DR. KAWAS: I am not sure I completely understand how we could get around this issue but I have a low level also of concern.

DR. GILMAN: Dr. Penn?

DR. PENN: I think the solution is simple, and that is that the FDA should ask for the data from the studies that have been presented to us, should review it and make nimodipine available for all grades of patients with subarachnoid hemorrhage if they think that is appropriate, and then we would be done with the issue. It seems terrible to be out of sync because a company has not gone back to ask for this permission. I think something could be worked out reasonably smoothly with the data that is now available.

DR. GILMAN: But you would have to have a control group without and a group with and you would need placebo control to do a rigorous study of the effect of nimodipine in grade IV/V compared to grades I through III cases.

DR. PENN: I think the weight of evidence on that issue is in now, and I don't think that it is deleterious in those groups and I think there is no way that you are going to get more information on that than we now have, and the experts in the field feel strongly that it should be used and we are out of step just because of a technical thing that happened when there wasn't as much information available.

DR. TEMPLE: Even if we can't find strong evidence supporting effectiveness in grade IV and V it may be that the evidence supporting detrimental effects is much weaker. Currently the labeling really makes a point of that and I think we need to look at it to see whether that is reasonable or not.

DR. GILMAN: Well, it might be advisable to go back and review the primary studies again because we have heard about one study. Dr. Wiers, who I think had to leave, had pretty contradictory information about that. Grade III was the grade most at risk. That was puzzling.

DR. TEMPLE: That is what I meant by taking a look.

DR. GILMAN: We are still trying to come to grips with the question that Dr. Katz has posed for us so let's move on. Dr. Lacey?

DR. LACEY: I have some concern about nimodipine and its administration but in view of the contradictory information that was presented, I am encouraged that perhaps there is no need for real concern. So, I would hope that there would be a review of the literature and if it supports the use of it, then there is all reason to go with that. But if it does not support it, then for me there is still a quandary.

DR. GILMAN: Dr. Van Belle?

DR. VAN BELLE: No opinion.

DR. GILMAN: Dr. Grotta?

DR. GROTTA: I think that you compare your drug to standard of care, and I think standard if care is the use of nimodipine then it has to be included. I agree with reviewing the criteria. In fact, I would expect theoretically and pharmacologically that the two drugs, if they are both neuroprotective, would act in a complementary fashion and not contradictory.

DR. GILMAN: Dr. Brooke?

DR. BROOKE: I would second that. Nimodipine is best medical practice. You can't really avoid its use, and there is not enough in this data that we have been presented with to make me think that nimodipine was clearly having a deleterious effect in combination. So, I don't think that I would have any problem with using nimodipine.

DR. GILMAN: Dr. Brooke has to leave us shortly but he has given me a statement related to the two final questions that we will get to.

Question four concerns the effects, if any, of baseline differences between treatment groups. Are there concerns about the baseline differences between treatment groups?

Well, I have significant concerns about the differences between the treatment groups in the trials that

we have examined. To go back again, the initial two studies, as I reviewed them retrospectively, left me a bit puzzled as to why the FDA did not recommend a large men and women study rather than women alone. I have heard the answer. Obviously hindsight is 20/20. I think it would have been better perhaps to have a large group of both men and women all grades examined with drug and with placebo, double-blinded. So, I do have concern about the baseline differences between treatment groups in the studies that we have reviewed here today. There are gender differences. There are drug dose differences, age differences, etc. So, yes, there are concerns.

Let me go the other way. Dr. Grotta?

DR. GROTTA: Again, I think the whole data set should be looked at for the predictors of outcome, and I think that those need to be within the study -- if you do another study you just need to ensure a balance between the different groups on those variables.

DR. GILMAN: Dr. Van Belle?

DR. VAN BELLE: Yes, I think the issue is that the way the endpoints were defined retrospectively were bound to give a fairly high chance of having groups that differed at baseline, and no amount of adjustment will take care of that problem. We will always be left with the question what does it really mean.

DR. GILMAN: Dr. Lacey?

DR. LACEY: Yes, I feel that there are differences that should be of concern to us, but I think enough has come up in the various discussions that for future study things can be identified reasonably.

DR. GILMAN: Dr. Penn?

DR. PENN: I don't have anything to add.

DR. GILMAN: Dr. Kawas?

DR. KAWAS: Just to say there are always baseline differences between groups, otherwise the FDA and the sponsor wouldn't have something to massage to make the result look more in their direction. None of the baseline differences that are in any of the studies, however, that we reviewed really concerned me and I don't think they were responsible for the outcomes of the studies in any of these cases in a convincing way. So, in the sense of the effects of the baseline differences between groups I actually have pretty much no concern.

DR. GILMAN: Dr. Drachman?

DR. DRACHMAN: Well, if there really were no differences the very dramatic result in 32 and not 29 would be very puzzling. I have sort of looked at that and worried about it over and over again. I still don't quite know why men did so dramatically better in the one than the other. So, I think there must be baseline differences or we have

tossed an unfair coin one way or another and got a very strange result. Nevertheless, the retrospective grouping is always a way of finding imbalances, and the effort to redress that leaves one open to the failure of the notion of randomization. So, in the future randomize; say what you are doing. But I am still very puzzled by 32 versus 29.

DR. KAWAS: Can I just comment? I think that one of the main issues with regard to baseline differences might flow into the mandate that Dr. Temple gave us, which is should any of these differences be stratified in future studies.

DR. GILMAN: Of course, that is the concern with retrospective studies. The cases were not gathered with stratification in mind to test particular questions in particular subgroups. So, one can get into all kinds of trouble with retrospective analyses and I think that is just what we are seeing here.

But would you still maintain though that you are not concerned about baseline differences, Dr. Kawas?

DR. KAWAS: Yes, I guess I would only because all the ones that we have seen -- I am not convinced. They are just as convincing as the other things. I mean, the first study would say that the baseline difference that was irrelevant was sex. Being a man was the important thing. And, I realize we have limited evidence to look at even

gender because two out of the three remaining studies don't even give us an opportunity to look again at men. The data doesn't coalesce in any way that makes me think that there is a particular baseline difference that is very important for creating these results right now. That is not to say there isn't one; I just can't identify it.

DR. GILMAN: All right, thanks. Let's then go to question six, and that has to do with the sponsor's integrated analyses.

I feel very strongly about this issue. I guess it was pretty obvious earlier that I don't see the rationale for and, in fact, I take strong exception with the integrated analyses that we have seen. The sponsor has mixed together different studies with different genders, different drug doses, and had us look at a bar graph that was just totally misleading. In addition, we want to show that a particular effect can be replicated. It is not always necessary now with the change in the law. It is possible to prove a particular drug with a single trial provided a series of guidelines are followed. I am not going to review them at this point.

But I would certainly like to see replication, and the frustrating aspect of these data has been that one study shows a significant effect but the next study doesn't replicate that effect and we have just gone on with four

studies now, almost getting nowhere. We see something interesting and then it vanishes, until finally we have a prospective study that shows something. It does show something that appears to be significant for women but then I have very little confidence that replication of that will show it again unless it is done correctly, done well. So, I don't think that integrating the various studies, putting them together, gets us anywhere. It just confuses the matter. Dr. Grotta?

DR. GROTTA: Well, I also feel strongly about this because I think that actually we have missed an opportunity here. I agree with what Dr. Gilman said. I think that I don't like the integrated analysis, and I am not a biostatistician but I think, had the data been presented differently we, as a group, might have reached a different conclusion.

So, let me take a minute to explain why I think that. Three out of these four studies showed a very strong trend, if not a significant effect, on the outcome of mortality. Study 32 -- and you correct me if I have got the figures wrong, but for all males, which is the subgroup of interest in study 32, for all grades the mortality rate was 25.3 versus 2.1. In study 29 for all males the mortality rate was 12.7 versus 8.6, again, both of those in favor of tirilazad. In study 63 for all women the mortality rate was

15.1 versus 12.9, again in favor of tirilazad. In study 65, which is the other large study and all women, and even there, there was a little trend, 18.8 versus 18.0. So, in all four studies the mortality rate was less, and in one of them it was highly significant and in two of the others there was a strong trend.

Had you done a meta-analysis on mortality in the populations of interest, I think that that would have probably turned out to have a positive meta-analysis for mortality. That is the way a lot of the anti-platelet drugs for stroke prevention got approved. A lot of the studies were underpowered to detect a significant effect but they showed a trend, and in a series of studies all going the right way I think I could have been convinced.

DR. GILMAN: Dr. Van Belle?

DR. VAN BELLE: Well, let me respond to that. A meta-analysis assumes that you have independence of studies in some sense, and I think you would be hard-pressed to argue that these studies, the way they were set up, were in fact independent. That is point number one.

The other point is that most analyses are integrated analyses in some form or another. When you randomize subjects to treatment one and treatment two you can always get subgroups out and say, you know, that things were integrated over that. So, to my mind, the important

thing is are you integrating homogeneous groups or heterogeneous groups? In this case it was clear that there were heterogeneous groups, and that is where my concern would come about. That is all.

DR. GILMAN: Thank you. Dr. Temple?

DR. TEMPLE: Can we inquire, would you explain what you mean by not being independent? They were separate studies? Why were they not independent?

DR. VAN BELLE: They were not independent in the sense that when we go to categories IV and V they were defined by looking at the previous studies. So, that introduces a kind of dependence into the four studies.

DR. TEMPLE: I think the suggestion was that they should have simply done a meta-analysis of the four studies as originally randomized.

DR. VAN BELLE: I am sorry, I didn't get that point.

DR. TEMPLE: I think that would not come out --

DR. GROTTA: Those figures that I mentioned were for all grade patients in the first two studies, just limiting it to men, and the second two studies, of course, were just women. But all women, all grades for the second two studies and all men, all grades for the first two studies, and they were independent studies. So, I don't see why you wouldn't be able to meta-analyze them.

DR. VAN BELLE: Your point is well taken. I was thinking that you were talking about the studies as we were presented with today. There still is the second aspect though of doing a meta-analysis of studies that are not homogeneous.

DR. LACEY: I think the sponsor's integrated analysis as presented today -- it seemed to be intended to be convincing and I looked at it in that way, that someone was trying to convince me of something. I looked at it more as a cumulative percentage, as you would look at that. I had seen the data separately and, therefore, I feel that I was able to make a judgment regardless of that having been presented. So, I would hope in the future that they would use a more appropriate analysis, whether that is meta-analysis or what, but a more appropriate analysis than the one given today but I didn't find it terribly distracting.

DR. GILMAN: Dr. Katz?

DR. KATZ: Yes, maybe to make this more explicit, Dr. Grotta, you are suggesting -- well, let me ask this as a question, are you suggesting that if they performed the sort of meta-analysis that you described and it turns out significant that you would not require additional studies to look at some replicated finding? Would that be enough to provide substantial evidence in your mind?

DR. GROTTA: Yes, in my mind because, as has been said multiple times here, all these trials have trended in the right direction. One of them was highly significant, one of them was borderline and two of them weren't. So, I mean, it depends on whether you believe in approving a drug on the basis of a meta-analysis or whether you require two independent studies. I suppose that is a matter of how many studies go into the meta-analysis, the quality of them and the clinical situation. I guess that in this situation, where -- of course, more studies would always make me feel more comfortable, and I tried to convey earlier that I have a nagging feeling that there is a biological signal here that there is some activity and I just don't think that we are picking up on it right. I am bothered by the possibility of type-2 error but if a proper meta-analysis of these four studies, four randomized studies that have been carried out in a prospective, controlled fashion came up positive I think I would be convinced.

DR. TEMPLE: Before we leave that, remember the numbers. Study 32 was positive overall. Study 29 is a wash overall. So, it is not going to add to anything.

DR. GROTTA: Correct me if I am wrong, but I think in study 29 the mortality in males, all males, was 12.7 versus 8.6.

DR. TEMPLE: So, you are not talking about a

meta-analysis of all data, just in males?

DR. GROTTA: Well, I think if the basic premise is that the dose was wrong -- and I am willing to give that part of it away but, again, I am on thin ground, but it seems to me illogical -- and reasonably appropriate to separate by gender for this particular problem given the different bioavailability of the drug in the two genders.

DR. KATZ: I am not a biostatistician either, but we heard earlier that the integrated analysis which was presented in terms of a histogram did exclude women in the first two studies because that is what the company wanted. In other words, they wanted 6 mg in men and 15 mg in women. We all want things. The question is whether or not it is appropriate to do that. To say that women exposed to 6 mg is inappropriate to include because 15 mg is the correct dose, that has yet to have been established I think in women. So, again, it would be interesting to hear what the statisticians in the room think, but the methodology is complicated; it is not straightforward. At least to me, it would seem that those women would need to be included at least.

DR. GROTTA: The only thing about gender is that it is hard to get it wrong. In trials, when you start splitting data and studies, were they recognized right and all the rest? At least as far as gender is concerned, it

should be a pretty easy thing to segregate.

DR. KATZ: Right, but as I understood it, the reason that the women in 32 and 29 were excluded from this so-called integrated analysis was because they weren't studied at the right dose. It is not the dose that the company is going for. We don't know what, if any, dose is right in women, or men for that matter. All we know is what was studied. As I say, if we had independent evidence I suppose that 15 mg in women was the correct dose and 6 mg was clearly incorrect perhaps a case could be made for excluding them. But, nonetheless, you do in general want to include all patients randomized in an analysis.

DR. GROTTA: But we heard yesterday that for anti-platelet drugs, particularly aspirin, that the dose of aspirin was approved, or changes in the dose of aspirin had been made based on going back and looking at the burden of evidence in trials, and sometimes the trials were done with multiple doses and you take the 50 mg patients from this study and the 30 mg patients from this other study and it looks like there is an effect so we are going to approve a lower dose. I think we have to be consistent here, and I think that there are certain things in trials -- again, I am talking now from logic more than I am from strict biostatistical rules and I would have to defer to a biostatistician, but I think it would be appropriate to get

their input at this point. But it seems to me that there are certain things that can go into trials and you can use for meta-analysis. Dose and gender seem to be two of some of those things.

DR. TEMPLE: The problem with meta-analyses, just as is the problem with individual studies, is that you develop multiplicity when you have ten ways to do it. So, a perfectly logical analysis to carry out is all four studies as planned. One can object to the fact that one didn't have men, though I am not sure I would make that objection. One could do that. One could then look at only the men in one and only the women in the other for the logical reason that they got the wrong dose in the first two. Then one can do, which is what they did, the grade IV/V people in all the others. None of them are inherently absurd. They are all perfectly sensible.

The thing is there is such a large choice that you have to figure out what sort of correction you make. It is really the same problem as with any other subgroup kind of analysis. I think that is the problem. I am not as outraged by the attempt to put the data together. I think what they were trying to do is show you that if you look at this plausible subset and you throw all the data together it has a certain strength to it. Personally, I think it is never all that much stronger than the individual components are

anyway, but that was the idea. I think everybody knows that those kinds of analyses aren't the prospectively defined analyses and have to be given a certain amount of skepticism when you look at them, and you have treated them with considerable skepticism.

DR. GILMAN: Dr. Cui?

DR. CUI: I just want to make comments about if we really see a consistent result due to the nature of this kind of assay, sort of the data dredging strategy, say, you give me 4,000 patients; now you give me the freedom to choose a subgroup and endpoint I can easily work out four subgroups with similar patient populations and a certain endpoint to give you all consistent results. So, you have to bear that in mind in interpreting.

DR. GROTTA: And I agree, and that is why I don't like the grade IV/V and all this because I do think it was very retrospective and post hoc data dredging. But I do believe that dose gender issue is sort of like treating a patient that doesn't have the disease. There are certain overriding things in a trial that define whether the population is being treated. I don't believe the women in studies 29 and 32 were being treated. Okay? It was basically like they were being given placebo. So, I do think that when performing this sort of analysis there are certain overriding biological considerations that might allow you to

make a single assessment. I think in this case the women in 29 and 32, it is logical to exclude them from analysis because of the fact that I think they were not exposed to the drug basically.

DR. GILMAN: To continue then, I think we are up to Dr. Penn.

DR. PENN: I dare not wade into meta-analyses. I feel very uncomfortable with them.

DR. GILMAN: But without dealing with them, how about your thought about integrated analyses, meta or otherwise.

DR. PENN: Well, if I had an integrated analysis I would rather have it be a meta one that I don't understand than an integrated one that I do.

[Laughter]

DR. GILMAN: Dr. Kawas?

DR. KAWAS: I agree with Dr. Temple basically. I am not as disturbed as some people are. When I first started hearing the studies I wrote a note to myself how can we put this data all together. But then I realized that the studies were just too dissimilar to do that. I think we are fairly agreed on this point and what effect it has on our interpretation of the data.

DR. GILMAN: Dr. Drachman?

DR. DRACHMAN: The minute we talk of doing some

study in subarachnoid hemorrhage we are immediately beginning to integrate many different processes. We have sort of danced around this, but I think we really should deal with it. My old mentor, E.P. Richardson said when an aneurysm ruptures, that is rather like turning a fire hose on a bowl of jello, which I think really describes it rather well. Death or bad result in aneurysmal subarachnoid hemorrhage may be due to the initial bleed, rebleed later on, thrombosis, death of adjacent tissue, bad surgical results, and on and on. Were this merely blood that appeared in the subarachnoid space we would have only one thing to deal with. What are we dealing with here? We are dealing with so many heterogeneous mechanisms that the notion that one miraculous drug will rescue many patients whether they have herniated their brains and compressed their brain stems, or whether they have jetted blood into their frontal lobes, or whether in fact they have developed emboli from the aneurysm that then led to an infarct in another part of the brain seems highly implausible.

So, at the very least, no matter what we do, we have integrated seven or eight different mechanisms to begin with. Therefore, I do believe that the idea that you would pick out a subgroup based only on severity, without even exploring whether that is due to herniation or whether that is due to dural hemorrhages and brain stem, and on and on,

becomes very unlikely. Since we are looking at a very, very heterogeneous entity, therefore, we must I think integrate data. The way Dr. Grotta recommended makes sense to me. Picking out subgroups based on severity may be helpful in one or another way but it does not say whether we are dealing with infarction, damage due to hemorrhage, herniation of whatever.

So, the short answer is that I do believe that some sort of integration is needed, but that this problem is a severely vexed one because we have lumped under a single rubric something that is so heterogeneous in mechanism that the notion that one drug would fix much of it seems highly unlikely to me.

DR. GILMAN: Dr. Katz?

DR. KATZ: Just to be fair, many of the diseases that treatments are offered for are heterogeneous and complicated, and we have no hesitation in approving drugs that do just a little bit maybe for just one part of it. So, I don't want the impression to be left -- you may find the findings sort of hard to put together in your mind but there is certainly no requirement that there be a major effect on all mechanisms of a disease process for a drug to get approved.

DR. DRACHMAN: No, no, I never would think that there must be a major effect but the notion that by slicing

this pie in a variety of different ways -- gender, the grade -- we will tease out that group without also considering what it is we are treating seems rather unlikely. So, I think we started by integrating a disease, and when we then subdivide that we are in more trouble. I think you have to integrate the data, but it must be done fairly rather than retrospectively.

Just a word on that, that is the entity I am sure you are very familiar with which I refer to as the 6 ft. left-handed women syndrome -- you give a drug and you look through all the data and discover that only women over 6 ft. who are left-handed seem to benefit. Well, you can always find if you have enough entities. Here, I am not sure that the various maneuvers that were done to subdivide make more sense going forward. Going backwards, retrospectively you can find anything.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: Again, this sort of raises the question of what to do next, and I know you want to get to that later. Are you suggesting as a preliminary matter that you are not persuaded that the most promising place to look is in the more severe group? I mean, there was one attempt to look at that group specifically that was prospective, and there was in that study a clear difference in the kind of benefit seen. The excluded group didn't really show

anything; it went the wrong way, and the prospectively determined group looked good. Are you suggesting that lead should be ignored for future studies?

DR. DRACHMAN: I would never want to ignore a lead. The lead is good. But I really would worry that when you look at the IVs and Vs you are still looking at a very heterogeneous group. You may be looking at people with dural hemorrhages and brain stem who have no chance of ever getting better again and, likely, will either be vegetative or dead, while you also may be looking at individuals who are transiently severely anoxic.

DR. TEMPLE: Understood, but having said that, what does that imply to you about where they should go?

DR. DRACHMAN: I don't know, but I agree that the drug may have biologic properties, as was suggested by, first of all, the sponsors, secondly, by Dr. Grotta recently, a moment ago. How one would go forward really would depend again on looking very closely. Herniation is bad news. That is very different from anoxia or ischemia. I have heard very little about that and how those data look. I think going forward to make a major investment, yes. The IVs and Vs look somewhat promising but why were they IV and V? I know very little about that.

DR. GILMAN: Dr. Katz?

DR. KATZ: Let me just ask the other obvious

question. What is your view about whether or not a meta-analysis done on the data that exist by protocol, in other words, all patients, all neurogrades. Is that something you would like to see? Is that something, if the results were positive, you would find compelling? I am sort of interested that the issue has been raised. I mean, meta-analysis is a can of worms, but since it has been raised I am just wondering what people think about whether or not that is something that, if it was positive, would carry the day for you now, without additional data.

DR. DRACHMAN: Not now, not carry the day, but it surely would point out that one of the more important mechanisms was included within this heterogeneous group. I mean, sure, it may be that some large proportion have in common enough so that by looking at all the data you would be able to find it. You may even be able to slice it better. But I rather doubt that a meta-analysis, given what we have seen, would be significant. So, again, subjunctive; contrary to fact.

DR. GILMAN: Dr. Grotta?

DR. GROTTA: But what if it were? Let's just give a hypothetical that you have the amount of uncertainty -- let's say the studies maybe wouldn't be positive. Let's say the studies were a little bit more positive than they are, and a proper meta-analysis were done and it showed

statistical significance.

DR. DRACHMAN: That I would need to see. It would be much more persuasive. We can, I am sure, be very certain that it wouldn't or we would have seen that and not all the other stuff. I mean, if frogs had wings they would fly but I don't think that is the case here.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: Well, you can already predict the results of this. I don't know what happens if you throw all the studies together, but we know there was only one study that was overall positive for the entire population. So a meta-analysis would be driven by that study if it remained positive after dilution by the other three which I do not, just intuitively, think it would. It doesn't really provide you any more information than you had before. One of the trouble with meta-analyses where you know all the components going in is that you can predict the outcome or come very close. It is only when somehow you take a bunch of small studies that individually don't show anything and then at the end you have a p that is a long as your arm, those can be sometimes very convincing. But in this case it is not easy to see how that would become persuasive.

DR. GROTTA: But aren't met-analyses affected by the size of the study? So, the first two studies aren't going to nearly lend the weight that the second two studies

would.

DR. TEMPLE: The first two studies are good sized. It is just that the grade IV/V men are rather small but they are pretty big on their own.

DR. GROTTA: The number of men, right, and the number of women. The Ns in the second two studies were twice what they would be in the first study because the second studies were just women and the first studies were both men and women.

DR. GILMAN: A lot of this discussion I think is past the point. The point is do we have an effect, do we have a beneficial effect of a drug on a serious illness that convinces that the drug is better than placebo, first. Second, if that is the case, can it be replicated independently? This is the scientific method, that you have a hypothesis, you test the hypothesis, you get an answer. The answer could be due to chance or could be due to any of a number of factors and so you want a separate method of verifying it independently, presumably or hopefully using the same techniques, the same cases and so on. I think we beg the question when we get to looking back over four studies that, from my perspective, had different baselines, different genders, different drug doses, etc. So, I am not persuaded that a meta-analysis would do anything more than show us that one of these studies prospectively showed

something important, maybe important. Dr. Van Belle?

DR. VAN BELLE: I still want to go back to the point that I made earlier about meta-analysis. Before you do the meta-analysis, that is to say before you integrate, you see whether what you are integrating is comparable or not, and I think in this particular case that is not so. So, I would doubt the usefulness of a meta-analysis.

DR. GILMAN: I think you have said that more succinctly than I could. That is exactly what I was trying to say.

Let me ask the agency, do you wish more of this or shall we get to the two final questions? Can we proceed?

Well, we have been asked to answer two questions that are posed for us, and they are the following: First, has the sponsor submitted substantial evidence of effectiveness for the proposed indication sought for the treatment of aneurysmal subarachnoid hemorrhage to improve survival and functional outcome in patients with poor neurologic function following the initial hemorrhage?

Let me again start off by saying no, in my view the sponsor has not submitted substantial evidence showing that there is any beneficial effect. Let me follow that up by answering Dr. Temple when he asked what sort of study should be done to answer this question. We have studies that initially suggested that perhaps all men would benefit from

this treatment. Then we had a study suggesting that perhaps only grade IV/V men would benefit from this treatment. Then we had a study, the one prospective study suggesting that perhaps women at grade IV/V might be benefitted. Then we had a question about whether grades I through III might be damaged. Those are questions; there are no answers. I don't think we know this yet. Then we have to throw in the problem with respect to nimodipine.

So, my suggestion is that first you go back to the literature, as Dr. Temple indicated they will do, the agency will do, and look at what you have there with respect to nimodipine effects in good studies, well-controlled studies on these various different grades and see if you can verify what appears to be common knowledge in the neurosurgical community, that all grades seem to benefit from nimodipine. I don't take that at face value. I would like to see data to verify that issue.

If you do, if you find that in fact they are correct, then I would suggest that maybe the sponsor would want to go back and do another trial. And, my suggestion is that this trial be a large one on both men and women, I would hope with the same kinds of approaches with respect to grading, and I would personally prefer that they use a commonly used grading scale, whatever that scale may be. It is probably not hard for the experts in the room to say,

well, a modified GOS is fine; we can do it in a couple of minutes, but often this is the sort of treatment that would be applied to people in critical situations with changing status for patients rapidly over time and it is obviously much better if you can have a simple, rapidly applied grading scale to determine the grade of the patient. So, I would like to see grades I through V evaluated in another study, both men and women.

DR. KATZ: Let me just explore that a little. Obviously, there is a fair amount of conflicting data here but study 32 suggests that in men there is a chance that it may work in everybody. Subsequent data suggests that if there is anything in the women it is only in the high neurogrades. The question is which of those findings -- in other words, suppose they did a second trial only in IV/V men, women, whoever, is that what you would like to see? I know you want to include all neurogrades, the question is in which group of patients has there been, if any, a sufficient finding already that it is sort of ripe for replication?

DR. GILMAN: None. As I see it, there are conflicting data irrespective of which grade you look at. There are some suggestive data that grades I through III may be damaged by the treatment. There are some data suggesting that grades IV/V may be benefitted by the treatment. However, none of this is clear from what we have. We have

one study in which there is a positive beneficial effect prospectively, and that is grade IV/V women in the final study done. I think they need to go back and do a proper trial.

DR. TEMPLE: Let me press that point. Suppose, because of efficiency and a desire to get there, the company said, well, fine, the first thing we are going to do -- we are going to do more later maybe but the first thing we are going to do is replicate the finding in 63 because it was prospective and that would then be a replicated finding in women with high neurogrades. That wouldn't be the first time someone had studied one part of an array of a disease. Would you have a problem with that, or do you think it is less optimal, where do you come out?

DR. GILMAN: I have a problem with it because some years back when you had studies 29 and 32 your recommendation was to go back and study just women, hoping that you could replicate a finding in grade IV/V men. Now here we are, some years later.

DR. KATZ: Briefly, we were hoping that they would replicate a finding in all women, not just IV/V.

DR. GILMAN: I am sorry, you are right. That is correct, in all women. But we wind up now, with the committee having deliberated over this day and having read thoroughly for a considerable period of time, and we are

saying no, the sponsor has not -- at least I am saying the sponsor has not submitted substantial evidence of effectiveness. I am concerned that there are so many questions before us that if the sponsor goes back and tries to replicate the findings on grade IV/V women, those findings may not be replicated. We won't know, even if they are replicated, whether the medication will help men grade IV/V or men grade I through III or whether it will be deleterious to men or women at grades I through III. We will still have multiple questions even after that is done. That is the concern.

DR. TEMPLE: I suppose one could do a study in, say, both men and women with your primary hypothesis being that there is a benefit in grade IV and V and studying other people to see what happens.

DR. GILMAN: What other people?

DR. TEMPLE: The other grades.

DR. GILMAN: Other grades?

DR. TEMPLE: Yes. It makes a big difference in the likelihood of success if the hypothesis is correct.

DR. GILMAN: Let me understand you. You are saying study all grades of men and women?

DR. TEMPLE: Well, not really different from what was done with study 63. That happened to be just women.

DR. GILMAN: It was just women.

DR. TEMPLE: The hypothesis testing component would then be grade IV/V or whatever scale one decides to use, and the exploratory component would be the other grades where the data in support of benefit is much weaker.

DR. GILMAN: Well, I would have no problem -- in fact, yes, I would suggest a study in which you look at men and women, all grades. Your hypothesis can be focused on grades IV/V. There is reasonable evidence suggesting that may be correct. But I would look at grades I through III as well to see whether, in fact, it is damaging. I rather doubt that it will prove to be damaging but that remains to be seen. So, yes, you can use the hypothesis that you recommended.

All right, let me go back around the table. So, the question then is, first, whether the sponsor submitted substantial evidence of effectiveness. I will just start with Dr. Drachman.

DR. DRACHMAN: No. I do not believe the evidence was sufficient.

DR. GILMAN: Do you want to comment on Dr. Temple's question about what should be done?

DR. DRACHMAN: I would agree with that, that it should be a broader trial but, as you say, with men and women at all grades, and with the primary hypothesis that IV and V would benefit the most.

DR. GILMAN: What would you say about the use of nimodipine?

DR. DRACHMAN: That would be very difficult not to use. I believe that that should be used but, again, the review of the literature would be of value.

DR. GILMAN: Dr. Kawas?

DR. KAWAS: I am not going to add very much. I would be satisfied to see replication of almost any of the findings, and the design suggestions I think are dependent on what somebody wants to prove. If the indication that people are interested in is for grade IV and V and they just brought in IVs and Vs and did the study and had a positive effect, then that is fine with me.

But I think the thing that is bothering everybody in this group is that when we get conflicting results from the different studies we all have the sense that there is something going on here, that there is some benefit here and we don't want grades I, II and III to be left out. We don't want women to be left out. We don't want whatever, and I think that is why everyone is pushing for more inclusive studies which are really sort of a way of looking at all of the questions once again.

DR. GILMAN: So, your response to whether the sponsor submitted substantial evidence of effectiveness is no?

DR. KAWAS: Right, correct.

DR. GILMAN: Thank you. Dr. Penn?

DR. PENN: The response is no, and I am afraid it is a very difficult decision as to what to do next in terms of study design, and if the company wants to go ahead with anything more is going to have to make a guess. We are not dealing with a major effect because we have such a messy field in terms of trying to change the outcome with just one measure or drug interposed. I think unless they guess right they are probably not going to have a significant finding unless they have a huge number of patients that probably is not practical to run.

So, I think it is a major dilemma as to how to design the next stage because if you take three hypotheses up front and test them, you are going to need many more patients than we have seen before to get significance. If you choose one, you may once again choose the wrong one.

DR. GILMAN: Your comment on nimodipine? I think I know what you are going to say but would you tell us?

DR. PENN: Oh, I hope the FDA straightens out nimodipine. As a neurosurgeon, it would make me feel a little bit better using it if it were on the label, but not too much.

[Laughter]

But it would certainly make other studies easier.

DR. GILMAN: That is an honest answer. Dr. Kawas, we didn't explore your thought about nimodipine.

DR. KAWAS: I think from an ethical perspective, nimodipine has to be used in the studies.

DR. GILMAN: At all grades?

DR. KAWAS: Yes.

DR. GILMAN: Dr. Lacey?

DR. LACEY: My response is no. I feel there needs to be replication of the studies on men, and there needs to be replication regarding findings on women. So it has to include both women and men. What I have seen so far suggests that the neurogrades IV and V are more promising but I am certainly open to it being all grades.

On the issue of women, of course as I have expressed, I don't know that there is any support for it but I do feel that treatment should be examined by stage of ovulation of women.

DR. GILMAN: You mean whether ovulating or not?

DR. LACEY: Yes.

DR. GILMAN: Thank you. Dr. Lacey, do you want to comment on the nimodipine issue?

DR. LACEY: I already commented about the FDA looking at what is in the literature and everything. So, I would echo what I said already about that.

DR. GILMAN: Thank you. Dr. Van Belle?

DR. VAN BELLE: No, and I think the important thing would be to come to some agreement between the FDA and the sponsor, if a future study were to be done, about what the appropriate outcome is. In these reports you always get a bit of a feeling that one group says one thing and the other group says another thing, and if there were some agreement a priori as to what the game plan is and what the ground rules are it might save us some time as well. With respect to nimodipine, I have no opinion.

DR. GILMAN: Dr. Grotta?

DR. GROTTA: As the data were presented and as I have seen them, no, I am not persuaded, but I am semi-persuaded that there may be in effect in all subarachnoid hemorrhage subgroups if they were properly dosed. So, I too would like to see another trial done in both men dosed at 6 mg and women dosed at 15 mg, patients treated within 24 hours compared to standard care. I would stratify patients between those that are a Glasgow Coma Scale of 9 or higher versus those less than 9, or using some other easily applied measure, so that if you saw an effect in the severely affected patients you could recognize it with certainty.

But if the company decided to do just a study in poor grade women and came up with a very positive study, then I probably would be persuaded that that would be

enough.

DR. GILMAN: Thank you. Dr. Brooke had to leave, as you know, but he has left a statement so I will simply read it into the record: For question one, has the sponsor demonstrated effectiveness? No. The sponsor has claimed an effect of the drug on mortality. I have two serious misgivings. One, the methodology of the trial and its interpretation is marred by changing primary endpoints and retrospective analyses. Although the results are intriguing, they do not convince me that this drug should be approved.

Two, prolonging life without improving function in the severely disabled may not be a useful or humanistic act. Then he quotes, no, thou shalt not kill but neither shall thou strive officiously to keep alive. I am sure he would have read it better than me. Prolongation of life is better justified when quality of life is improved. The sponsor has not demonstrated any effect on function and has selected a target group which is very severely disabled.

So, I don't think we need a vote but there are eight of us and all have voted no to question number one. Question number two --

DR. KATZ: Question number two presupposes really in a sense that question number one would have been voted yes. In other words, you can discuss whether or not you think there is some overwhelming safety concern that we need

to pay attention to, but if you have found that there is no substantial evidence of effectiveness safety is sort of a moot point, at least from a decision-making point of view.

DR. KAWAS: I would just say I at least personally have no overwhelming safety concerns either.

DR. GILMAN: Do you want us to go around the table and get a sense of whether there are concerns from the group? Let me lead off and say that there has been some concern about the quality of data presented to the agency with respect to safety. We heard from Dr. Racoosin that it was rather difficult to read the records and understand exactly what had happened to these patients, and I think the quality of the data reported back is an issue, and another study, hopefully, would have a better mechanism of reporting those data or perhaps more full and complete records and final diagnoses and autopsy verification when there were autopsy studies done.

I think the question has been raised as to whether there is a significant safety issue here, and I think the question is open, myself. I am on the fence about that. Dr. Drachman?

DR. DRACHMAN: I am not clear on it. No major safety issue but data are not really sufficient.

DR. GILMAN: Dr. Kawas has commented. Dr. Penn?

DR. PENN: I don't have anything different to say.

DR. GILMAN: Dr. Lacey?

DR. LACEY: Nothing different than what has been said.

DR. GILMAN: Dr. Van Belle?

DR. VAN BELLE: The same thing.

DR. GILMAN: Dr. Grotta?

DR. GROTTA: Nothing to add.

DR. GILMAN: All right, is there anything further that the agency would want from us? If not, let me thank the committee. Thank you all. We are adjourned.

DR. KATZ: I want to thank the committee also. It was a lot of work; two long days. I appreciate it very much. I would also like to thank Dr. Titus and her staff for arranging this and making this run smoothly.

[Whereupon, at 4:00 p.m., the Committee was adjourned]

- - -

CERTIFICATE

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.

Alice Toigo

ALICE TOIGO

Lawyer's Notes

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z

Lawyer's Notes