a very small effect  
13 on mortality or no effect on mortality, then if we really  
14 require that mortality trend in the right direction we are  
15 going to wind up failing a lot of trials simply because of  
16 chance. Half of them will go the wrong way if there is no  
17 effect on mortality. So, I would agree with Ray's  
18 observation in that regard.

19           You may want to put some limits on how much of a  
20 bad trend in mortality you are willing to accept, or there  
21 are other more sophisticated things like a composite can be  
22 a rank composite in which death is scored as a worse outcome  
23 than MI so that trends in that direction weigh a little  
24 more. But to actually require a trend is probably not  
25 appropriate.

1 DR. PACKER: Just to clarify, Ray and Jay, when  
2 one uses clinical composites, not just in this area in every  
3 single therapeutic area, although we generally say we like  
4 things to be concordant across the components, there is  
5 considerable leeway in terms of how that is conventionally  
6 interpreted, especially if a component is represented  
7 infrequently and goes in the wrong direction to a very small  
8 degree. I don't think this committee, and I don't think any  
9 process that I am aware of has held it against the sponsor,  
10 even for an important endpoint like death, when the number  
11 of deaths has been small and the numerical difference --  
12 small compared to the number of non-fatal events, and the  
13 numerical difference has been very small. Isn't that fair?

14 DR. SEIGEL: Well, to the extent to what this  
15 committee has done, I don't know -- I think that is  
16 appropriate, and that is the point I am making, that to  
17 actually require -- if you saw 10 treatment deaths and 8  
18 placebo deaths to say, well, that is a failed trial on that  
19 basis would be a rather extraordinary and inappropriate  
20 thing to do.

21 DR. LIPICKY: Since I am sort of winning --

22 [Laughter]

23 -- the other thing then is that I think the  
24 indication shouldn't read "death and" if we really know  
25 death just absolutely was not evaluated. I don't mind

1 including it. But then this thing should not be known for a  
2 mortality effect and something else. So, I would be  
3 comfortable leaving death in there if I didn't have to put  
4 it in the indication.

5 DR. CALIFF: Now, wait a minute. I went through  
6 this when I was a guest on the neurology committee where  
7 they approved a combination of drugs for prevention of  
8 stroke but not death and stroke. It is the same issue. The  
9 problem with that is just what Tom said. You have  
10 informative censoring of the deaths.

11 DR. LIPICKY: Once you see the results, if you  
12 really know that deaths are not different, then they can't  
13 have influenced your analysis for time to MI.

14 DR. CALIFF: Yes, they could.

15 DR. LIPICKY: How?

16 DR. CALIFF: If the people died in the different  
17 groups for different reasons or were at different risk of MI  
18 if they hadn't died.

19 DR. LIPICKY: Oh, I see.

20 DR. PACKER: I think what Ray is concerned about  
21 is not so much the statistical issues but the perceptual  
22 issues --

23 DR. LIPICKY: You don't know you prevented death.

24 DR. FLEMING: The essence here is death/MI, which  
25 does not mean you have proven death alone has been impacted.

1 That is the understanding we have to have.

2 DR. LIPICKY: Understanding how the drug becomes  
3 known is having influenced both.

4 [Multi-member discussion]

5 DR. FLEMING: You have influenced the composite  
6 endpoint of MI-free survival, that is true, but that does  
7 not mean you have proven an influence on survival itself.

8 DR. LIPICKY: Correct, but it is known to have  
9 done that the way these drugs are currently labeled with  
10 that kind of combined endpoint.

11 DR. SEIGEL: Well, they are labeled accurately,  
12 but I think in the sense that they are labeled to have had  
13 an effect on a composite endpoint, death and MI --

14 DR. LIPICKY: You and I understand that, but I  
15 think the average doctor doesn't.

16 DR. THADANI: Also the patient doesn't. The  
17 patient thinks you are going to make him live longer when  
18 you say death or MI to him. I think that is more implication  
19 so --

20 DR. LIPICKY: Oh, sure.

21 DR. THADANI: So, what really you are suggesting  
22 perhaps is making MI as the primary endpoint and put that as  
23 a secondary endpoint.

24 DR. PACKER: No, no, no.

25 DR. THADANI: Could you do that?

1 DR. PACKER: That would create a second disease to  
2 treat the first disease.

3 DR. THADANI: But you are treating the first  
4 disease to prevent death.

5 DR. PACKER: If you wanted to, you could fix this  
6 problem by saying that a treatment effect was shown on the  
7 combined endpoint of death and MI, and then put a second  
8 sentence in "but no effect was seen on mortality alone." If  
9 you wanted to fix it, if this is a problem, that would be  
10 the solution.

11 DR. LIPICKY: Well, there are a number of  
12 solutions but I wouldn't put the combined endpoint in there.

13 [Laughter]

14 DR. KONSTAM: I think it could be easier than that  
15 because, you know, I think that what people are saying --  
16 what Rob is saying, and I think everybody should agree with  
17 this, is that it could happen that there are deaths  
18 occurring that are preventing -- that if your primary  
19 endpoint was just MI, there could be deaths occurring that  
20 are preventing people who would have been having MIs from  
21 having MIs, and you don't want to have that happen, and so  
22 if you say, well, MI is where the money is and that would be  
23 my endpoint but you are going to have to look at the  
24 composite of deaths or MI for those reasons that, de facto,  
25 becomes the endpoint.



1           But what Ray is saying is when you start wording  
2 it that way, and I was on the same panel with you and I  
3 think we agreed and still wound up saying different things,  
4 which is common, because I don't know that there is a way of  
5 wording it that gets you away from the concept that you  
6 have, in fact, impacted on death.

7           So, maybe you just say when you word it, and this  
8 is what Ray is saying, you say the effect is on MI but we  
9 accept the fact that when we count MIs we cannot construct  
10 an endpoint that does not include death in the endpoint.

11           DR. PACKER: I am going to have three other people  
12 comment on this and then we are going to go on to the next  
13 presentation, regardless of any other points raised by their  
14 comments. Bob Fenischel first?

15           DR. FENISCHEL: Yes, I think that this in part  
16 repeats what Marvin just said, which is that the notion of  
17 what goes into the label and what constitutes a  
18 statistically defensible set of endpoints for use in  
19 defining a trial may be entirely different. What goes into a  
20 label is the summary of what we think happened in the body  
21 of trials and everything else we know about the drug, and a  
22 little bit of a hint about what we think we know about  
23 sister drugs, and all sorts of other information that  
24 somehow all pulls together.

25           I think in the past few years there has been a

1 tendency, reinforced fairly heavily by the committee, to say  
2 that labeling ought to reflect in exquisite detail what  
3 happened in the trials, as opposed to reflecting what we  
4 think we understand from the trials. I don't see that there  
5 is any contradiction in the law, certainly, to saying the  
6 trials must be constructed as Tom has instructed us, which  
7 is to say a composite endpoint has to include miscellaneous  
8 occurrences which might cause informative censoring, and  
9 then we step back and say what we know about the drug; what  
10 is the drug supposed to do; what may the drug be expected to  
11 do. Well, what we see from the trials is the drug prevents  
12 MIs.

13 DR. PACKER: David, you had a comment?

14 DR. KONG: Two issues. One is you can reflect the  
15 labeling for combined MI and death as this drug will reduce  
16 the likelihood of MI but not kill you while doing so. Number  
17 two is --

18 DR. PACKER: You can't get there from here because  
19 your confidence intervals go from here to New York.

20 DR. KONG: Right, but, you know, the idea being  
21 that you can demonstrate that you don't have a significant  
22 adverse effect on mortality --

23 DR. THADANI: You can't say that. The sample size  
24 is too small to say that. You need thousands and thousands  
25 of patients.

1 DR. KONG: Right, and that is why we can't use  
2 mortality alone. Number two is with respect to determining  
3 endpoints from investigator-adjudicated decisions, in the  
4 setting of active-controlled trials one of the potential  
5 biases if you are using non-inferiority arguments is that  
6 the investigators could potential bias the outcome by simply  
7 saying, "the more outcomes we report, then the more likely  
8 the treatments are going to look like each other," and that  
9 would be a reason for using central adjudication perhaps  
10 even blinded to whether you are doing a superiority or non-  
11 inferiority analysis.

12 DR. PACKER: Jeff, you have the last word.

13 DR. BORER: I would like to propose a principle  
14 here, which is that the reason to develop drugs and to  
15 approve them is to reduce the burden of disease on a patient  
16 as opposed to just reduce death. If that is true, then, you  
17 know, we have talked about death as one of the endpoints, MI  
18 as one of the endpoints, but I want to come back to the  
19 refractory ischemic symptoms because the existence of these  
20 is a situation that is not tolerable for a patient, and it  
21 is not unreasonable for a drug to minimize that burden.

22 Now, I think Rob's point is a very good one, as  
23 usual, that is, if you add that you don't know whether the  
24 power of your study is going to be improved by adding more  
25 endpoints or reduced. We don't know. It depends on the

1 pathophysiology underlying the problem and the action of the  
2 drug. But I want to ask, and I would like to hear Tom's  
3 comment even though Milton may not allow him to do it --  
4 Tom's comment about the impact of eliminating the refractory  
5 symptoms. What do you do with them? Do you censor a patient  
6 at that point? If so, we know that people with unstable  
7 angina actually are more likely to have an MI or die than  
8 people who don't have unstable angina. So, you are clearly  
9 informative censoring. If you leave them in but forget about  
10 the fact that they had unstable ischemic syndrome and say,  
11 well, did they have an MI or death after they had a PTCA or  
12 after they had a bypass, doesn't that confound the data in  
13 some unusual and totally unpredictable way, and probably  
14 adds events, and perhaps adds events in a biased way? I  
15 mean, how would you deal with it if you forget about the  
16 fact that people have refractory ischemic syndromes?

17 DR. FLEMING: If we viewed that those events were  
18 of comparable clinical importance to death and MI for the  
19 reasons you pointed out, it provides in essence a cleaner  
20 endpoint to include them. On the other hand, if they are not  
21 and, as a result, it really alters the interpretation of the  
22 endpoint I would continue to favor death/MI. As you point  
23 out, the occurrence of that endpoint, death/MI could be  
24 influenced by supportive or concomitant therapies. In my  
25 view, that doesn't require that those concomitant or

1 ancillary therapies, when they occur, have to be factored  
2 into your endpoint. Generally, I would argue, they should be  
3 described so my believe is I would still follow for  
4 death/MI. If someone had an urgent revascularization I am  
5 still following that person to the endpoint of death/MI if  
6 they hadn't yet had an MI at that point. I would then  
7 describe in my report, in addition to the effects of  
8 intervention on the primary endpoint, whether there was a  
9 differential experience with these other interventions.

10 DR. PACKER: Thank you, Rick, very much. Let us  
11 proceed to Keaven Anderson's presentation. Everyone will be  
12 reassured that we are right on schedule.

13 [Laughter]

14 **Timing of Endpoint Analyses**

15 DR. ANDERSON: Thank you.

16 [Slide]

17 I am going to talk in practical terms somewhat  
18 about what our recommendations would be using trial results,  
19 talking basically about trial results supporting abciximab  
20 as an active control.

21 [Slide]

22 There are basically two points I want to try to  
23 make through the talk, and I will focus mainly on the second  
24 one. First of all, based largely on the discussion that has  
25 already been reviewed here today, we think that there is no

1 really appropriate active control established for ACS trials  
2 without PCI, and that abciximab is the appropriate active  
3 control for PCI trials.

4 [Slide]

5 So, very briefly, in trials without PCI, first of  
6 all, with tirofiban in PRISM and PRISM-PLUS the short-term  
7 but not longer-term death and MI benefit shown in PRISM and,  
8 obviously, PCI was encouraged to some extent, or at least  
9 cath, and if PCI was performed it was encouraged during the  
10 course of the study agent. Eptifibatide, PURSUIT, there is a  
11 small absolute benefit in the 30-day primary endpoint when  
12 you have mixed the population as they have. Michael  
13 certainly discussed the advantages and disadvantages of a  
14 large simple versus more direct trials. But, in any case, it  
15 was noted that with different strategies and different  
16 subgroups within consistent results it would become possible  
17 in active-controlled trial to rig it in some sense so that  
18 you can more easily get a positive result in your trial.

19 Along these lines, we are currently doing a  
20 medical therapy trial essentially where PCI is discourage  
21 during the study drug infusion. It has a placebo control and  
22 a 30-day time point of death and MI.

23 [Slide]

24 The one trial that we have done where there is a  
25 little bit of information on medical therapy for abciximab

1 is the CAPTURE trial. These were patients who had refractory  
2 unstable angina, and also had had an angiogram and were  
3 planned to have PTCA, but there was a medical therapy period  
4 of 18-26 hours prior to PTCA.

5           What you see at the 30-day primary endpoint was  
6 that death, MI and urgent intervention was reduced from  
7 about 16 percent to about 11 percent, about a 5 percent  
8 absolute difference, and this was in 1165 patients. So, it  
9 is over 500 patients per arm.

10           [Slide]

11           This kind of classic slide from CAPTURE is looking  
12 at incidence of myocardial infarction before and after PTCA.  
13 On the left-hand side we censored patients when they went to  
14 PTCA. In this case, it was mainly because PTCA was planned.  
15 Also, in the placebo group, more often when they went to  
16 PTCA it was due to urgent symptoms. So, the differences may  
17 have been even greater even though the censoring could be  
18 partially informative.

19           In any case, there is a fairly small event rate  
20 during the medical therapy period. Then, actually we reset  
21 time zero to the time of the PTCA and you see that after the  
22 PTCA is when really a lot of the events started occurring.

23           Unfortunately, in this trial we did not continue  
24 abciximab for more than an hour after the intervention, and  
25 that is when a lot of the events were occurring. So, we

1 didn't really even cover the appropriate time period perhaps  
2 with medical therapy.

3 [Slide]

4 Now going on to abciximab as an appropriate active  
5 control for PCI trials, basically I want to argue that there  
6 is consistent and substantial benefit across diverse trials.  
7 There are different patient populations. There is a high  
8 risk population in EPIC. There is a broad intervention  
9 population in both EPILOG and EPISTENT. There are three  
10 acute MI trials, RAPPORT, ADMIRAL and the Munich trial.  
11 There are different heparin regimens; there are different  
12 devices. These trials were conducted over a period of 8  
13 years. They had approximately 10,000 patients in them. They  
14 also have very consistent endpoint definitions.

15 [Slide]

16 So, the primary endpoint in these trials, or one  
17 of the pieces of the primary analysis has been 30-day  
18 analysis of death, MI and urgent intervention. For the large  
19 trials, EPIC, EPILOG and EPISTENT, you see the results here.  
20 Now, death definition is obvious. MI, we consistently  
21 required multiple measurements with at least a 3 times  
22 elevation of CKMB or, in the absence of MB, measurement of  
23 total CK. Urgent intervention generally would require  
24 recurrent ischemia requiring intervention, usually the  
25 criterion we would use was within 24 hours of the ischemic



1 event.

2           So, you see fairly consistently, in EPIC about 700  
3 patients per arm, about a 4.5 percent reduction in death, MI  
4 and urgent intervention at 30 days. This is a high risk  
5 population. EPILOG, about 900 patients per arm -- here we  
6 had 2 heparin strategies that had very similar endpoint  
7 rates so I combined them here. There is over 5 percent  
8 reduction in death, MI and urgent intervention at 30 days.  
9 That is highly significant. In EPISTENT, again this is a  
10 broad population here, these were patients who were amenable  
11 either to stenting or to PTCA. In the placebo group all  
12 patients got stent. There were two abciximab arms, one  
13 received abciximab and PTCA; the other received abciximab  
14 and stent. The results for this endpoint were nearly  
15 identical and, again, you see close to a 5 percent absolute  
16 reduction in death, MI and urgent intervention. Obviously,  
17 the relative reduction is about 35 percent here and over 50  
18 percent here in the EPILOG trial, and a little under 50  
19 percent here, in the EPISTENT trial.

20           [Slide]

21           We have also conducted three trials in patients  
22 receiving direct angioplasty for acute myocardial  
23 infarction. In ADMIRAL the primary endpoint was death, MI  
24 and urgent revascularization. The secondary endpoint was  
25 studied also in the RAPPORT and the Munich trial, conducted

1 by Franz Joseph Neumann.

2           There were 500 patients in RAPPORT, death, MI and  
3 urgent intervention, reduced again by absolute 5 percent,  
4 and that did reach statistical significance, less than 0.05.  
5 In ADMIRAL just 300 patients, about an 8 percent advantage  
6 in death and MI, 300 patients that reached statistical  
7 significance, 0.02. That was the primary endpoint. Neumann,  
8 this trial really wasn't powered for a clinical endpoint but  
9 that endpoint, death or MI or urgent intervention, was  
10 reduced substantially, by over 7 percent in this trial.

11           [Slide]

12           There has been a lot of discussion of mortality  
13 here, and we would like to propose that there actually is  
14 some reasonable evidence for a mortality benefit with  
15 abciximab.

16           First of all, just to remind you how this works,  
17 basically the one line means that the placebo and abciximab  
18 would be equivalent for mortality and the vertical dash is  
19 the estimate of the hazard ratio for mortality with  
20 abciximab relative to placebo. Left of that one line  
21 indicates that there is lower mortality with abciximab.

22           What we did in this analysis, and I can discuss  
23 related analyses for those who don't like this particular  
24 one, is to look at all follow-up for patients who received  
25 the most commonly used IIb/IIIa inhibition regimen, which is

1 a bolus of abciximab immediately prior to intervention,  
2 followed by 12-hour infusion. So, we used all follow-up and  
3 we studied in this analysis patients who got the same  
4 intervention. So, balloon is being compared to balloon  
5 within each trial and stent to stent within each trial.

6 In each trial you got consistent results. The  
7 combined results suggest that the hazard ratio for mortality  
8 is actually 0.69, with a p value of 0.006. This is intent-  
9 to-treat analysis, and the results are for 3 years in EPIC,  
10 1 year for EPILOG and EPISTENT. We had 6 months of follow-up  
11 for the remaining trials. Basically, the results were  
12 consistent whether balloon was used or stent was used.

13 [Slide]

14 In terms of when the mortality benefit accrues,  
15 this is a combined analysis of EPIC, EPILOG and EPISTENT,  
16 which are the trials where we have 1 year of follow-up. So  
17 there are 600 patients essentially in this analysis. You can  
18 see that there is a little bit higher mortality rate  
19 immediately, in the first couple of weeks, but most of the  
20 mortality actually accrues after the first couple of weeks  
21 although it is occurring at a slower rate.

22 You can also see that there is a slight divergence  
23 of the curves, say, in the first month but there is  
24 continued divergence of the curves after that. If you  
25 actually divide the analysis into the first 2 weeks versus

1 later, the hazard ratio is 0.67 in the first 2 weeks and  
2 0.69 after the first 2 weeks, and the p value -- again, this  
3 is a subgroup analysis, after 2 weeks does go below a  
4 nominal 0.05 level. So, that may not be conclusive evidence  
5 but certainly it is very suggestive that there is some late  
6 benefit here with abciximab.

7 [Slide]

8 So, basically, we feel like we have shown  
9 consistent substantial benefit with abciximab in PCI trials.  
10 There is a 30-day benefit that is maintained through 6  
11 months, 1 year, in EPIC 3 years. I haven't shown the other  
12 endpoints for that. And, there is a consistent long-term  
13 mortality benefit across the trials.

14 [Slide]

15 This shows the longer term follow-up that we are  
16 aware of in the small molecule trials that have been  
17 presented today -- mortality at 6 months. Basically, in 3 of  
18 the 3 trials the mortality was slightly higher at 6 months,  
19 but essentially it is identical. So, is there any real  
20 difference between the drugs that may affect long-term  
21 outcome is an interesting question to us.

22 [Slide]

23 The things that may cause a difference between  
24 these, we feel, would be the unique abciximab pharmacology,  
25 and that there are unique receptor binding characteristics

1 due to E3A but also to alpha-v-beta-3 and Mac 1. Abciximab  
2 inhibits not only platelet aggregation through IIb/IIIa but  
3 also thrombin generation with IIb/IIIa and alpha-v-beta-3  
4 inhibition, possibly it inhibits atherogenesis and  
5 angiogenesis by alpha-v-beta-3 inhibition, and inhibits  
6 inflammation by Mac 1 inhibition. But, finally, there is  
7 unique gradual and tapered recovery of platelet function  
8 with abciximab in that abciximab is something whose half-  
9 life on the platelet is measured in days while the small  
10 molecules are measured in hours.

11 [Slide]

12 So, the rationale for the use of abciximab as an  
13 active control in PCI trials is the unique pharmacology,  
14 consistent substantial results across diverse trials at 30  
15 days and long term, possible mortality benefit, and we feel  
16 that in PCI trials it is really not adequately demonstrated  
17 with the other compounds when patients are undergoing  
18 immediate PCI. So, we think it is reasonable to use  
19 abciximab as an active control in future PCI trials.

20 [Slide]

21 To actually give a practical recommendation in  
22 this regard, we combined three trials with a substantial  
23 amount of data to look at the death, MI, urgent intervention  
24 endpoint again. You see the same 5 percent-plus absolute  
25 benefit that basically you have seen consistently in all the

1 large trials and in the small trials. When you look at the  
2 hazard ratio, it is about a 50 percent reduction in the  
3 hazard ratio, and the confidence interval for that, the  
4 upper limit, is 0.61. So, the hazard ratio estimate is  
5 actually quite tight and the benefit is quite substantial.  
6 This is the ideal sort of situation in which to do an  
7 active-controlled trial.

8 [Slide]

9 Just in terms of a practical recommendation -- and  
10 these are assumptions that can be changed, obviously, with  
11 slightly different recommendations, abciximab as an active  
12 control in a PCI trial, the population would be immediate  
13 PCI. From our trials, it does not seem to matter which  
14 population you use in immediate PCI, you get the same 30-day  
15 results for death, MI and urgent intervention. Pretty  
16 consistent, you get around 11 percent event rate. Again, we  
17 did use uniform screening of enzymes. I think that would  
18 probably be important.

19 We would also propose that there should be a  
20 secondary endpoint of 1-year mortality to exclude possible  
21 mortality increase relative to abciximab when there has been  
22 enough evidence starting to accrue that there is a possible  
23 mortality benefit. It is very easy to go back at 1 year and  
24 measure mortality with a phone call.

25 In terms of sample size computation for this

1 trial, if you assume that the new therapy is equivalent and  
2 you want 80 percent power to show retention of 50 percent  
3 abciximab benefit and, again, if you want to show less  
4 retention you can get a smaller sample size, you would need  
5 2800 patients per group. So, this seems to us like a fairly  
6 straightforward proposal for an active-controlled trial in a  
7 PCI indication.

8 [Slide]

9 In summary, as has been discussed all day and  
10 there doesn't seem to be any consensus about any way to do  
11 an active-controlled trial for ACS trials where PCI is not  
12 immediate essentially, we feel again that abciximab is the  
13 appropriate active control for PCI trials, again, due to  
14 possibly its unique pharmacology, consistent substantial 30-  
15 day benefit and the possible long-term mortality benefit  
16 that has been suggested. Thank you.

17 DR. PACKER: Thank you. It may be recognized by  
18 all who have been listening to the discussion this afternoon  
19 that each of the sponsors' presentations highlights a  
20 different issue as regards to the conduct of an active-  
21 controlled trial. Dr. Kitt's presentation focused on  
22 delineation of the appropriate patient population and the  
23 syndrome, and Dr. Sax's presentation focused on the issues  
24 related to definition of endpoints, and this particular  
25 presentation, Dr. Anderson's presentation, focused on the

1 selection of a comparator agent.

2 In that spirit, before we go over this issue in  
3 detail, let me ask Dr. Reid to present his meta-analysis  
4 which, in fact, deals with the same issue of the selection  
5 of a comparator agent, and we will bring both of these  
6 presentations up for discussion.

7 **Meta-Analyses**

8 DR. REID: Dr. Packer, ladies and gentlemen, thank  
9 you.

10 [Slide]

11 Since being invited here and realizing the nature  
12 of this discussion, we decided to change the name as shown  
13 on this slide from "Yet Another Meta-Analysis" to the one  
14 you see there. We thought it was a little more specific.

15 In this, what we will do, through mechanisms that  
16 I suggest would create discussion, is compare the various,  
17 in this case three, GP IIb/IIIa receptor inhibitors.

18 [Slide]

19 While I am presenting the data, I am deeply  
20 indebted to the team with whom I have worked, the internal  
21 team at Eli Lilly and the external part of our team at  
22 Metaworks. We were specifically using and working with  
23 Metaworks to provide independent outside statistical  
24 consultation so as to help validate those preliminary  
25 results which we felt applied to the conclusions which you



1 will see.

2 [Slide]

3 The purpose then of this talk is to compare and  
4 contrast the efficacy of parenteral GP IIb/IIIa inhibitors  
5 in the management of PCI patients. This will then be  
6 restricted to those agents which are used in patients  
7 clinically today, that is, those so-called FDA-approved  
8 parenteral agents.

9 [Slide]

10 Let me start with the presentation outline. First,  
11 these findings, we would suggest, will show consistent  
12 results using various statistical methods in PCI patients at  
13 30 days with the endpoint of death and myocardial  
14 infarction. The second conclusion will demonstrate that  
15 these analyses will show that abciximab appears to  
16 differentiate itself from the other agents.

17 Now, our purpose is not to display a variety of  
18 powerful statistical techniques but more, speaking as a  
19 clinical trialist, I would offer to you that it impresses me  
20 when one can use a variety of statistical techniques that  
21 appear to be giving you the same result or trends in the  
22 same direction time after time. I would certainly leave it  
23 to the experts to prioritize which of those is more  
24 important.

25 [Slide]

1           Every one of us who had the opportunity to speak  
2 with you this afternoon have all talked about heterogeneity  
3 and we are no exception. Since you have seen so many of  
4 these slides presented, I probably will run through them a  
5 bit quickly, if I may.

6           The first point is that we can recognize that drug  
7 dosage in any trial, and particularly when comparing across  
8 trials, can create heterogeneity.

9           Secondly, the patient population studied, and this  
10 has been amply illustrated, talking particularly between ACS  
11 and PCI patients where, within that diagnostic category we  
12 may have additional obfuscation appearing in the form of  
13 disease definition -- regional differences. For example, you  
14 saw the data from Europe and the United States. Or,  
15 inclusion and exclusion criteria, particularly those that  
16 are what one may call more subjective.

17           The next point is that the selection and the  
18 timing of the endpoints, something that we have talked about  
19 and I think we are going to hear more about at the end of  
20 this next discussion -- these two things can influence the  
21 heterogeneity.

22           Finally, the differences among agents, the  
23 mechanism of action and, as Dr. Anderson has pointed out,  
24 abciximab, in contrast to the other two agents, appears to  
25 inhibit the GP IIb/IIIa receptor by a mechanism which is

1 referred to by our chemists as stearic hindrance, that is,  
2 it is not specifically binding to that receptor and, while  
3 all three affect the same result of platelet inhibition, it  
4 appears to be doing this by a different mechanism of action.

5 In addition, as Dr. Anderson showed you, it has  
6 binding to the Mac 1 and victronectin receptor which  
7 differentiates it clearly from the other two smaller  
8 molecules.

9 Finally, perhaps these mechanisms of actions and  
10 other effects appear to provide substantially  
11 differentiating pharmacodynamics when one compares abciximab  
12 with the other two small molecules.

13 The result, of course, of all this list could be  
14 two things, efficacy differences or inability to detect  
15 these if the heterogeneity is not controlled.

16 [Slide]

17 We, then, undertook, in conjunction with Metaworks  
18 in Boston Massachusetts, a meta-analysis. What I want to do  
19 is to try to summarize for you the methods that we used to  
20 collect these data. I would hasten to add that the data that  
21 we will be presenting to you must be considered preliminary  
22 since the analysis is currently under way. These are merely  
23 stopping point and then bringing out the data as they appear  
24 now.

25 First, we prespecified the experimental

1 hypothesis, which will be summarized for you. Secondly, we  
2 prespecified a study design, such as you would with any  
3 clinical trial. Thirdly, we pre-wrote a protocol and a case  
4 report form before any data were collected. Fourthly, we  
5 prespecified the statistical plan which was to be used in  
6 the analysis of the data once they were collected.

7 [Slide]

8 Fifthly, we prespecified the patient population,  
9 and when one adds this all up and looks in the ICH  
10 guidelines, you find that this meta-analytical plan will be  
11 consistent with the statistical principles of the ICH  
12 guidelines.

13 [Slide]

14 This, then is a summary of what we did in terms of  
15 the methodology, as well as some of the features that would  
16 then be under these various labels. The total sample size  
17 for this analysis was 13,350 distributed across the three  
18 agents, as shown on the first row of this slide. The patient  
19 population in order to reduce heterogeneity, from a  
20 statistical perspective, was limited to PCI. I would add  
21 that it also allowed us to exercise two other important  
22 features. As we look across the trials that we have reviewed  
23 today, all agents have demonstrated their best odds ratios  
24 in PCI trials. So we felt that this really gave everybody an  
25 equal opportunity to sort of show his best.

1 Thirdly, from a pathophysiologic perspective, and  
2 not unrelated to the first two, it would appear that one of  
3 the possibilities of benefit that is derived from IIb/IIIa  
4 antagonists is that they prevent the events that PCI induce.  
5 Thus, it allows one to derive benefit which otherwise may  
6 have been deprived if that agent were not present.

7 The dosage in these trials that we reviewed was  
8 consistent with current labeling. We chose an objective  
9 endpoint, as objective as we could, across these trials,  
10 which was death and myocardial infarction. We fixed it to a  
11 single time point for purposes of the interim analysis to 30  
12 days, and the number of studies is shown at the bottom.

13 [Slide]

14 So, these now will be the results. If we look at  
15 what comes in when one talks about the effects with the  
16 entire class or group of agents, we have the first point and  
17 this is the so-called combined effect, shown here with its  
18 odds ratio of 0.6, and then the confidence intervals ranging  
19 from 0.49 to 0.73. Much as was shown in the previous  
20 presentation, we would have 1 then as showing no difference  
21 between placebo and the treatment. To the left of this line  
22 would be favoring therapy, or to the right actually would be  
23 favoring placebo.

24 So, from this part we can conclude that we have  
25 redemonstrated that which has been shown by previous

1 analyses, and that is, there, indeed, appears to be among  
2 these three treatment agents a significant effect in favor  
3 of the therapy that is employed.

4           The next point shows you, as we broke it out now  
5 for tirofiban, we have an odds ratio of 0.68; the ranges are  
6 shown here. The next agent is eptifibatide is shown here,  
7 with an odds ratio of 0.82; the ranges shown to the right of  
8 that. Then for abciximab we have an odds ratio of 0.46, with  
9 the confidence intervals as shown here.

10           The next step that we wished to take was to ask  
11 the question how would you compare these and what  
12 conclusions could you reach? In order to do this, we  
13 undertook the analytical technique which will be shown on  
14 the next slide.

15           [Slide]

16           First, we performed an ANOVA to do paired  
17 comparisons, and when we did that we found that abciximab  
18 against tirofiban gave us an ANOVA of 0.02. Next, we  
19 compared it against eptifibatide and found an ANOVA value  
20 with a p of 0.001. Finally, tirofiban against eptifibatide  
21 gave a p value of 0.156.

22           [Slide]

23           Because of the statisticians' concern of  
24 variability among the controls, we then undertook one  
25 additional analysis, an analysis of covariance, and

1 repeating these same types of comparisons between abciximab  
2 and tirofiban we derived a p value of 0.048. When we  
3 compared abciximab against eptifibatide we obtained a value  
4 of p equal to 0.002, and finally tirofiban against  
5 eptifibatide gave a p value of 0.082.

6 So with these two types of analyses of a subset of  
7 the data, it appeared to be consistent among the p values  
8 which suggested that what was shown in the previous slide  
9 may, indeed, point to an effect that differentiates  
10 abciximab within the combined group effect.

11 [Slide]

12 Finally, being a clinician I always like carry-  
13 away messages -- how would this translate to how many  
14 patients do I have to treat to prevent something I don't  
15 want them to get? So, fortunately, our statisticians came up  
16 with what is referred to as NNT or, simply expressed, it is  
17 the number needed to treat to prevent one event. In this  
18 case, the endpoint is death or myocardial infarction at 30  
19 days.

20 [Slide]

21 When we do this -- shown on the ordinate is the  
22 NNT or the numbers needed to treat to prevent an endpoint,  
23 we find that one must treat 23 patients to prevent death or  
24 myocardial infarction in 1 patient or, with tirofiban 38 or,  
25 with eptifibatide 67 patients, these again being compared

1 against placebo.

2 [Slide]

3 In conclusion then, first we suggest that the  
4 combined group effect of GP IIb/IIIa inhibitors shows a  
5 distinct decrease in death and myocardial infarction at 30  
6 days compared to placebo therapy in PCI patients.

7 Secondly, abciximab appears to show a  
8 significantly greater decrease in death or myocardial  
9 infarction at 30 days when compared to either eptifibatide  
10 or tirofiban. Thank you for your attention.

11 DR. PACKER: We are going to open up committee  
12 discussion on both Dr. Anderson's presentation and Dr.  
13 Reid's presentation at the same time. Could I ask both David  
14 Kong and Tom Fleming to address the methodology used in the  
15 meta-analyses, the issues that they would like to raise in  
16 terms of the techniques used or the conclusions reached?  
17 David, do you want to start?

18 DR. KONG: Yes, I think that I have already sort  
19 of described my position on what to make out of indirect  
20 comparisons. I think once you start shrinking the available  
21 number of patients that you have in each of the groups to  
22 what is represented by the individual compounds, the  
23 variability in the data will enlarge in order to make  
24 indirect comparisons among agents.

25 Certainly, I would commend the use of a random-



1 effects model for this type of analysis. A random-effects  
2 model assumes that each of the effects falls along some  
3 certain distribution. So, in terms of attempting to  
4 incorporate the heterogeneity and variability among trials,  
5 I think that is certainly appropriate. However, yes, I still  
6 do have a deep concern among indirect comparisons amongst  
7 agents.

8 DR. PACKER: Tom?

9 DR. FLEMING: Certainly, it is complex as we try  
10 to glean as much as we can from current data, and there is a  
11 strong interest in wanting to be able to compare agents in A  
12 versus placebo and B versus placebo assessments to be able  
13 to say something about A versus B. It is intrinsically  
14 difficult and, obviously, the larger the signal then the  
15 more confidence one has that there is a difference.

16 The question that I might ask the committee to  
17 consider as they are thinking about this is to what extent  
18 were these trials the same? If we are pooling the data  
19 predominantly over four to five different studies, are these  
20 studies really comparable in terms of their patient  
21 populations, in terms of the manner in which the endpoints  
22 were defined and assessed and monitored? Were the quality of  
23 the data in the trials consistent? These are among the  
24 issues that need to be considered and understood with some  
25 considerable confidence in order to be able to justify a

1 conclusion that A is better to B when A was compared to  
2 placebo and B was compared to placebo.

3 DR. PACKER: Let me just make sure that we can  
4 define why we are having this discussion. We are not here to  
5 provide any sponsor with the opportunity to claim that their  
6 agent is better than any other. We are here entirely to  
7 address the issue as to whether any comparator agent for an  
8 active-controlled trial can be selected with some degree of  
9 confidence.

10 If I understand it correctly, Dr. Anderson's  
11 presentation primarily made the point that you would suggest  
12 that the consistency of the data was greater with abciximab  
13 than with others, therefore making it your preference. Dr.  
14 Reid's presentation was not so much based on consistency but  
15 based on superiority as opposed to consistency. Is that a  
16 fair representation and summary?

17 DR. REID: I think that is fair, Dr. Packer. I  
18 would just add one other feature, and that is one cannot  
19 simply reach in the GP IIb/IIIa basket, pull any agent out  
20 and expect to get the same efficacy.

21 DR. PACKER: Okay. Let us go through the committee  
22 concerns. Dr. Kitt, I promise you, you will have more than  
23 ample opportunity but I want to get the committee concerns  
24 on the table first. We will begin with Ray, and we will go  
25 to Marv, Udho and Rob.

1 DR. LIPICKY: Well, I guess I would just like to  
2 say what I usually say, and that is, you know, if we ignore  
3 all of the stuff about meta-analyses and are the populations  
4 the same, and everything else, as a single trial to sort of  
5 come to the conclusion that something really has been shown  
6 you have to think about p's at 0.00125. I didn't see  
7 anything -- sort of close maybe. My understanding of when  
8 you start believing meta-analyses is when another zero gets  
9 added before the significant digit, and then you might start  
10 paying attention.

11 So, fundamentally, I haven't seen anything that  
12 would make me think that there was a difference between  
13 agents, nor that there is nothing different between agents,  
14 and I will leave it at that.

15 DR. KONSTAM: Let me just say, I mean, I think  
16 that Dr. Anderson's and Dr. Reid's presentations are  
17 powerful and make a very good point that abciximab is an  
18 adequate agent for being employed as an active control, and  
19 I accept that. I accepted it before their presentation and I  
20 am, if anything, strengthened by their presentation.

21 Getting beyond that I think is where we get into  
22 trouble. I was convinced earlier by Tom Fleming that  
23 comparisons across these agents at this point in time, or  
24 maybe at any point in time, in the absence of head-to-head  
25 comparator data, is treacherous. I don't know whether Tom is

1 getting tired, or what it is, but he didn't seem to come  
2 across as clearly about it in his statement a moment ago,  
3 but I think it is extremely treacherous across these trials.  
4 I think these trials are enormously different from trial to  
5 trial, population to population, dose regimen used,  
6 endpoints used. So, from a general perspective, I don't get  
7 much of anything from comparisons across them.

8           But I just want to take that a step further and to  
9 an extent just comment on the direction that things appear  
10 to be in relative to them, I would propose, and ask for  
11 comments to refute it, that the findings could represent  
12 more effective, a more aggressive antiplatelet regimen. I  
13 think they pointed out a number of points about abciximab,  
14 one of which is that it has a very long half-life, and I  
15 think platelet aggregation in these settings is bad.

16           Now, if that were the source of some great effect,  
17 if we believe them, I think one would also see high rate of  
18 bleeds and, in point of fact, what I didn't see in your  
19 meta-analyses is a comparison of the relative major bleeds  
20 across the different groups of agents. I am sure you are  
21 going to pull out slide number 432 -- actually, I would like  
22 to see it. But, to my reading of the literature, having not  
23 done a meta-analysis or comparison, I see a significant  
24 increase in the rate of major bleeds in the EPIC trial and I  
25 don't see it clearly in the other studies as well. So that

1 would be what I would propose as a possible explanation if I  
2 were to believe the differences.

3 DR. ANDERSON: We do have a slide but I don't know  
4 the number of it.

5 DR. PACKER: Remember, the issue we do not want to  
6 discuss is whether the agents are different, materially  
7 different either in efficacy or in safety. The issue that we  
8 want discuss is whether the data that exist now allows us to  
9 identify a comparator agent with confidence.

10 DR. KONSTAM: I am comfortable with that. I think,  
11 to be fair, Dr. Anderson's and Dr. Reid's presentations went  
12 beyond that. So, we could either just accept that we are not  
13 going to talk about it or say that we are not sure that we  
14 believe it.

15 DR. ANDERSON: Just very briefly in response to  
16 your point, we have found that really bleeding is not  
17 necessarily associated with how effective something is and,  
18 in fact, where we have had the best efficacy results, in  
19 EPILOG and EPISTENT, we had the lowest the bleeding rates  
20 and we had lower than placebo in EPISTENT and I believe the  
21 low-dose heparin regimen. So, if anything, we would claim  
22 exactly the opposite.

23 DR. THADANI: You showed good data. I don't think  
24 you can compare the agents because some patient populations  
25 are different in some of those studies. Some have included

1 patients with a recent MI and some studies not.

2           What I am struck by, which you did not conclude,  
3 is that as soon as you blow the balloon up or put a stent in  
4 you are driving your enzyme-driven infarct rate by at least  
5 6-10 percent. So, what you are telling me is, okay, if you  
6 need a PCI and order the primary therapy you can prevent an  
7 iatrogenic infarct. Is my conclusion right? Because each of  
8 the three you showed, at point zero, in the placebo group it  
9 goes almost up to 10 percent. So, here you are telling me  
10 that I tell a patient, okay, if I am going to blow a balloon  
11 up I am going to cause an infarct, and I will give you a  
12 drug which is going to drive you down from 10 percent to 6  
13 percent. I realize the benefit continues up to 30 days, and  
14 that is why I am having a problem when I ask do you accept  
15 MI as an endpoint just driven by enzymes. That is the  
16 difficulty I have as opposed to the natural history of a  
17 disease, because if you translate this that every patient  
18 with ACS has to go intervention like this, you are producing  
19 a lot of infarcts which you are treating the patient to  
20 prevent it.

21           DR. ANDERSON: No, I don't think we are suggesting  
22 they should all go to intervention, but that --

23           DR. THADANI: So, what you are saying is if you  
24 have to go for intervention, this is the way to go? Am I  
25 right?

1 DR. ANDERSON: I am saying if you go to  
2 intervention and, if at that point, you are making a  
3 decision to give a IIb/IIIa inhibitor, abciximab is very  
4 useful in that setting as a potential active control.

5 DR. THADANI: But not for ACS alone?

6 DR. ANDERSON: For medical therapy, you know, we  
7 didn't feel like there is an appropriate active control at  
8 this point.

9 DR. SEIGEL: I want to extend a little bit the  
10 observation or the comment you made a couple of times, Dr.  
11 Packer. It is not on the table whether one of these agents  
12 is superior. It is on the table which could be used as a  
13 positive control. It may be on the table, and this has been  
14 unclear to me from the wording of the papers and from the  
15 discussion, but one thing that may be on the table that is  
16 addressed here is could you use a class-specific group  
17 estimate of effect size to estimate the effect size for the  
18 purpose of planning a clinical trial in which one member of  
19 the group could be used as the active control, something  
20 that has been done, for example, in thrombolytics?

21 There, I would say that if you believe that one  
22 can make even a plausible case -- not proof, but if you can  
23 believe that one can make a plausible case that there are  
24 real differences in effect size, then you have to ask very  
25 seriously whether you would want to get a pooled estimate of

1 effect size from different therapies and then apply that  
2 effect size to an assumption of any one therapy within the  
3 class.

4 DR. PACKER: That is actually a question that we  
5 should focus on for a moment, but before we do, Rob?

6 DR. CALIFF: I think Jay has already gotten a  
7 large part of the way that I wanted to go, which is to get  
8 away from comparing the drugs to see which one is better,  
9 and more try to generalize the issue which we will see over  
10 and over now, that you are developing a new therapy and you  
11 are in a field where there is a bunch of therapies out there  
12 that are already being used. So, how do you approach it?

13 And, the only part of the presentation which I  
14 thought I really disagreed with was the use of the term  
15 "prespecification" because I don't think the ICH says that  
16 you do the trial without a hypothesis, look at the results  
17 and then specify what your hypothesis is. And, there is no  
18 way to do a meta-analysis of trials that are already  
19 completed without knowing what the results are ahead of time  
20 sort of qualitatively. So, it is not really prespecified the  
21 way we talk about an experiment, unless you prespecify  
22 before you do the individual trials and have a plan for how  
23 you are going to combine them before you have seen what the  
24 results of each individual trial are.

25 So, the generalized issue there is when thinking



1 of your strategy in a positive control trial, like  
2 everything else we have said, it is a matter of sort of  
3 taste -- which studies do you include or not include? We  
4 have been through this we ACE inhibitors, for example, with  
5 IRBs. There are a lot of different ACE inhibitor versus  
6 placebo trials in different types of heart failure. You can  
7 include or exclude various trials. And, if you already know  
8 the results you might have a tendency to prespecify the  
9 trials that you really liked.

10           The second point is that there is a problem here  
11 in terms of selecting one of the agents that is not  
12 intuitively obvious, I don't think, and that is if there is  
13 heterogeneity in your analysis, which this analysis clearly  
14 shows and I think it is very well done, if you select the  
15 one that shows the greatest effect it may seem that that  
16 would be the most difficult obstacle in terms of a non-  
17 inferiority trial. But when you get into the putative  
18 placebo argument, in fact, if you select the one that has  
19 the least effect it is harder to show that you are actually  
20 different than the putative placebo. So, it would see like  
21 when you first look at it, you will take the most difficult  
22 choice and that is the hardest thing to do but, in fact, if  
23 you take the least effective agent in your meta-analysis  
24 that is the hardest one to show you are better than placebo,  
25 and you may have a higher chance to show that you trend in

1 the right direction compared to the active control. But  
2 since the confidence interval butts right up against no  
3 effect in the least effective agent, you have a difficult  
4 time in your putative placebo argument, which we haven't  
5 gotten into here but becomes a critical part.

6           Lastly, I don't think biological differences  
7 should be any part of the discussion today because show me a  
8 result and I can give you a biological difference that might  
9 explain it. I think when it comes to this kind of an  
10 analysis we have to be talking about the outcome data.

11           DR. PACKER: Let me see if we can move the  
12 discussion forward the way that we want to. Tom, I know you  
13 probably want to say something in your own right but could I  
14 ask you to deal specifically with the question as to whether  
15 an appropriate comparator here for any active-controlled  
16 trial should be either one agent or a pooled estimate. The  
17 one agent issue Rob has already outlined has certain  
18 advantages or disadvantages depending on which agent you  
19 use. The other question which Jay brought up was is it more  
20 appropriate to use a pooled estimate. If this committee  
21 three years from now were to see a trial in which a  
22 comparison was done using a pooled estimate or a comparison  
23 was done with a single agent, what are the considerations we  
24 should be worrying about three years from now that would  
25 influence the design now?

1 DR. FLEMING: That is what, in essence, I wanted  
2 to address. I would though like to just briefly endorse  
3 again Rob's comment about prespecification. It bothers me  
4 greatly when we have all the studies in hand, plan a meta-  
5 analysis -- we know what the results are and, obviously, you  
6 want to do as best you can to prespecify but it is not the  
7 same as having specified a hypothesis before any of the data  
8 were in hand.

9 The issue that you raise, Milt, I would like to  
10 comment on. We have made the point that if you have an array  
11 of studies that look at A versus placebo, B versus placebo  
12 that one has to be extraordinarily cautious in using those  
13 data to conclude relative efficacy of A versus B.

14 Having said that, that doesn't mean that in the  
15 absence of having considerable convincing proof that A and B  
16 are different that the net fall-back is that A and B are the  
17 same. You have just as much difficulty in proving that A and  
18 B are the same. So, if I have an array of studies that look  
19 at A versus placebo, B versus placebo, and I have decided to  
20 choose arm B for my active control, the fall-back isn't to  
21 presume that I can estimate the efficacy of arm B with the  
22 global analysis because the burden of proof is on me when I  
23 do that to be able to conclude why the efficacy of A versus  
24 placebo is reliably giving me further insight about B versus  
25 placebo. If I believed, if I truly believed that it was

1 highly likely that A was better than B and I was going to  
2 follow the paradigm that is evolving here for an active  
3 control study, I would want to pool the information from A  
4 and B, get an inflated estimate of efficacy, then I have to  
5 preserve half of that level of efficacy, then I want to  
6 compare myself against B which is much easier to beat than A  
7 -- if I truly believe from looking at the data that there  
8 was a difference in efficacy between A and B.

9           So, it really is important here -- the fault here  
10 is if I am going to use B as my active comparator, B data is  
11 what I have to use from past experience against placebo to  
12 estimate B. The burden of proof is on me to establish why A  
13 data is as relevant as B data when I am trying to estimate  
14 efficacy of B.

15           DR. LIPICKY: But there is another set of  
16 considerations that you might want to comment on. For  
17 example -- and I may be wrong in the assertions that I am  
18 making now -- if you have concluded that there is ample  
19 evidence that there is a class effect and you have not been  
20 able to conclude that there is a difference between the  
21 members -- you certainly can always say, well, there could  
22 be but you can't conclude that there is, I would make the  
23 argument that your best estimate of the population's  
24 treatment effect is, in fact, the meta-analysis of all of  
25 the trials versus placebo.

1 DR. FLEMING: Of the class.

2 DR. LIPICKY: Of the class, and that in fact the  
3 confidence limits beyond around that point estimate are as  
4 small as they can get. That is your best estimate of the  
5 treatment effect of the class. So, I don't see that it is  
6 necessary to choose A or B. Your control could be all of the  
7 members against new drug because you really, in fact, have  
8 your best estimate of the class effect and that gives you  
9 your best confidence limits and your best position. So, that  
10 would just mean that your control arm would include randomly  
11 all of the members of the class.

12 DR. FLEMING: I have no concern if you done  
13 studies and you have established a class effect, and those  
14 studies have been incapable of definitively concluding that  
15 A is better than B in that class. I have no problem if you  
16 choose A as your active control, B as your active control or  
17 a combination thereof.

18 My concern is by virtue of your inability to prove  
19 a drug difference if efficacy within that class, that  
20 doesn't lead to the conclusion that they are the same. You  
21 may be under-powered. There may be true differences that  
22 don't reach your 0.00-whatever difference that you are  
23 suggesting you would need to see. And, there are relative  
24 degrees of confidence that there may be heterogeneity. If  
25 one looks at the data and believes that it is entirely

1 plausible, if not likely, that within this broad class  
2 effect there is drug-specific effect as well, in those  
3 settings I am uncomfortable attributing the entire class  
4 effect to one of the given agents.

5 DR. LIPICKY: Right, but in fact uncertainty of  
6 then saying I am going to choose an agent -- there is an  
7 alternative to choosing an agent from the class, and the  
8 uncertainty in choosing an agent would be you have a trial  
9 or maybe two trials that, in fact, estimate the magnitude of  
10 treatment effect and the variance that is associated with  
11 it. So, you have less certainty there. You may have more  
12 certainty -- you may be more comfortable because you are not  
13 sure there is a difference between drugs, but if you choose  
14 a drug then you have more uncertainty in this vector that  
15 you are chasing for establishing the non-inferiority. So, it  
16 is a trade-off and it is not clear to me where that trade-  
17 off sits.

18 DR. FLEMING: I agree. I guess the bottom line of  
19 what I would want to come through with here is lack of  
20 evidence of a difference is not evidence of a lack of  
21 difference.

22 DR. LIPICKY: Right, but there is a question that  
23 can be addressed and should be answered with a yes or no,  
24 that is, does what we have looked at today fit in the  
25 category of no difference has been shown so there is

1 reasonable comfort with saying that it would be okay to  
2 choose all of the controls, or is it the statement that you  
3 are making, that no difference doesn't establish that there  
4 is no difference?

5 DR. FLEMING: My summary is that there is strong  
6 evidence for a global effect of the class, and we are far,  
7 far short of having adequate data to conclude that all of  
8 the agents within the class are equally effective.

9 DR. PACKER: Let me see if I can understand the  
10 implications of the distinction. Ray, what you are proposing  
11 is that if one is going to use a pooled estimate one could,  
12 as a control group, use all three agents in some randomized  
13 fashion in a manner similar to the cooperative nitroglycerin  
14 study.

15 DR. LIPICKY: Right.

16 DR. PACKER: On the other hand, if a sponsor  
17 thought that that was too complicated the alternative was to  
18 select one agent, and Tom's argument is if you are going to  
19 do that you shouldn't use the pooled the estimate, you  
20 should use that agent's estimate to do that.

21 DR. LIPICKY: Right.

22 DR. PACKER: Is there any disagreement between the  
23 two of you on this conclusion?

24 DR. LIPICKY: No, absolutely none.

25 DR. PACKER: Terrific. Please identify yourself.

1 DR. OLKIN: Ingram Olkin. I am from Stanford  
2 University. I think the points raised are actually pretty  
3 treacherous in terms of making conclusions but, to put it in  
4 the vernacular, if the Yankees are better than the Braves  
5 and Cleveland is better than the Braves, it is very  
6 difficult to compare the two.

7 But I would like to focus on what Tom's point.  
8 Statisticians have developed a technique called analysis of  
9 variance, and what the analysis of variance does is it does  
10 give you an overall effect, an overall mean effect, and then  
11 it gives you an effect due to each of the agents. Now, that  
12 was not done in the Kong et al. study, namely, the  
13 designation of the agents was not really taken into account.  
14 It was a meta-analysis of all. And, that is actually fine.  
15 People do that and it is a legitimate point. However, the  
16 analysis of variance does both. It is a more powerful  
17 technique than just combining all because it does give you  
18 the overall effect regardless of the three agents. Then it  
19 tells you whether there is a difference between agents. For  
20 that, if there is a difference between agents, you can do  
21 multiple comparisons which will make comparisons. The key  
22 problem is the comparisons are not between an agent and an  
23 agent but each agent versus its placebo. That is the rub.

24 So, in order to resolve that, you either have to  
25 have some hypotheses; you have to build a model, or you have



1 to do something in which there is a direct comparison. So, I  
2 think the point is I am not disagreeing, and I think the  
3 statisticians would agree that analysis of variance is  
4 probably a better procedure.

5 DR. FLEMING: If we were in an ideal world, we  
6 would look at three experimental agents in the same trial  
7 against a common placebo. That way, you only have to put  
8 one-fourth of your population on placebo and you get placebo  
9 comparisons of each and you also get direct head-to-head  
10 comparisons where you have more standardization of  
11 populations, intervention, definitions, etc. That is not the  
12 world that we are in with the data that we have, as I think  
13 Ingram is getting at, and that is the essence of where we  
14 have a much weaker basis to conclude that each of these  
15 agents is providing essentially comparable effect to the  
16 global class effect.

17 DR. PACKER: I am going to ask Jeff to address his  
18 question. I want to take a poll of the committee and then I  
19 want to give Drs. Kitt and Sax the last word.

20 DR. BORER: There are two issues that I would like  
21 to raise. First of all, we are talking now about pooling, or  
22 possibly pooling data, or not pooling data for a comparison.  
23 I think it is important not to lose sight of the point that  
24 Marvin raised earlier and that I certainly agree with, which  
25 is that we really are looking at two very disparate

1 conditions. So, if we are going to talk about comparisons,  
2 pooled or unpooled, whatever, we really need to be thinking  
3 about PCI and ACS separately.

4           The other point is that although intuitively,  
5 barring some reason not to do it, it seems appropriate to  
6 think about or move towards pooling all the data to have a  
7 more stable point estimate, if one does. We are talking here  
8 about three agents that have, it seems to me, very  
9 importantly different molecular structures and  
10 pharmacological effects. That is, when you take eptifibatide  
11 and tirofiban on one side and abciximab on the other side,  
12 there seem to be important differences here. So, I wonder if  
13 it is reasonable to call these agents a class altogether. It  
14 seems that that is a potentially important confound. Forget  
15 about the fact that the data look the same, or they don't  
16 look the same, or there seems to be a difference but that  
17 doesn't mean there is one or there isn't a difference. The  
18 molecular structure and pharmacological effects seem to be  
19 importantly different. I would be concerned about pooling at  
20 this point given that fact.

21           DR. PACKER: But you can never underestimate the  
22 ability of sponsors to describe differences. We have seen  
23 that with beta blockers and ACE inhibitors.

24           DR. BORER: You can describe differences in  
25 pharmacological effects just by looking, but when you talk

1 about a small peptide and a big antibody, to me intuitively  
2 it seems like you are talking about two different species.

3 DR. PACKER: Let me get a sense of the committee.  
4 Would anyone -- and this includes our invited guests --  
5 would anyone object if a sponsor wanted to design a trial  
6 that would compare their drug to abciximab assuming that all  
7 the other issues of a positive control trial could be  
8 addressed? Would anyone object to that comparison?

9 DR. GRINES: I still think there is a major role  
10 for placebo-controlled trials. We have discussed this a  
11 little bit before but there are a lot of trials you can  
12 design to make it look equivalent by patient selection or  
13 concomitant medications.

14 DR. LIPICKY: That is correct. No one has said you  
15 can't do a placebo-controlled trial. But the exercise today  
16 is to try to figure out how you do a positive controlled  
17 trial.

18 DR. GRINES: I wouldn't object to a positive  
19 controlled trial as long as you had a placebo-controlled  
20 trial to show efficacy as well.

21 DR. PACKER: I understand.

22 DR. LIPICKY: No, no, no. That is not the name of  
23 the game today. It is a positive controlled trial from which  
24 you would conclude that this drug works. How would you do  
25 that? And, the question that Milton asked was if you did a

1 positive controlled trial that, in fact, would be of  
2 approval quality and you chose abciximab who would object?  
3 That was the question.

4 DR. PACKER: Right. Cindy, I have to help you  
5 because I am going to assume that all of the issues you are  
6 worried about, that have nothing to do with the selection of  
7 the drug, will be adequately resolved to your satisfaction.  
8 That may be impossible.

9 [Laughter]

10 But there is another question that is coming right  
11 after this. If one could resolve all of the levels of  
12 uncertainty that you have, would you object to a positive  
13 comparison trial with abciximab, using the abciximab point  
14 estimate and confidence intervals? Anyone who would object  
15 to that? No one would object.

16 Would anyone object to a similar trial being done  
17 with tirofiban, using the tirofiban point estimate?

18 DR. THADANI: I think there are problems on the  
19 whole because if you are saying, as Tom said, you can't have  
20 one agent to another and if most of the data is driven by  
21 drug A, I think there are problems and I would like to see  
22 one placebo-controlled trial as well.

23 DR. PACKER: That is not the question.

24 DR. THADANI: I realize that. I am not going to  
25 buy that you can do it with any drug given because I think

1 most of --

2 DR. PACKER: Then abstain. The third question --  
3 no one objected to tirofiban. Right? Oh, Jeff -- maybe  
4 someone did.

5 DR. BORER: My recollection of the tirofiban data  
6 was that they were importantly split between PCI and ACS  
7 data, and that leaves me with the concern that there may not  
8 be enough data in either one of those pools to support a  
9 reasonable comparison, whereas the abciximab seemed to be  
10 plunked in one area and that leaves me with a feeling, a  
11 believing that there is a more reasonable point estimate for  
12 a single entity disease.

13 DR. PACKER: That would support Dr. Anderson's  
14 contention, not based on differences on effect but his  
15 contention that the point estimate shows a consistency with  
16 abciximab which lends itself to solving the issues of a  
17 positive controlled trial more readily. Is that the point  
18 you are making?

19 DR. BORER: Right, for one particular disease  
20 entity.

21 DR. PACKER: Okay.

22 DR. CALIFF: Milton, you asked the question  
23 hypothetically and I wouldn't object, but what a sponsor  
24 would find would be that they couldn't do it because for PCI  
25 the confidence intervals for tirofiban actually overlap 1.

1 So, by the rules of the game, you couldn't create a case  
2 that you could hypothetically beat a putative placebo.

3 DR. PACKER: Fine. Then let's turn to the next  
4 question which is the point estimate for eptifibatide  
5 doesn't overlap 1 --

6 DR. CALIFF: But it would take a large number of  
7 patients.

8 DR. PACKER: But it would take a very large number  
9 of patients.

10 DR. THADANI: Are you talking about an ACS trial  
11 or are you talking about --

12 DR. PACKER: No, PCI.

13 DR. THADANI: The PCI trial, if I remember  
14 correctly, the high dose didn't work, the low dose worked,  
15 which we haven't seen today.

16 DR. PACKER: It is irrelevant to the discussion.

17 DR. THADANI: I realize that. But if you are  
18 driving the PCI trial from the placebo data, it is very  
19 different patient populations from the primary PCI trials.  
20 Primary PCI trials I don't think have the confidence to show  
21 -- the doses used in PURSUIT are totally different than were  
22 used in the PCI trials. So, I don't think you can even  
23 discuss that, or I would have objection to say that you have  
24 enough data on the PCI group. If you are going to use the  
25 PURSUIT data -- okay, I buy that you can't do a mortality

1 trial, and if you can define how you are going to define  
2 infarction, then you have to have a huge sample size because  
3 even PURSUIT took -- what? -- 10,000 patients.

4 DR. CALIFF: So, Milton, there are really only two  
5 practical options. I mean, Keaven's plan I thought was quite  
6 rational in saying the other option is to pool the three --

7 DR. PACKER: And go against all three.

8 DR. CALIFF: Yes.

9 DR. PACKER: According to Tom's suggestion that if  
10 you are going to use a pooled estimate you need to against  
11 all three agents as the comparator. This is the result of  
12 Tom's and Ray's discussion. Jay?

13 DR. SEIGEL: I guess implicit in the comments  
14 about different doses, or ACS and PCI is the notion, and I  
15 assume it is implied in your question and the answers, that  
16 the conditions from which the estimates of treatment effect  
17 are made should be, at least vis-a-vis importance, the same  
18 as the conditions of the active-controlled trial. So you  
19 should have similar drugs. You should have similar entry  
20 criteria. There should be some level of similarity in the  
21 way, the amount and timing of the introduction of important  
22 procedures, although if we are talking about PCI that is  
23 implicit, and those other factors that are generally  
24 considered to be important. With that combination it is a  
25 little bit hard to do because you would have to weight the

1 combination comparable to the weight of the data from  
2 different agents, and then you would have to manage the  
3 patients in a way that reflects a lot of different  
4 management. But, conceivably, one could work through that.

5 DR. FENISCHEL: I just wanted to respond by saying  
6 what Rob said, which may be a little bit misleading -- it  
7 really is not true that an active control has to be  
8 distinctly better than placebo to be usable. All it has to  
9 have is some sort of defined position on the continuum. I  
10 mean, one could, for example, use as an active control a  
11 drug which was surely worse than placebo. It is just that  
12 one has to beat it rather more definitively than one has to  
13 beat placebo to show that one is successful.

14 I think one of the traps, one of the many traps of  
15 the unfortunate idea of preserving 50 percent of the benefit  
16 and so on, you know, when you try to look at that a little  
17 more closely you come up with ideas that some active control  
18 results are simply non-informative and, of course, that is  
19 not true. The example that Rob gave of tirofiban in PCI,  
20 where the confidence limit overlaps 1 -- suppose that that  
21 is true, well, all that means is it is still true that the  
22 point estimate is better than 1. It is still true that  
23 beating it is better than beating placebo. It is not a whole  
24 lot better than beating placebo but it is better than  
25 beating placebo. You go through the statistics and you are



1 better off than going against placebo as far as how good you  
2 have to be.

3           As I said, there are multiple pernicious effects  
4 of the formulation, for which I was partially responsible,  
5 of talking about preserving 50 percent of the benefit, and  
6 so on. It is a statistical dead end that leads into a  
7 variety of anomalies and paradoxes.

8           DR. PACKER: I think we have reached equipoise on  
9 the committee, but we do want to give the other sponsors the  
10 last word. We, by the way, never-ever give the sponsors the  
11 last word so this is unprecedented. Dr. Kitt?

12           DR. KITT: I will start by saying that it appears  
13 as though the subtleties of PCI versus ACS studies have  
14 again not been clearly understood, or at least have not been  
15 fully accepted or discussed during this presentation.

16           The meta-analysis that was presented -- there were  
17 assumptions in there, and there is always the problem of not  
18 having seen this information in advance but just reading  
19 from the slide, the meta-analysis took as assumptions that  
20 these were all PCI studies. Well, I don't know the actual  
21 details but I know how to do my math, and if I look at the  
22 Integrilin data, there were 5238 patients. If I subtract  
23 4010, which is the entire IMPACT II study, I get left with  
24 the number of patients who were in the PURSUIT study.

25           Well, we spent the whole morning discussing that

1 PURSUIT was not a PCI study, and combining those results  
2 into these results doesn't seem to make a lot of sense.

3           The second assumption that was made in that meta-  
4 analysis was that these were package insert doses, but it  
5 looks to me that all of the IMPACT II information was folded  
6 into the data in that meta-analysis.

7           Along the same lines, conspicuous by its absence,  
8 I believe although I am not 100 percent sure is the CAPTURE  
9 study, but I will come back to the CAPTURE study in a minute  
10 when we talk about the mortality presentation.

11           I am assuming the same is true for tirofiban, by  
12 the way, but I don't know my numbers with tirofiban nearly  
13 as well as I know for Integrilin. But I want to just point  
14 out that this discussion that has just taken place is really  
15 about PCI studies and should not be confounded with studies  
16 in acute coronary syndromes. I agree with the original point  
17 that we have not really come to a conclusion as to what the  
18 control event rate or what the actual effect is with these  
19 studies because of the different designs.

20           I want to then turn to the mortality presentation  
21 that Keaven Anderson gave, where he compared the mortality  
22 benefit in all the PCI studies and then put up three  
23 studies, two with Agristat and one with Integrilin. Two of  
24 those three studies were not in PCI; they were in acute  
25 coronary syndromes. So, taking that information in that way

1 is sort of misleading.

2 Last but not least, I want to come to the CAPTURE  
3 study which was very conspicuously absent. I understand why  
4 it would not be included in there because the sponsor  
5 believes the dosing and the dosing regimen may not have been  
6 ideal, but neither was it for the other studies that you  
7 have already included. Just to be complete, I have the  
8 CAPTURE paper here. The 6-month placebo event rate was 2.2  
9 percent. This is mortality. Whereas, with Reapro it was 2.8  
10 percent. So, there was an increase in mortality at 6 months.

11 So, I just want to be sure that we have somewhat  
12 of a level playing field here. Again, my purpose is not to  
13 say one drug is better than another, but just to be sure  
14 that the information that is presented is equitable.

15 DR. PACKER: Dr. Sax?

16 DR. SAX: I don't want to comment on the analyses,  
17 except to say that I don't understand the mathematics either  
18 because there were two trials presented for PCI and the  
19 total N for that was half the size of the RESTORE trial. So,  
20 I think there are some methodologic issues.

21 Taking this aside, I guess I have the second to  
22 the last comment because the last comment always goes to the  
23 chair, just to say that I think there seems to be a  
24 consensus that it may be possible to an active controlled  
25 trial in the setting of PCI. But the issues are with

1 unstable angina, the acute coronary syndromes, non-St-  
2 segment elevation remain difficult, and I think that to the  
3 extent that there are difficulties it is going to require  
4 future sponsors to really look carefully at the things we  
5 have discussed -- the selection, the endpoints, in fact,  
6 interestingly, the make-up and design of the critical events  
7 committee which came out in the discussion today, and pull  
8 that together. I think those issues probably will have to be  
9 discussed on a trial to trial basis.

10 DR. PACKER: I promised the sponsors the last word  
11 and I will go in that direction. Can we move toward Dr.  
12 Throckmorton's presentation?

#### 13 **Timing of Endpoint Analyses**

14 DR. THROCKMORTON: Thank you.

15 [Slide]

16 The topic of my talk is the timing of endpoint  
17 analyses, and if the previous speakers today have plunged  
18 fully into the heterogeneous, complicated, subtle and, my  
19 all-time favorite, treacherous sea of issues in designing  
20 active-controlled trials in IIb/IIIa inhibitors, I would  
21 propose to put my toe in gently and hope to avoid the  
22 sharks.

23 As you have heard, the trials used to support the  
24 approval of the three available IIb/IIIa inhibitors have  
25 employed primary endpoints ranging between 48 hours and 30

1 days and, in general, have shown beneficial effects on  
2 combined endpoints, including cardiac morbidity and  
3 mortality at the earliest time points measured, usually 48  
4 hours, persisting with some variability out to 30 days. Some  
5 trials have, additionally, reported persistence for what I  
6 will call durability of efficacy through longer time points.

7           In addition, the meta-analyses presented have  
8 suggested, again, some variability in the results of the  
9 efficacy of these products between 48 hours, 30 days and  
10 perhaps later.

11           The timing of the primary endpoint has important  
12 implications for the size and design of any future IIb/IIIa  
13 inhibitor trial. Planning for possible active-controlled  
14 trials will require that we integrate the existing trials  
15 with their primary endpoints that vary and perhaps with  
16 varying durability of efficacy into a single effect size,  
17 with an ability to interpret this effect through time. A  
18 method for comparing this imputed control effect with a new  
19 drug effect at both the early and late time points, then,  
20 would seem to be desirable.

21           In my talk I will summarize four general patterns  
22 of data collection and interpretation that could be used for  
23 trials or have been used for trials of IIb/IIIa inhibitors.  
24 Then I will use data from some of the completed trials to  
25 illustrate a method of data interpretation that uses data

1 drawn from early and late time points to derive information  
2 not only about the acute effects of IIb/IIIa inhibitors in  
3 acute coronary syndrome, but to describe whether the acute  
4 effect is "durable" to later time points, in particular to  
5 30 days.

6 I should emphasize that while this talk will draw  
7 on examples from the databases of the three approved  
8 IIb/IIIa inhibitors, this is not intended to compare between  
9 them or to reopen a discussion of their approval. The  
10 methods proposed have been applied in a post hoc manner in  
11 order to investigate the adequacy of this method to assess  
12 the durability of future IIb/IIIa inhibitors. This is  
13 intended to explore the consequences of applying this method  
14 to the available clinical database in order to aid the  
15 advisory committee in answering the questions posed to them  
16 by the division.

17 [Slide]

18 The first method would use a 30-day primary  
19 endpoint, a time well after the onset of the acute coronary  
20 syndrome. This approach has the advantage that demonstrating  
21 significant superiority at 30 days eliminates most of the  
22 concerns about the persistence of any short-term efficacy.  
23 In addition, statistical analyses methods in order to  
24 evaluate such are trial are in place.

25 The disadvantages of choosing this endpoint come

1 from the difficulties of showing significance at 30 days.  
2 Here, where the majority of the clinical effects appear to  
3 be in the first few days following administration of  
4 IIb/IIIa inhibitors, indeed in the first few hours after  
5 administration of IIb/IIIa inhibitors, the intervening time  
6 period serves only to add additional events to both the  
7 control and treatment groups, making demonstration of  
8 superiority more difficult and increasing sample sizes.

9 I should add, on the other hand, that in the  
10 context of an equivalence or non-inferiority trial the use  
11 of a 30-day endpoint might not be a conservative approach as  
12 differences between the two treatment groups may be obscured  
13 by the events occurring between the acute administration and  
14 30 days.

15 [Slide]

16 The second type of trial would be to collect data  
17 only through 48 hours only, as has been discussed earlier  
18 today. This design has not been used for any drug that has  
19 been currently approved. Its advantages would be smaller  
20 sample sizes and, again, the use of standard analytical  
21 methods to assess superiority versus placebo.

22 The drawbacks to this approach are the smaller  
23 number of events that can be expected to occur and the lack  
24 of information about whether the treatment effect persists  
25 at longer time points.

1 [Slide]

2 A third method that has been used with some  
3 modification in two of the product developments would  
4 utilize an early primary endpoint between 48 hours and 7  
5 days, and to examine the 30-day data for evidence that the  
6 difference between two treatment groups has not narrowed too  
7 much of an extent.

8 In this approach, however, no formal mechanism for  
9 determining if the 30-day difference is still clinically  
10 significant is in place.

11 [Slide]

12 Finally, and the method that I am going to discuss  
13 today calls for the demonstration of clinical efficacy at  
14 the earliest time point, 48 hours, followed by an analysis  
15 of the data at 30 days to make inferences about the  
16 durability of the clinical effect.

17 What I am going to discuss is the analysis of the  
18 endpoints in terms of a classic superiority trial design  
19 compared to placebo. However, this same discussion is  
20 relevant to an active-controlled design, equivalence or non-  
21 inferiority trial.

22 I should also say that there are other methods of  
23 assigning primary endpoints and collecting data apart from  
24 those that I have listed, and one of those is included in  
25 the questions for you today. My intent is to give an



1 overview of the types of the possible approaches to provide  
2 a context for the method that I will describe next.

3 [Slide]

4 The method in general is depicted schematically  
5 here. In this particular trial one can look at the  
6 difference in the event rate at 2 days, shown in the green,  
7 and at 30 days, and it is relatively apparent that there is  
8 no difference. That is, the difference in the treatment  
9 group, shown in white, and the control group, shown in  
10 yellow, is the same at 30 days and at 2 days. And, no one in  
11 this auditorium would have difficulties, I believe, in  
12 saying that the effect that occurred by 2 days has persisted  
13 through 30 days.

14 [Slide]

15 A greater difficulty is shown in this schematic,  
16 where the effect is clear at 2 days. That is, the treatment  
17 group has a much lower event rate, but this event narrows  
18 through 30 days, and the 30-day event rate difference is  
19 shown in green. In such a case, we have in the past looked  
20 at the shapes of the curves to draw inferences about  
21 clinical durability, and the method that I am proposing is a  
22 more mathematical approach, if you will, to this.

23 In broad terms, what I am going to propose is  
24 using the difference from the 30-day endpoints to derive an  
25 imputed treatment group from the control group at 48 hours,

1 from the early time point. If this imputed treatment group  
2 is then different from the control group at 48 hours, the  
3 interpretation would be that durability of efficacy has been  
4 suggested. I will go through an example next.

5 [Slide]

6 This data comes from PURSUIT and, as you can see,  
7 at 48 hours, the early time point, there was a significant  
8 difference between the control and the treated groups, with  
9 an incidence of the endpoint of 7.6 percent in the control  
10 versus 5.9 percent in the treated. At 30 days there was a  
11 15.7 percent incidence rate in the control versus 14.2  
12 percent in the treated, which achieved a p value of 0.043.

13 The method that I am proposing will take the  
14 difference in the event rates at 30 days, that is, 15.7  
15 minus 14.2, and subtract it from the 48-hour time point to  
16 derive a 48-hour treatment group that will coincide with the  
17 difference in the event rates at 30 days.

18 Here is the math for that, 7.6 percent which is  
19 the event rate in the control group at 48 hours, subtracted  
20 from the difference in the event rates at 30 days, yielding  
21 an event rate of 6.1 percent. Multiplying that figure by the  
22 number of patients in the treatment group, 4722, gives you  
23 the number of patients in the imputed treatment group at the  
24 48 hours that would have had an event. Again, the number is  
25 6.1 percent. If you then apply Fisher's Exact Test to the

1 baseline control and the adjusted treatment group, one  
2 obtains a so-called durability p value of 0.004.

3 [Slide]

4 Schematically, this looks like this. At the early  
5 time point then, the first step, the trial has demonstrated  
6 clinical efficacy as suggested by the p value of 0.001. The  
7 30-day p value is larger, however, the durability p value,  
8 computed as I went through, 0.004, suggests that there was  
9 clinical durability of efficacy through the 30-day time  
10 point.

11 [Slide]

12 There are at least two other patterns of results  
13 that exist in the database that we currently have that are  
14 worth going into briefly. First, from the PRISM-PLUS trial,  
15 if you look at the 7-day data and the 30-day data the  
16 percent reduction at 7 days was 5 percent, and this was  
17 nominally statistical significant. At 30 days the 3.8  
18 percent reduction did not achieve nominal significance,  
19 greater than 0.05.

20 When the durability p value was calculated,  
21 however -- and, again, that would be calculated by  
22 subtracting the 22.3 minus the 18.5 from the incidence rate  
23 in the control group at 7 days, which is 17.9, one gets the  
24 following result: the early p value again, the first step,  
25 was nominally significant, 0.011, so that we could ask

1 whether durable clinical efficacy existed. The late p value  
2 of 0.071, on its face, might suggest that at 30 days the  
3 clinical efficacy was waning. However, this imputed  
4 durability p value, taken as a number alone, would suggest  
5 that in the PRISM-PLUS trial, in fact, there was significant  
6 clinical efficacy that persisted to the 30-day endpoint.

7 [Slide]

8 In distinction, in the IMPACT II trial there was a  
9 2.3 percent reduction in the event rates at 48 hours --  
10 difference in the event rates at 48 hours compared with a  
11 1.6 percent reduction at 30 days. The 2.3 percent reduction  
12 at 40 days (sic) achieved nominal significance, however, the  
13 30-day did not and when the durability p value was  
14 calculated the following results are seen:

15 The early p value, again 0.015, is significant so  
16 the question of durability could be entertained. The late p  
17 value, 0.127, suggests again that the durability was not  
18 sustained in this particular trial and the durability p  
19 value in this case does not change that impression. One  
20 interpretation of this would be that this trial alone would  
21 not be sufficient to demonstrate persistence of clinical  
22 efficacy for this product at 30 days.

23 [Slide]

24 In written form then, the methods for establishing  
25 the durability of efficacy that I am going through and that

1 have been proposed by the agency are as follows: From a  
2 trial measuring early and late time points, 48 hours and 30  
3 days, you first determine the event rates at those early  
4 time points and determine whether clinical efficacy is  
5 demonstrated at the early time point, in this case by  
6 demonstrating nominal statistical significance. If that  
7 significance is not present, obviously examining questions  
8 of durability or lack of efficacy would be moot.

9           However, if that efficacy is demonstrated you next  
10 determine if the difference in the event rates at the late  
11 time point would be nominally significant if it was applied  
12 to the control group of the earlier time point, the 48-hour  
13 mark. If nominal significance is retained, this supports the  
14 durability of the clinical effect at the later time point.

15           [Slide]

16           In conclusion then, the available trials using  
17 IIb/IIIa inhibitors have employed primary endpoints between  
18 48 hours and 30 days, and the method of analysis proposed  
19 examines the acute effects of IIb/IIIa inhibitors, as well  
20 as incorporates information about the durability of the  
21 drug's efficacy through 30 days. Thank you.

22           DR. PACKER: Tom, can I ask you to comment on this  
23 proposal?

24           DR. FLEMING: I believe the rationale behind this  
25 is certainly well motivated. If you have an agent that you

1 fully anticipate to have its signal essentially in the  
2 earliest stage of follow-up and you have a strong  
3 expectation that evolves after that will reflect neither  
4 further benefit nor unintended adverse effects, it is very  
5 compelling to say let's look at the signal at the time  
6 period where it is most evident, which would in this case  
7 be, let's say, at 2-3 days, and then let's explore and  
8 ensure that what happens at 30 days at least as showing a  
9 consistency of effect.

10           The issue though that concern me a bit is where  
11 this will be most useful is in those settings where a non-  
12 trivial additional number of events evolved between the  
13 earlier time point and the later time point. We have seen  
14 for example, in the PCI setting, if you look at death/MI,  
15 the vast majority of the 30-day events are there at 2-3 or  
16 by 7 days, even by 2-3 days. On the other hand, in the acute  
17 coronary syndrome setting there is more uniformity of  
18 occurrence of those events.

19           So, this method is even more attractive in that  
20 latter setting because there is the tremendous opportunity  
21 for diluting, and that is really what this analysis is  
22 trying to factor out, the diluting that is going to occur if  
23 truth really is major signal for the first, let's say,  
24 quarter of the events over the 30 days that occur by day 3  
25 and then no signal for the last three-quarters of the events

1 that occur between day 3 and day 30.

2           So, I think the rationale is well laid out; it is  
3 well motivated. The issues that I would raise though are  
4 what are the operating characteristics in terms of what I  
5 might call the traditional false-positive or false-negative  
6 conclusions?

7           So, let me at least just pose these and get some  
8 response or some thought about this. The first of these  
9 would be suppose, in fact -- I mean, is there a risk for a  
10 false-positive conclusion? Let's use this example that I was  
11 referring to, whether it is death or death/MI. Let's suppose  
12 that a quarter of the information that is going to be at 30  
13 days is already in hand at 72 hours. If that is the case --  
14 and let's suppose that the standard error for our estimated  
15 difference in death/MI rates is half a percent. That would  
16 mean in order to achieve statistical significance at the 7-  
17 day point you need to standard errors for the difference.  
18 That is about a 1 percent difference.

19           Well, if you have 4 times the data at 30 days than  
20 you do at 7 days, then the standard error of the estimate at  
21 30 days will be twice as large. Well, let's suppose in truth  
22 there is a 1 percent difference that exists at 3 days, and  
23 let's suppose in truth there is no difference -- the thing  
24 we are trying to rule out; the thing we are concerned about  
25 -- that there is in truth no difference at 30 days, well,

1 all you would need to see for this method to give you a  
2 positive result is you would need to observe the truth of 1  
3 percent difference, which would be 2 standard errors away  
4 from zero and, hence that would be a significant result at 3  
5 days. At 30 days, if you saw just a single standard error  
6 away from truth that would be a 1 percent difference, and  
7 the chance of seeing 1 standard error is 15 percent. So,  
8 this method has a 15 percent false-positive error rate that  
9 if in truth there is a 1 percent difference, which is very  
10 significant at 3 days, and no difference at 30 days, you are  
11 going to get the false-positive impression.

12           Okay, in addition there are false-negative risks  
13 with this. Let's suppose that there is this 1 percent  
14 difference, and let's say that 1 percent difference persists  
15 -- or, let me even go further, let's say there is 1.5  
16 percent difference, which is 3 standard errors, a p of 0.001  
17 at 3 days, and suppose that 1.5 percent difference truly  
18 persists out at 30 days, well, you only have to observe a  
19 half a standard error underestimate of that, which will  
20 occur with about 30 percent probability, for your observed  
21 difference to be less than 1 percent at 30 days which, when  
22 imputed back to 7 days, will no longer meet your criterion.

23           Worse yet, suppose the true difference is 1  
24 percent, just barely hitting 2-sided 0.05, now you have a 50  
25 percent chance, even if in truth that level persisted at 30



1 days, that the observed level would be less than that.

2 A third concern is what if in truth, as Reapro  
3 authors were trying to establish in their presentation, what  
4 if the effect isn't entirely observed in the first 3 days?  
5 What if there really is a cumulative effect over time? We  
6 will obviously not be taking advantage of that at all so  
7 that if, in fact, the difference isn't significant at 3 days  
8 but would have been highly significant at 30 days -- too  
9 bad, the method fails because you didn't satisfy the initial  
10 3-day condition in the first place and you don't get a  
11 labeling indication for 30 days under any of these  
12 scenarios. Your labeling indication under any of these  
13 scenarios is only for 3 days.

14 So, I believe the method is well motivated. I  
15 fully understand the concern, but there are three or four  
16 operating characteristics with the method proposed that  
17 leave me very concerned that we could have false-positive or  
18 false-negative inferences with this.

19 DR. SEIGEL: Tom, this method, as any method, has  
20 its false-positives and false-negatives, and whether it has  
21 more or less, first of all, compared to what? So, this has  
22 more false-positives for a 30-day effect than does a 30-day  
23 endpoint, but it has far fewer false-positives for a 30-day  
24 effect than does just a 48-hour endpoint with no additional  
25 controls. So, this is somewhere in between.

1 I am not advocating, as you know from earlier  
2 discussions, 48 hours and this, as you know, reflects a  
3 compromise between the greater certainty of a 30-day  
4 endpoint with the recognition that that includes more noise  
5 and that there is greater efficiency in determining effect  
6 early endpoints, and it may or may not have the right  
7 characteristics but it is important to see how it compares  
8 and make sure we understand how it compares with both of  
9 those.

10 As far as the issue of the false-negatives, one of  
11 the principles underlying this approach as opposed to one of  
12 the approaches that Doug mentioned, which was the idea that  
13 you could look for 48-hour effect and then eyeball whether  
14 you thought it was maintained, is that you can actually with  
15 any prespecified test power to deal with false-negatives.  
16 Yes, it is true that if your drug apparently works at 0.05  
17 in the first 48 hours and has no effect afterwards you have  
18 a 50 percent chance of failing, so that gives you 50 percent  
19 power, but you can calculate in advance under those  
20 assumptions exactly what you need for whatever power you  
21 want, which I think is tremendously superior to putting in  
22 any criteria which are both arguable at the end because it  
23 is not prespecified, and also not possible to power for.  
24 So, that is something at least to think about.

25 Finally, I would say it is probably noting or

1 thinking a little bit about where this came from and  
2 thinking about where the alternatives might be. First of  
3 all, where the idea of a compromise came from, it is  
4 important to historically note that initially sponsors were  
5 told 30 days. Later some sponsors were told 48 hours but you  
6 have to measure at least 30 days to make sure -- you know,  
7 to take a look at that. And, there are issues of a level  
8 playing field that got raised, especially by those sponsors  
9 who were told they had to have a 30-day primary endpoint,  
10 leading to some discussions about how to reconcile these,  
11 and to an approach --

12           If you accept that it is reasonable to look at a  
13 48-hour primary endpoint and to preserve benefit, and I am  
14 not suggesting necessarily that that ought to be accepted,  
15 and I won't speak to my personal views at this point, but if  
16 you accept that, then the question becomes what is the test  
17 to ensure that there is some sort of benefit retained? If  
18 you accept that it is desirable to have a test so you don't  
19 argue whether it has passed or not and so that you can power  
20 for that test, then actually I think the logic for choosing  
21 this sort of test was the following:

22           If the test is simply that you have to have any  
23 benefit in the right direction, and that is pretty  
24 unsatisfactory, you could lose all your effect but for 1  
25 patient and that means sort of nothing, if the test is that

1 it has to be significant at 30 days, well, then you are back  
2 with the 30-day endpoint which I understand you think we  
3 ought to be. If the test is that you have to retain a  
4 certain percent of effect, say half of the effect, that is  
5 really problematic because that penalizes a very good drug  
6 that may both prevent events and also defer some events. So,  
7 a drug that has a 6 percent effect and then at 30 days has a  
8 5 percent effect wins, but one that has a 20 percent effect  
9 but only has 10 left of that 20, even though it has 10  
10 compared to the drug that had 5, loses. So, a percentage of  
11 effect doesn't do it.

12 So, that sort of led to the idea of having some  
13 specific amount of effect, an amount of effect that would be  
14 necessary had it appeared at 48 hours.

15 Let me ask a different question of you, which is  
16 if you believe that the data were such that you had some  
17 level of comfort that 48-effects were probably retained but  
18 you wanted to see data from the trial to ensure that this  
19 wasn't an exception to that rule, is this a reasonable  
20 approach to look at that in terms of ensuring that you have  
21 a prespecified effect size at 30 days, that which would have  
22 been significant at 48 hours?

23 DR. FLEMING: I think this is reasonable but you  
24 get what you pay for and I think sponsors ought to be  
25 entirely aware that you are paying less and you are getting

1 less. The basis in terms of the false-positive, I would say  
2 is if I believe that 48 or 72 hours is enough the issue is  
3 much less complicated. The issue is simple. You just get the  
4 data over 48-72 hours. It is clearly a time when we expect  
5 the greatest sensitivity. The signal would be large. The  
6 sample size will be smaller. That is definitely the easiest  
7 solution here.

8 I am amongst those though that believe that if  
9 there is an effect at 48 hours and it is gone by 30 days  
10 that it has to be an incredibly non-toxic, convenient and  
11 safe intervention to say I have a positive risk/benefit  
12 profile if I see a difference that is there at 3 days that  
13 is completely gone by as short as 30 days. So, that is  
14 motivating me to believe that the benefit conclusion here  
15 must be based on data that would establish benefit at 3 days  
16 that is convincingly still persistent at some level at 30  
17 days.

18 Now, what has motivated all of this discussion is  
19 the assumption that no difference is going to occur between  
20 3 days and 30 days. The scenarios that I was giving for  
21 false-negative conclusions are based on that assumption.  
22 What sponsors would need to know, in terms of "you get what  
23 you pay for," is that if you power this study to a 30-day  
24 endpoint you have a much larger study but, in fact, you have  
25 the ability to conclusively establish benefit based on an

1 achievable difference at 30 days.

2           If you come in with a much smaller sample size, as  
3 this allows, even if you see a 3 standard deviation  
4 difference at the 3-day time point -- let's say a 1.5  
5 percent difference, you have a 30 percent chance if the  
6 truth is that there is no differential effect between 3 days  
7 and 30 days -- a 30 percent chance that the imputation at 30  
8 days back to 3 days is not going to be satisfying.

9           So, there is truth in advertising here. People  
10 have to know that you can mount this trial and the truth  
11 could be big effect early; no difference later on. And,  
12 there is so much noise in that no difference that it is well  
13 within random variation that you are going to see an unlucky  
14 result that will not satisfy this criterion, and that is the  
15 price you are paying by going with the smaller sample size.

16           DR. PACKER: Ray, you have the last word.

17           DR. LIPICKY: I would like to see -- because I  
18 think it is the first time that I have ever seen curves of  
19 how events go as a function of time on the screen today. I  
20 don't know where I have been! As I looked at the shape of  
21 the curves, they didn't seem to me to be determined by a  
22 single function. It looked like they changed their  
23 inflections with time.

24           So, I am going to make a proposal. Let's say that  
25 the time course of events as a function of time after zero

1 time, in fact, showed that they were best fit by a two  
2 exponential fit, something that had a fast time constant and  
3 something that had a slow time constant and that, in fact,  
4 the drug effect that was present clearly affected the fast  
5 time constant and not the slow time constant, and that the  
6 fast time constant had a number that was equal to 2 that is  
7 its time constant. So, that means by the end of 10 days,  
8 whatever that process is that is affected, has expended its  
9 total business. If it turned out that way, I would say there  
10 is no sense about talking longer than 10 days. You just have  
11 to be comfortable that you have truly affected this process.

12 DR. FLEMING: Let me just allude back --

13 DR. LIPICKY: And, at 30 days the clinical  
14 significance -- to me, clinical significance is getting out  
15 of the hospital.

16 DR. FLEMING: I would like to go back to one of  
17 the first comments that I made about this, and that is the  
18 properties that we have been discussing depend greatly on  
19 what fraction of the 30-day events are already apparent at  
20 day 3, and in PCI it is a large fraction. So, the concerns  
21 that I am raising are far less in that setting but you are  
22 buying much less as well.

23 Where this method is really motivated is where a  
24 fraction of the events where the signal would be expected to  
25 occur, i.e., day 3, are a small fraction --

1 DR. LIPICKY: That is ignoring shape. It is  
2 fraction of events. What if the events that you can  
3 influence, in fact, are all influenced within 3 days?

4 DR. SEIGEL: Rob showed us some hazard functions,  
5 not simply event rates, and hazard functions are not exactly  
6 the slope but closely related to the slope of the event rate  
7 for patients still at risk.

8 DR. LIPICKY: Not at all, it is simply dividing  
9 two numbers.

10 DR. SEIGEL: Okay, and clearly the hazard ratio  
11 shows that it isn't the same over the course of time. On the  
12 other hand, it doesn't get down to baseline until two or  
13 several weeks afterwards. Part of the problem with your  
14 argument, Ray, is if there is a separate event that occurs  
15 that is a short-term event and you prevent all of those  
16 events, you have to distinguish between preventing those  
17 events and delaying those events. So, there is a time course  
18 without treatment and there is a time course with treatment.  
19 And, if you have a type of lesion that might cause a  
20 complication by an MI over 3 days, and you give somebody a  
21 drug that prevents platelet aggregation for 3 days, you  
22 don't know, unless you include days 4, 5, 6 and 7 in your  
23 endpoint, whether once that drug wears off those events  
24 occur just as often --

25 DR. LIPICKY: That isn't the result I described.



1 The result I described is that two exponentials occur. The  
2 fast exponential has the entire drug effect and the slow  
3 exponential is exactly unchanged.

4 DR. SEIGEL: Yes, but there is no way you can  
5 measure that about a drug.

6 DR. LIPICKY: I mean, I can certainly fit the  
7 curve --

8 DR. SEIGEL: Because you get a different curve  
9 when you treat it with the drug.

10 DR. LIPICKY: Not time constant-wise.

11 DR. CALIFF: Well, you can test that. I mean, that  
12 is something you could test.

13 DR. LIPICKY: Yes.

14 DR. CALIFF: You could estimate that.

15 DR. LIPICKY: I mean, either I am right or I am  
16 wrong. I don't know whether I am right or wrong. I haven't  
17 done it.

18 DR. SEIGEL: But you can't test it by just testing  
19 for the first 10 days with that fast curve because you don't  
20 delay --

21 DR. LIPICKY: No, no, no --

22 DR. CALIFF: This is interagency dialogue.

23 DR. PACKER: If I could suggest that this  
24 discussion is further compounded by the fact that the  
25 definition of the components might change because of the

1 fact that enzymatic monitoring may occur only early and not  
2 late, which I would contend is a far greater confounding  
3 factor than any confounding factor that anyone has discussed  
4 and which I have not yet heard a solution for.

5 Let me suggest in the interest of time, that we  
6 have actually discussed all the questions, whether anyone  
7 has noticed or not, and we have provided you with all of the  
8 answers.

9 [Laughter]

10 There is clearly a substantial number of issues  
11 that pertain to the design, the execution and the analysis  
12 of positive-controlled trials, including the delineation of  
13 the patient population, the delineation of an endpoint, the  
14 timing of an endpoint, the selection of the comparator, and  
15 you will probably notice that none of those of issues has  
16 been resolved today -- none. You have gotten hints today as  
17 to how the thought processes may be working, and you have  
18 heard some very specific proposals from some very informed  
19 and experienced people as to how they might view this. But  
20 this is a process that must continue for the future. There  
21 are no answers today, but this is a step in the right  
22 direction, and I think that the data and the discussions  
23 that we have seen today move this process one step forward  
24 to try to come up with some way of designing and  
25 interpreting positive-controlled trials in this field.

1           The difficulty, of course, is that we can say  
2 anything, design anything, propose anything but databases  
3 don't necessarily come out as interpretable as we would like  
4 and the proof of the pudding will be when the first  
5 positive-controlled trials come in to see whether they, in  
6 fact, teach us anything about the efficacy of the drug in  
7 the absence of a conventional placebo-controlled trial.  
8 Hopefully, we will be able to take a look at the existing  
9 data, as well as the data from ongoing and incompletely  
10 analyzed trials in order to shed further light on whether  
11 these issues can be satisfactorily resolved.

12           I would like to thank all of the invited experts,  
13 our invited guests from industry and all of the committee,  
14 and we will consider ourselves adjourned.

15           [Whereupon, at 4:58 p.m., the proceedings were  
16 adjourned.]

17

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**C E R T I F I C A T E**

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script that reads "Alice Toigo". The signature is written in dark ink and is positioned above a horizontal line.

**ALICE TOIGO**

**Lawyer's Notes**

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**Lawyer's Notes**

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