such as Aggrenox, is vital to our efforts in reducing stroke occurrence in patients at greatest risk, including those who have suffered a stroke or TIA.

As you know, Aggrenox combines two extensively studied antiplatelet agents. Clinical studies of the combination have demonstrated its efficacy for the secondary prevention of stroke, with no additional risk of adverse events.

Such combination therapy may also enhance patient compliance by reducing the number of pills that a patient has to take in a given day. Making this medical available to patients at risk for secondary stroke will add a valuable new option to our stroke prevention armamentarium and thereby decrease the number of Americans who suffer the consequences of a stroke. The ultimate result will be that fewer families will suffer the emotional as well as financial hardships that are commonly associated with stroke.

I urge you to recommend too the FDA that this new treatment be made available to patients and their physicians as rapidly as possible.

Thank you very much for your attention and for the opportunity to speak to you this afternoon.

DR. GILMAN: Thank you, Dr. Alberts.

Does anybody else in the room from the public who

wishes to make a presentation?

[No response.]

DR. GILMAN: Thank you. If not, we will go back into our regular mode and we will hear from the Food and Drug Administration now.

Dr. Robie-Suh.

FDA Presentations

Overview of NDA

DR. ROBIE-SUH: Good afternoon. I will try to be brief.

[Slide.]

This is the order of FDA presentation this afternoon on Aggrenox. I am Kathy Robie-Suh. I am going to introduce to you issues that the Division has identified as being important and warranting some consideration in the committee's deliberations today.

Dr. Ann Farrell will then present the results of the medical review, and Dr. Rashid will present results of the statistical review of the application.

[Slide.]

These are issues that the Division has identified as being important. First of all, the product Aggrenox is a combination product, and as we have talked about earlier today, that has some specific implications for the evidence for effectiveness.

There is, second, a single study presented for demonstration of effectiveness.

Third, there is the uncertainty somewhat about primary endpoints as specified in the protocol and what is appropriate, and so forth, as we have talked about earlier today.

Finally, there are considerations with regard to the study population.

[Slide.]

Aggrenox is a fixed combination of an extended release dipyridamole 200 mg and aspirin 25 mg to be dosed twice daily, providing a total of 50 mg of aspirin and 400 mg of dipyridamole.

We might ask what do we know about the individual components of this combination product. The professional labeling for aspirin recommends once daily dosing with 50 to 325 mg for the purpose of reducing the combined risk of death and nonfatal stroke in ischemic stroke or TIA patients, and this is the indication being sought for the combination product today.

Dipyridamole is not approved for the desired indication. The extended release formulation is not approved here in the U.S., and the immediate release product that is approved here, is approved only as an adjunct to coumadin therapy to prevent postoperative thromboembolic

complications, cardiac valve replacement.

[Slide.]

In order to demonstrate effectiveness of a combination product, our regulations do allow combination of the product when each component makes a contribution to the claimed effects and the dosage of each component is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.

So, therefore, Aggrenox has to demonstrate superiority of the combination product over each of the individual components.

[Slide.]

For this purpose, we have submitted a single efficacy study. Normally, in our approval process, the standard of evidence that is required is substantial evidence, and usually, this comes from substantial evidence that should come from adequate and well-controlled investigations (plural), and the reason for the investigations has been the need for independent substantiation of the efficacy result, but sometimes we can find independent substantiation in a single study.

In May of 1998, a Guidance to Industry was published describing what is needed for demonstration of effectiveness, a demonstration of efficacy of drugs and

biological products.

With regard to single studies, these are some of the criteria that were laid out as being highly desirable in a study presented for such purpose. You probably recognize this slide from a prettier picture earlier this morning, so it is nice to know our guidances are getting out there.

I am going to say just a word about each one of these, but before I do that, all of this presupposes that that single study certainly is adequate and well controlled in the usual sense that we look for a clinical trial.

That means that it has to be well designed, adequate measures need to have been taken to minimize bias. This includes minimizing baseline imbalances, being balanced with regard to risk factors, taking care to protect the blind, also with regard to having a predefined hypothesis that is being tested, and so forth.

So, all that being said, then, with the single study, look at these factors. Large multicenter study. Here, for each one of these factors, considering ESPS-2 for this purpose.

[Slide.]

In this study, there were over 7,000 patients randomized. One site was excluded because the data were felt to be unreliable, but you still have over 6,000 patients.

[Slide.]

Is there consistency across study subsets? The effectiveness results were examined across centers, across gender, entry event, and a number of types of analyses. Dr. Farrell will show you some more of these results.

[Slide.]

Other multiple studies? Sometimes one study can be viewed as having two or more studies embedded within, and I know the example in the guidance talks about a factorial analysis, but I think for this combination product, we have talked about why pairwise is more appropriate for looking at effectiveness here, but certainly having the placebo group there and both of the component arms being shown superior to the placebo for an endpoint strengthens the trials.

You can also subdivide the trial and look for effectiveness in subdivisions, for instance, by geographic areas I think was one thing that was done for this trial.

[Slide.]

Are there multiple endpoints examined in this study, and endpoints that are independent, but still related to the indication we are interested in, and, yes, ESPS-2 had a number of endpoints. Again, Dr. Farrell is going to present a little bit more about some of these results.

[Slide.]

Finally, is the study statistically persuasive?

Again, a number of analyses were done, and looking at the efficacy analysis versus the components, I think we came up with p-values of 0.002 for Aggrenox versus dipyridamole, and 0.008 for Aggrenox versus aspirin for the reduction of risk of stroke.

[Slide.]

Now, when you have a single study, you can either have a single study all by itself or usually there is some confirmatory evidence, as well, and two additional studies were submitted as additional information on this product.

ESPS-1 was a study which tested combination of immediate release dipyridamole 75 mg plus aspirin 330 mg, given three times a day, versus placebo for 24 months. There were some problems with the study, the protocol was not uniform, for instance.

Also, Study U88-0473 tested that same combination versus dicumarol. That was a small study with few events.

[Slide.]

With regard to primary endpoints, I don't think I need to say a whole lot. The identification of primary endpoint, of course, has some impact on the statistical analyses, possible interpretations of what I saw in the protocol could have been either death alone or stroke alone, win with a benefit on both death and stroke when you analyze them individually, or win with benefit on the composite

endpoint.

[Slide.]

Finally, with regard to the study population, ESPS-2 was a European study. There may be differences in th U.S. and European diagnosis of stroke and the practice of medicine. Also, we have to consider the target population for whom Aggrenox would be indicated, you know, considering, for instance, that the daily dose is 50 of aspiring, would be 50 mg, whereas, in the aspirin monograph a dose of 75 mg is the lowest dose labeled for the cardiac indications basically, so these are things that I would like for you to consider and discuss.

[Slide.]

Again, this is just those issues again.

That concludes this part of the presentation. Any questions?

DR. GILMAN: Any questions from the panel?

[No response.]

DR. ROBIE-SUH: Then, Dr. Farrell will present the clinical efficacy data.

Efficacy Issues

DR. FARRELL: Thank you very much.

ESPS-2 was a single trial involving 7,040 patients in 60 centers in 13 countries. One trial was excluded from the efficacy analysis, leaving 6,602 patients in the

modified ITT population.

The trial was reasonable well balanced with respect to sex, age, qualifying event, risk factors for stroke and center among treatment groups.

[Slide.]

This is the table of carotid endarterectomies that occurred prior to or during the trial. As you can see, there are a few more patients in the dipyridamole and aspirin group who underwent carotid endarterectomies and remained in the trial although this is a very small number and constitutes less than 1 percent of each treatment group.

[Slide.]

As the sponsor has already shown you, the benefit of the combination product on stroke. What I wanted to show you was the subset analysis for nonfatal first stroke showing that the combination product gives you a statistically significant benefit over its components. This was not true for fatal first stroke. In fact, all of the categories were not significant.

[Slide.]

This is looking at stroke with respect to qualifying event, and you can see the numbers across. For patients who entered the trial with a qualifying event of TIA, who experienced a stroke, there was not a significant difference between the combined product and aspirin.

Patients who entered the trial with a qualifying event of stroke did much better, did not reach statistical significance, but the trial was not sized to look at these separate endpoints, and it was sized for the European definition of stroke.

[Slide.]

This is basically going over the primary efficacy endpoint of death and just looking at the numbers, and there is no significant benefit here.

[Slide.]

This is a slide that I showed you earlier, looking at the cause of death as classified by the Morbidity and Mortality Assessment Group, and there was no real change for the combined product nor for the components over any of the categories of death.

[Slide.]

Looking at the efficacy endpoint of stroke and death, the combination product does not show a statistically significant benefit for the composite endpoint.

[Slide.]

This is a further analysis of the subcategory contributions to stroke and death, and it is only the subcategory of nonfatal first stroke and never died where there is a significant contribution.

There is virtually no change for fatal first

stroke, nonfatal first stroke and later died due to stroke, nonfatal first stroke and later died to other causes or death due to other causes.

[Slide.]

The sponsor did a very interesting analysis looking at the first stroke handicap categories. What your first stroke is, is the stroke you have on trial and during treatment. This is how they classified minor stroke, major stroke, and fatal stroke.

[Slide.]

Looking at the first-stroke handicap categories, the combination product appears to show some benefit in terms of having an increased number of patients experiencing a minor stroke and a decreased percentage of patients experiencing a major stroke. There appears to be no effect on fatal stroke.

[Slide.]

Here is the pairwise analysis for first stroke handicap categories based on this classification for minor and major stroke, and as you can see, the combination product produces a statistically significant benefit over dipyridamole for that endpoint.

[Slide.]

Another important category was transient ischemic attack. This is how the number of patients who reported

greater than 1 TIA during follow-up did. As you can see, the lowest percentage of patients is seen in the combined treatment group.

[Slide.]

Here is the pairwise analysis, which shows that the combined product produced a statistically significant benefit over dipyridamole alone. This was not seen with aspirin.

[Slide.]

This is looking at TIA by qualifying event. Certainly, the combined product was associated with the lowest frequency of TIA - 64 for those who entered the trial with a qualifying event of TIA versus 102 for placebo, and those who entered the trial with a qualifying event of stroke, 108 for the combined product versus 165 for placebo.

[Slide.]

This is first ischemic event, and certainly there appears to be a significant benefit to the use of dipyridamole and aspirin for first ischemic event, and those are the numbers - 206 for dipyridamole and aspirin versus 271 for dipyridamole, 266 for aspirin, and 307 for placebo.

[Slide.]

This is the pairwise analysis which shows a benefit for the combination product over its components. One important thing to realize about first ischemic event,

that stroke patients made up 78 percent of the data here.

[Slide.]

In terms of adverse events, there as a high incidence of adverse events for all treatment groups throughout the trial. There was no significant difference between treatment groups for adverse events categories.

Some adverse events did lead to treatment cessation.

[Slide.]

Treatment cessation due to medication side effects. For headache, there was approximately a 9 percent treatment cessation rate compared to 2 for placebo and aspirin. Gastrointestinal contributed 8 percent. That was nausea, vomiting, sometimes diarrhea. Bleeding contributed 1.7.

It is interesting to note in the data that the patients who were on either the combined product or dipyridamole tended to go off study or have to stop their medication earlier than the patients on aspirin and placebo.

[Slide.]

There was no category of serious adverse events that were greater in the dipyridamole and aspirin treatment group than other treatment groups.

That's it. Any questions?

DR. GILMAN: Thank you.

Questions? That was very clear and brief, appreciate that.

If there are no other questions, then, we will move on to Dr. Rashid, mathematical statistician.

Statistical Review of Aggrenox

DR. RASHID: I am going to summarize the statistical review, and since I am the last speaker, I had to cut down some of my transparencies.

[Slide.]

As Dr. Temple mentioned, that for combination drug, we looked for two combinations here, the combination versus the ingredients, in this case, Aggrenox versus DP alone, and DP was dipyridamole, and Aggrenox versus ASA, which is aspirin alone, and both test required statistical significance in favor of the combination drug.

[Slide.]

Now, this is for the stroke data. We have seen this several times. First, we look at the column, which is the p-value of Gehan-Wilcoxon test, which compares the survival curves over the two years.

The p-value is 0.002 for Aggrenox versus DP, p-value of 0.008 for Aggrenox versus aspirin, which is significant.

The next column gives information about Kaplan Meier stroke free rate, 89.9 percent for Aggrenox and 86.7

percent for the dipyridamole.

Similarly, for Aggrenox versus aspirin, 89.9 versus 87.1.

The risk reduction, the sponsor has shown it, which is 24.7 percent reduction for the Aggrenox versus DP and 23 percent for the Aggrenox versus aspirin.

Another measure which gives increased is stroke-free rate increase, which is the last column, which is essentially the difference between the stroke-free rate, 89.9 minus 86.7 divided by 86.7. The stroke-free rate increase of Aggrenox relative to dipyridamole, which is 3.7 percent, and the same measure for the other comparisons, for Aggrenox versus aspirin, we have 3.2 percent, and those numbers in the last column look consistent, over 3 percent, but if you look at the risk reduction, the fourth column.

The next one, for the death endpoint, we get the p-value for Aggrenox versus dipyridamole, 0.79, so we don't have any evidence there. If you look at the Kaplan-Meier survival curve here, this is at the end of the two years, which is 88.7 percent versus 88.5 percent, only 0.2 percent increase.

The risk reduction is 1.3 percent, but if you look at Aggrenox versus aspirin, we see the p-value of 0.74, so we have no evidence there, and if you look at the third column, which gives Kaplan-Meier survival rate, for Aggrenox

it is 88.7 and for the aspirin it was 88.9, and the risk reduction is minus 2.7 percent.

I would say the Aggrenox group has 2.7 percent death rate than aspirin group. Survival increase we see the same thing, 0.2 percent increase and minus 0.2 point decrease. So, that is important to look at, the second row.

[Slide.]

Now, stroke or death, we had a lot of discussion about this, but I thought I should give a transparency on this. Let's look the p-value for Aggrenox versus dipyridamole, which is 0.079. I should say that is weak evidence. If you look at the Kaplan-Meier stroke and death free rate, which is 82.4 percent versus 80.3 percent, so if you go back to stroke, this is much less.

Now, risk reduction is 10 percent, for the stroke case we have seen it about 24 percent, and the survival rate increase in this case, 2.6 percent for again Aggrenox versus aspirin, which is second column, we have 0.084 p-value for Gehan-Wilcoxon test. Again, we have weak evidence here.

If you look at the stroke or death free rate, we get 82.4 versus 79.9, the risk reduction 12 percent, and survival rate increase is 3.1 percent.

[Slide.]

So, in the protocol like we had two endpoints, stroke and death, and in the clinical summary report it said

the other endpoint is death or stroke, so we need adjustment. If you consider two primary endpoints, we need to adjust for the error rate, so I adjusted for the two endpoints for stroke or death, and I found that for unadjusted, Wilcoxon is 0.079, which you have seen before, and if you adjust it for the multiplicity, we get 0.1579, which is double the 0.079. So, we have weaker evidence now if you adjust for multiplicity.

The same for DP/ASA vs aspirin group, we have 0.084 for the Wilcoxon, and if you adjust for multiplicity we have 0.167, again we have weak and weaker evidence.

[Slide.]

Now, Dr. Robie-Suh discussed about the single study like you need some consistent result and substantial evidence, so I looked for composite endpoint, then region. So, there are four regions in this study - Scandinavia, Northern Europe, Southern Europe, and United Kingdom, can I compared four pairs here.

The first column gives you Aggrenox versus dipyridamole, and we see that only in Southern Europe Aggrenox beats dipyridamole. Also, if you look at the second column we see that Aggrenox versus ASA, only Southern Europe Aggrenox beat aspirin.

But if you look at the other components here, like 0.51 for DP versus placebo for Southern Europe, so DP is not

effective there, so that drives the significance here.

The same thing if you look at aspirin versus placebo for Southern Europe, we have 0.27, and again if you look at Aggrenox versus ASA we have 0.05.

DR. KONSTAM: Can I stop you for a second?

DR. RASHID: Yes.

DR. KONSTAM: I mean so in these subsets, I mean I wouldn't expect any of these p-values necessarily to reach significance, but is there any inconsistency across these different regions?

DR. RASHID: I don't think so.

DR. KONSTAM: I mean that would be the question I would think would be asked.

DR. RASHID: I agree with you.

DR. KONSTAM: More subgroups, you are not going to see a positive p-value.

DR. RASHID: I am going to say that, for a single study look at the internal consistency. For example, suppose you had some centers in the United States, then, how would have been the results.

DR. TEMPLE: Did you do the same thing for stroke? Are we about to see that?

DR. RASHID: I think we have similar answer. I have that in the review, but not--

DR. TEMPLE: Okay, because I mean this wasn't

strongly positive overall. It has no chance of being positive by region, but stroke was positive overall, so that might be a more profitable place to look for consistency.

DR. GILMAN: It is in his review.

DR. RASHID: Now, the summary of issues. Primary endpoints are not well defined in advance, as you know by now.

Adjustments to p-values needed for multiple endpoints.

Two, sample size is increased at the interim analysis, so adjustment to p-value is needed for the increase in sample size.

The internal consistency not well supported.

DR. DRACHMAN: What was the third point there? What do you mean by number 3?

DR. RASHID: What I am saying like we have defined regions here, but we don't have the identical results here.

DR. PENN: If I understood you, didn't you just say that the regional comparisons didn't reach any--we wouldn't expect them to reach any statistical significance?

DR. RASHID: You can reject the null hypothesis, but if you look at the components, you still have--you can accept the null hypothesis, interaction there, but still you go by components, you can get significance.

DR. PENN: Can you tell us one clean example of

internal inconsistency in the study that makes you worry about the quality of the study?

DR. RASHID: For example, Southern Europe, like patients here had less hypertension, and patients were younger, that may be the reason it was doing bad here.

[Slide.]

So, the study has shown that the combination drug product is effective only in stroke. It is not clear that there is any added or any benefit for fatal stroke. Dr. Farrell mentioned that.

Significant efficacy results are not demonstrated for either mortality or the composite endpoint.

DR. GILMAN: Thank you. Further questions from the panel?

DR. CALIFF: Two things. One is you said at the beginning there was a site excluded and it was written up in the booklet. I just wanted to know how you arrived at the decision to exclude the data as opposed to including it.

DR. RASHID: The company will answer better.

DR. CALIFF: So, the company makes that decision?

DR. RASHID: Yes, yes.

DR. PENN: They listed all those reasons why they didn't include it. I mean it sounded awful.

DR. TEMPLE: It was sort of obviously made up.

DR. CALIFF: So, it was made-up data.

DR. TEMPLE: It sure looked that way.

DR. GILMAN: Other questions or comments from the panel?

DR. KONSTAM: You know, I mean you showed different things, and I guess the way I interpret these remarks is that there are different ways within a single trial of potentially making the argument that it is equivalent or may be good enough that you don't have two trials.

So, you showed some ways in which you can't necessarily support it, but I guess, to me, the way that I will wind up trying to rationalize it to approve it if we do, is, first of all, it makes it or breaks it on the stroke endpoint. That is the one that is really positive.

So, the question to me is going to be is that endpoint very statistically convincing, and I guess I didn't really get an analysis of that from what you showed, I mean with regard to the p-values for stroke.

I noticed also the other thing I would thing I would say you avoided the factorial design--

DR. RASHID: Yes.

DR. KONSTAM: --analysis, and I am not sure whether that is--I mean I actually got attracted to the factorial design during the course of the day. So, I guess I would ask are we going to be left at the end of the day

with a strong p-value for dipyridamole, that it is effective. We believe aspirin is effective.

DR. GILMAN: You mean Aggrenox or do you mean dipyridamole?

DR. KONSTAM: Well, I guess, number one, is that we say that in order to have a combination product, the standard is each one is effective, so I guess the first question I have been asking myself is, is dipyridamole effective, and then, secondly, is dipyridamole plus aspirin better than aspirin alone.

I guess the question I have is I see very low p-values for those analyses, and I guess the only question I have is should I be increasing those p-values based on any of the corrections that you think we should do, like the fact that stroke wasn't the only endpoint that was measured, the fact that there were a questionable number of interim analyses.

I am struck with these very low p-values for what I am looking at.

DR. RASHID: The first thing like we are here for the combination drug, not for the components. Okay. We are looking at the effect of the combination drug. Even we don't need placebo in the arm for the combination drug, and the literature said that.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: There is no question that is true. The crucial analysis for a combination is the two-drug versus each of the one-drug treatments. There is no doubt about that.

But with respect to the question of what makes one study believable, we gave as a specific example--I am not breaking any new ground here--in our document that was referred to earlier, the evidence document, a case where you might choose to believe that a drug was effective from a single study, if it showed an effect, you might be more likely to accept a single study if it showed both an effect when you added it to something and when it showed an effect when it was used alone, not that the used alone is relevant to the combination, but it might add to the believability of the study.

So, that is a slightly subtle distinction that maybe we made more of than we should have, but I think that is the sense. It doesn't contribute to the--I mean aspirin is effective, but the question here is, is it effective when you add it to dipyridamole. That is the crucial question. We already know it is effective, but it might not add anything when you add it to dipyridamole. So, that is a legitimate question.

The other thing, I am looking at the analysis of the factor analysis by region, looking only at stroke, and

they are actually nominally significant values in the various regions, which considering that it's only half of a study, is not so shabby--I am sorry--I mean with the regions only each representing about a quarter of the study.

So, for stroke, which is obviously the more powerful endpoint, there was a certain consistency across regions, right, that is what you said?

DR. RASHID: Yes.

DR. GILMAN: Dr. Robie-Suh.

DR. ROBIE-SUH: I also wanted to say also for stroke, that also with region, there was some variability in the risk factors that may have contributed toward the little imbalances that were seen in some geographic areas.

DR. GILMAN: Dr. Grotta.

DR. GROTTA: But wouldn't the Cox analysis have taken into consideration the baseline imbalances that existed in the population or among the different groups, and that apparently was done, and still the differences were there in the treatment groups.

I don't know. I guess we heard this morning a very detailed analysis of the protocol, but I guess what I would sort of like to get is, is there something that we haven't already discussed that you have discovered in the data and in the analysis that you need to bring to our attention that would diminish the impact of these results,

because I haven't heard anything.

DR. RASHID: The first thing, that the sample size was based on the composite endpoint, and the sample size was not based on the death or stroke. So, there is one problem there.

DR. GILMAN: Dr. Kawas.

DR. KAWAS: I just want clarification. When you say the sample size was based on the composite endpoint, at what point in the study?

DR. RASHID: In the protocol, it said there are two primary endpoints, stroke and death, but the in the clinical trial report, they said the sample size was based on the composite endpoint, death or statistical stroke.

DR. KAWAS: So, was that at the interim time when they increased the sample size, that they said they were increasing it based on the composite endpoint?

DR. RASHID: I think at both times they estimated the sample size based on the composite.

DR. KAWAS: Both times.

DR. RASHID: Both times.

DR. KAWAS: So, even at the initiation of the study, they were generating their sample size based on the composite endpoint even though they didn't specify that initially.

DR. RASHID: Yes.

DR. KAWAS: Well, that sort of implies that maybe that was their endpoint at the beginning, which I didn't realize.

DR. RASHID: I talked to the sponsor on telecon. They said the statisticians identified the composite endpoint at the primary, but the clinicians identified death and stroke as two primary endpoints, so there is kind of a problem there.

DR. KAWAS: At the beginning.

DR. RASHID: Yes.

DR. GILMAN: At the beginning, as I understand it, there were two primary endpoints, stroke, death, not a composite endpoint.

DR. KAWAS: But what he just told us, I believe, Dr. Gilman, is that when they did the sample size calculation at exactly that point, somebody was calculating it based on a composite endpoint actually.

DR. GILMAN: Exactly right. They then changed and had three primary endpoints, as I understand the situation.

DR. RASHID: Yes.

DR. GROTTA: And why is that a problem? Enlighten me, because I don't know these things, but tell me why is it important if they then changed and based their samples size on the composite endpoint.

DR. RASHID: Like if they used only death, they

had one sample size, right? If they used only stroke, another sample size, and composite, another sample size. So, it appears to me if they just used death, then, sample size would have been higher than 5,000. That was a problem.

DR. TEMPLE: It would have been 50,000.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: It is perfectly possible for there to be more than one primary endpoint, but the sample size will be based on the one that you think you need the larger sample for.

So, if you had any hope of winning on the death plus stroke endpoint, and you thought the effect wasn't going to be as large, you would make the sample size larger and then you would be way overpowered for the stroke endpoint, and you would feel good about that.

So, we see lots of studies designed that way. It doesn't really prove anything. But what seems to be is that there was not crystal-clear agreement on what the primary endpoint was, so there might be as many as three, they are not mutually independent, so there is going to be some correction, and you sort of have to struggle to figure out what that correction should be.

But as people have pointed out, you multiply these things by 3, and you are still there for the stroke, only for the stroke.

DR. GILMAN: Dr. Katz.

DR. KATZ: Dr. Grotta asked if there was anything that might make you question the p-values for the stroke endpoint that you haven't heard, and there has been an issue that the statisticians have alerted me to, and I think we have sort of been very tangentially discussing it, but not explicitly, and it is probably worth just, at the risk of entering even more arcane territory, it is probably worth just airing it and sort of dealing with it, and I will ask Dr. O'Neill from our statistical group to talk about it in detail, but it has to do with the fact that the choice of stroke as an endpoint in a trial like this may be problematic because mortality is related to stroke, or at least they might be correlated at least theoretically, and that just looking at stroke without taking mortality into account might possibly give you a biased estimate of the treatment effect.

Therefore, under that theory, you would have to look first at the combined endpoint, and if it doesn't reach the usual standard for statistical significance on that endpoint, then, it may not really make any sense to go back and look at stroke independently, so that the p-values, even though they appear to be quite small for stroke, might be difficult to interpret anyway.

He is here. He can elaborate.

DR. O'NEILL: I am Bob O'Neill. I am in the Office of Biostatistics.

The discussion I had with Dr. Katz goes along the following lines, and this is in the spirit is there anything else that is sort of percolating around that you want to sort of think about.

The issue of how many primary endpoints you choose is important because you look at that in terms of at the end of the day, how many different ways do you agree clinically that you can win, and if you can win in more than one way, endpoint A or endpoint B or endpoint C, if any of those are positive, and you can win any one of those ways, then, some adjustment is needed.

So, the issue of whether one chose just death and stroke as the two endpoints, or whether one chose three endpoints, which was the union of both of those, essentially A or B, or both, is germane.

It is probably not crucial to the focused interpretation of stroke alone, but this isn't the only area, this medical area, that struggles with do you include mortality in a composite endpoint, and the reason you do that is because although you would like to clinically measure the incidence of stroke, you might not be able to do it because you have other things that get in the way, and mortality gets in the way, and the statistical analysis

essentially has to estimate the incidence of stroke by making an assumption that if these folks had not--because it is a denominator issue, who is in the denominator--so, you have to make an assumption about had these people had not died, would they have gone on to have the same stroke occurrence as those who didn't die, so it is a competing risk issue.

So, what often happens in these trials is that folks union the composite endpoint, just as Bob Califf was talking about sort of earlier saying there was a fair amount of sudden deaths that were in this trial, how do we explain them, and there was a certain amount of probing of whether those events, those mortality events were really more related to stroke than not.

But the issue is to get out of that trying to find out what the true state of nature is, one unions the events, you say, stroke and/or mortality. So, if you look at that as the primary endpoint, and then you go and look at the subcomponents of that primary endpoint, you get a different picture of this.

You essentially say that on the main comparison of the combo versus the single ingredients, on classical basic comparisons, there was not a significant difference, therefore, one can say there is really no reason to go into the components, and one of the reasons not to go into the

component is that you really don't know if you have the right estimate of what the stroke incidence is, because in order to estimate it, you had to use statistical procedures that censored out mortality, and the censoring is informative, because mortality is related to stroke.

It is sort of a roundabout way, and this is not the only time this has been thought about. This has been thought about in terms of defining endpoints in AIDS, progression to AIDS or mortality, or it has been thought about in other endpoints where you have mortality that gets in the way, and it is very related to the clinical endpoint.

Now, this may not be crucial to your overall thoughts, but in the spirit of what else is floating around, one could conceivably say that had you designed this study in the beginning, a priori, with the primary comparison being the union, meaning A or B, and then depending upon what you find there, you go further, you would have a different decision than you are now dealing with, essentially is I am looking at these two endpoints and possibly three endpoints on equal footing, which is not necessarily the way you might want to look at it had you planned it a little differently.

The other thing that I find somewhat retrospectively interesting--and it is always easy to do this--is to say, look, if this trial was sized with the

union endpoint, as I understand it, not with that or stroke, but it was sized originally, 5,000 on the union argument, and it was sized to essentially detect with high power the difference between the combo and the placebo, not to size it to look at the difference between the combo and A, and the combo and B, but that is what we are dealing with right now.

That is the comparison we are dealing with. So, this trial was resized halfway through on the basis of several things. Taking a look at what the relative difference was, let's say, halfway through the trial, and upsizing the trial, not just to maintain the original power, but to maintain power against a reduced effect size, which originally was thought to be 33 percent, and is now somewhere on the order of 20 percent.

Anyway, these are just some other considerations around the interpretation.

DR. GILMAN: Thank you.

Dr. Konstam.

DR. KONSTAM: I actually am thinking about it a little bit differently. You know, I mean I understand, I mean your point is very clear, and it is that if somebody dies, they can't get a stroke, and Rob made that point earlier, so that is the issue.

So, if you are going forward and starting a trial new, I think this is analogous in heart failure, for

example, using a combined endpoint of hospitalization plus death, not hospitalization alone, so it is the same issue.

But I guess to me the real question is are you going to have this screwy positive endpoint because the drug is associated with some excess mortality, and therefore preventing the patients from developing stroke.

I guess that if you start out, as they did, saying that--there are multiple issues, but let's just assume for the sake of argument there was one question, that is, the stroke question, we think that this thing is going to win on stroke, that is going to be our endpoint, and they went with that, and now here we are at the end of the day and saying, well, wait a minute, we have this problem.

Now, we go back and look at the combined endpoint, the p-value goes up, but there certainly is no hint that the drug is associated with excess mortality. So, in the absence of any hint that the drug is associated with excess mortality, I guess I don't concern myself too much that you wind up with a higher p-value when you look at the combination given the fact that I take stroke as the predefined primary endpoint.

So, I am not sure, I mean I have to defer to you, but I am not sure that you have to revert to go to the combination endpoint that wasn't predefined in the absence of an excess mortality effect of the drug.

DR. O'NEILL: I hear you, and intuitively I don't feel very much different than you do. I don't know whether this is a big issue or not. I am just saying that the reason it has been dealt with this way in all the other disease areas, just as you have just indicated, is because there is some concern about whether you are able to accurately estimate what you think you are estimating, which is the stroke incidence.

What makes it worth thinking about here is, as Bob pointed out, a third of all the endpoints are deaths that are unexplained due to stroke. There is something else other than stroke. If you look at the collection of total endpoints, a third of the whole show is being contributed by something that is not being classified as stroke related.

DR. KONSTAM: Just this specific question. Is it possible that you are spuriously making the stroke endpoint more significant here through this mortality interaction in the absence of the drug being associated with an excess mortality?

DR. O'NEILL: That is a very good question, and I don't know. I am just speculating, I don't know. It would probably need a further look and at the end of the day may be able to say this is not the explanation for what is going on, so don't get too excited about it.

I am just pointing it out that there is a reason

why other areas deal with the composite endpoint because this is a tough one to disentangle, and there has been research on trying to decouple the contribution of individual components in a composite endpoint, and the problem with it is, it is not all that simple because some of those components censor you for being able to observe the other ones.

The point you are making is does it overly censor you in a way that is contributing all what you are seeing, and I don't know the answer to that.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: Let me throw something else into that mix. I would be interested in what Bob thinks about it.

There is another set of analyses here other than the pairwise one, which in some sense goes to the larger question of whether there is some funny interaction between death and stroke, and that is the factorial analysis.

The factorial analyses, of course, have twice as many people in them, don't suffer from the lesion you described before. They, in fact, are significant even for the combined endpoint. I wonder if you think that is a partial mitigation, irrelevant, or what.

DR. O'NEILL: I think I got the whole question. I think there is two things here. It is where the traditional factorial analysis weighs in, and certainly there is some

convinceness there. It is sort of the effect of each of the individual ingredients which is drawing strength from two out of the four treatment groups, and that is relatively strong, and there is no evidence for interactivity, negative, synergistic or antagonistic, so there is pretty good evidence for additivity here.

So, what Bob is saying that that counts for something. But as I recall, the results don't change a whole lot for stroke whether you look at it that way or whether you look at it on the AB versus A, so something else is going on, on the mortality side of this that I don't fully understand, because I think if I understand the p-values that were presented, there were strong p .001 or whatever, regardless of whether you did the factorial comparison or whether you did the pairwise AB versus A, AB versus B.

DR. TEMPLE: They are stronger for the factorial. They are just all pretty strong.

DR. O'NEILL: Right, but that still doesn't get at the point I am making with regard to the contribution of the mortality, which I don't know. Maybe Charley has got a view on this.

DR. HENNEKENS: I want to agree in concept with the points you are making, but it is also true in going into the design of cardiovascular treatment trials, one is

expecting a priori 20 to 30 percent plausible benefits on a nonfatal endpoint and 10 to 20 percent on death with the knowledge that the death one usually comes later than the nonfatal endpoint.

So, if I were designing ESPS-2, and I were interested in finding an effect on stroke, I would study about 5- or 6,000 patients. If I were interested in finding an effect on stroke plus death, I would study 15- to 20,000 patients, and if I really wanted to answer the death question, I would study 40- to 50,000 patients.

So, I think that the idea of increasing the sample size, implying that somehow that is moving the endpoint to making it more plausible that the death is assuming increasing importance, no, I think that what it is saying, and what I viewed that statistician on that ethics committee, who reported to the ethics committee, who looked at that combined endpoint, was basically saying, well, gee, you are going to have a much better chance to detect a 25 percent effect than a 33 percent effect, but I think that is fair to assume that the effect on fatal events is smaller and delayed, and if, in fact, fatal events were really the primary moving force in the design of this study, we would have to see 15- to 20,000 patients to really answer the question of superiority of Aggrenox over aspirin or dipyridamole alone on that combined endpoint.

DR. O'NEILL: I hear you. The only issue here is whether you are able to unbiasly estimate what you want to, and everybody wants to estimate, and that is stroke. So, another caveat to what you said is you would design the trial where you would hope that no one would die before they either had a fatal or nonfatal stroke, or had the opportunity to experience that, and that is the issue here.

The issue is you can't guarantee that. Other stuff gets in the way. In order then to estimate the stroke incidence, you have to make some assumptions about the other competing events that occur, and that is the crucial issue.

DR. HENNEKENS: Well, I agree with that and I think one way of doing that is to do this composite which has been done in other trials and other forms of vascular disease, and then one sees that the magnitude is smaller, as expected, the direction is in the direction of benefits as were the nonfatal, and it is not unexpected that they didn't achieve the same level of statistical significance.

So, I guess my own view is that I am comfortable with the fact that there is clear superiority on stroke, for what that is worth, and trends in the same direction on the combined endpoint, but though not achieving that level of significance because I know in advance that they wouldn't because I was adding a smaller effect size which I would have expected a priori in there.

DR. KONSTAM: But that is not necessarily true, Charley. I mean I think that, at least the trials that I have had experience with, in the majority of cases, a composite endpoint has been more convincing.

I mean your point about mortality is very well taken, that you need a lot more for that, but it isn't necessarily true that the composite endpoint would be associated with higher p-values than any of the components.

DR. HENNEKENS: It would depend on the relative numbers of both, but I think that, in general, one gets bigger effect sizes on nonfatal events, smaller effect sizes on fatal events, and the fact that the study had somewhat more depth than other studies like it, would lead to that conclusion.

If it had more nonfatal endpoints, as did the Physicians' Health Study, then, our composite endpoint remained statistically extreme and is driven totally by the MI result. This, I thought was more reassuring than alarming in the sense of showing the same direction and a smaller magnitude, but that is on stroke.

I guess one of the things about the FDA's analyses is that they were all on the combined endpoint, so they looked less consistent than the stroke findings. If one did the same analyses, which are expertly done, on stroke, one would come to the conclusion that they were quite consistent

across a wide range of subgroups.

DR. GILMAN: Dr. Drachman.

DR. DRACHMAN: The number of deaths may be less than the number of strokes, but the number of strokes plus deaths is greater than the number of strokes. Why, then, would you expect the significance to be less good?

I mean you have got a larger n, more event, even though it may not be as powerful.

DR. HENNEKENS: The point I tried to make is that I believe that, in general, in trials of vascular disease that occur over a two- to three-year follow-up time, the most plausible effects on the nonfatal endpoints are usually 20 to 30 percent, but on death, they are more like 10 to 15 percent, so that the overall composite endpoint risk reduction is a weighted average of a larger effect on the nonfatal events and a smaller effect on the fatal events, and whether that composite endpoint is more or less significant than the individual components will depend on the relative contributions of the nonfatal and fatal events in a particular trial.

DR. DRACHMAN: Give us some idea of the order of magnitude.

DR. HENNEKENS: Well, I can tell you in the Physicians' Health Study, as Bob Temple pointed out, it was stopped early because of this extreme benefit on MI, a 44

percent p, less than 1 in 100,000 benefit on MI, but there is only about a 4 to 5 percent reduction in the death rate, in part because the numbers of deaths were so small.

We had prespecified a combined endpoint of nonfatal MI, nonfatal stroke, and deaths, and when one combines that, one gets a statistically still extreme, less than .01 benefit on the combined endpoint, because there were so many more nonfatal MIs than deaths.

If the case had been reversed, there were more deaths than, in fact, it might have been reduced even in theory to nonsignificance in the combined endpoint.

DR. CALIFF: As we are finishing up the FDA analysis, I would just like a little guidance perhaps from the FDA about what--I mean I think the exercise we are going through here now is to start out with a fairly dramatic result on the endpoint of stroke, and then we sort of ate away at it with all these things that are not quite right, you know, three endpoints, competing risk, a site thrown out, all these are relatively small individually.

Are we using a single trial, looking for sort of an estimated p-value of less than .05 or less that 0.00125 or how are we viewing this in terms of after we add all these things up in our mind about our degree of uncertainty?

DR. GILMAN: I think that is why we are here. Our purpose if to take all of this into account, discuss the

individual points, and answer the questions that are before us.

DR. CALIFF: So, if we wanted to say 0.25 or 0.3 is okay with us, that would--

DR. GILMAN: No, I think we have to look at the data, discuss the data, speak about the caveats, and then answer the questions that are posed for us.

DR. CALIFF: Is it okay for me to ask at least for a point of view from the FDA about level of statistical certainty in a single trial as compared with two?

DR. GILMAN: Sure.

DR. CALIFF: The reason I asked that again is that if you assume you need two trial, it is 0.05-squared would be the approximate level of certainty that you would be looking for.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: Well, we wrote a document trying to explain when we might rely on the results of a single study, and there were really two parts. One situation is where you already know a lot of stuff from other studies.

You might, for example, find it easier to believe that aspirin does something because you know so much about aspirin, and in that sort of case, you might accept conventional p-values. But there isn't as much support for dipyridamole, so you probably want something stronger.

We listed the things that might make you feel good about relying on a single study. Obviously, one of them is an extreme p-value. Now, you have to decide whether you think 0.003 is extreme or not, it's not 0.00125, but it is pretty low.

A specific other thing we gave was that you might find replication within a single study pertinent if you believed, for example, that what dipyridamole did alone was relevant to what it did when you added it to aspirin. That is a judgment call. You know, you might find highly relevant. If you do, then, you might say, well, this is sort of two studies or you might think that is totally irrelevant because the only thing you want to know about it is its role as a combination, in which case you would say, well, I don't care at all.

We didn't try to settle those issues. We just tried to indicate the kinds of things one might think about in reaching this, and then also regional consistency, it is very hard to put your finger on what that means. If there had been an effect both on nonfatal stroke and overall death separately, you would say, well, those are two separate things, those are two separate findings, that is pretty convincing, but you don't have that here.

So, it is hard to go much beyond that, but there is lot of judgment in it, and that is why we call upon

outside experts to help.

DR. TALARICO: I think the clinical significance of the endpoint also is very important in dictating how low the p-value should be. Here, we are dealing with death and strokes. It is quite different than having endpoints like heartburn or some other less clinically compelling endpoint.

DR. GILMAN: That is very helpful.

Any other comments from the FDA?

[No response.]

DR. GILMAN: Any thoughts from the sponsor that you have not communicated to us?

DR. HENNEKENS: On this issue about this one particular study, I think it should be mentioned that it added 30 percent to the world's literature on the aspirin therapy of stroke and TIA, it added 300 percent to the world literature of dipyridamole to prevent stroke in patients with stroke and TIA, and provides a conclusive finding on stroke that the combination is better than either component alone.

So, it is not just some little single study out there. I think it is making an important contribution to the totality of evidence.

DR. GILMAN: Grotta.

DR. GROTTA: It obviously has been said multiple times we are really making a decision based on the incidence

of stroke, and you all have provided us with this information on how stroke was identified at each site, could you just finish up in answering my previous question, once a patient was identified by the site as a stroke, then, how was this deliberated and decided upon and adjudicated by the Central Committee, was there a definition, how often did they disagree with the local sites?

I think these are important in my mind. I am convinced that clinically, as has just been pointed out, stroke is an important endpoint. I think any other stroke prevention drug that showed this magnitude of an effect on stroke, we wouldn't be arguing about, but I just need to know or feel a little more comfortable how the strokes were adjudicated.

DR. RAKOWSKI: Hello. I am Dr. Rakowski from Boehringer Ingelheim. This is basically an overview where there were, as far as the entry of patients into the trial, as far as the adjudication by the Morbidity and Mortality Assessment Group, and it essentially provides a composite of understanding of a misinclusion where patients should not have been put into the trial versus misdiagnosis where the diagnosis by the investigator was initially wrong.

It gives you a basic understanding of all of the various types of misinclusions and misdiagnosis, but you can see a relative balance across the treatment groups as far as

the entry of patients into the trial.

DR. GROTTA: I am sorry, maybe I didn't make it clear. The issue isn't really the entry, although that was a previous question, but the endpoint stroke, the nonfatal strokes that occurred in the trial upon which, you know, the real statistical difference between the groups rests.

DR. HAEHL: Disagreement with the MMAG?

DR. GROTTA: Yes, what I want to know is, is when the investigator filled out this form, a general practitioner in Southern Spain filled out this form and said the patient has had a stroke because their face is not normal on one side, and that was the only neurological focality that was identified, you know, I want to know how that was dealt with by the Central Adjudicating Committee and how often they disagreed with the diagnosis of stroke, and whether there were rules that they had a priori as to what had to be on this paper before they would call it a stroke.

I would think that when you designed a study there and set up this committee, that they established rules for what were going to be your primary endpoint. After all, that was what the investigator identified as your primary endpoint was strokes.

DR. HAEHL: As Dr. Pathy explained before, the procedure was based on this case report form plus the

additional information available. I do not have the number or the incidence of disagreement between the investigator and the MMAG at the moment at hand.

Do we have that? No, not at the moment available, so I cannot give you a percentage or per-treatment group a number for disagreements at the moment.

DR. PENN: Can you at least give us a sense of the number of disagreements, was it half, was it a quarter, or was it rare?

DR. HAEHL: Dr. Pathy, can you please comment on how often of rare this had happened?

DR. PATHY: Thank you. There were 179 cases of doubtful eligibility and 138 were actually ineligible, but that was due to a multitude of reasons, because of protocol violations or misdiagnosis, but we don't have a figure for the disagreements in the endpoint strokes unfortunately, at least I don't have one with me here.

DR. PENN: Do you have a sense of what that figure is? I mean was it a lot, were you debating constantly about whether the diagnosis was right, or was it very small?

DR. PATHY: No, it was very small, it weighed no more than 10 percent.

DR. PENN: Well, that is all we need to know.

DR. PATHY: Where there was debate was most frequently in TIAs rather than established strokes.

DR. GILMAN: Are we discussing now entry into the study or are we discussing the event that is counted as a stroke once a patient is on drug or placebo and in the study? I think we are sort of at cross purposes here.

DR. HAEHL: Our understanding was we are talking about the event, the outcome.

DR. GILMAN: The outcome.

DR. HAEHL: The outcome.

DR. GILMAN: Is that what we just heard about? Yes. All right.

Dr. Drachman.

DR. DRACHMAN: Although I certainly firmly agree with you, Jim, that everybody with a stroke should be diagnosed by a very good neurologist, I am more and more impressed whether if obstetricians were making the diagnosis, that would be even more impressive because there would be so much noise that defined a signal like this shows that it must be much better than we thought.

DR. HAEHL: May call for the next slide? Yes, that is what I was making reference to before that a misdiagnosis would certainly not support a positive outcome of a trial when it is randomized.

[Slide.]

This slide is a summary of the MMAG decisions between April 1990 and June 1995, and it gives you the

number of agreements and disagreements for the different conditions, death, stroke.

DR. CALIFF: How could you have 209 disagreements on death? Oh, the cause of death. Okay.

[Laughter.]

DR. HAEHL: No, no, let me explain that.

DR. GILMAN: Please, give him a chance.

DR. HAEHL: What has also been mentioned before by Dr. Pathy, that is a change in the cause of death when, for example, the practitioner attributed the death to chest infection, and then they changed it to the primary event, which would have been myocardial infarction or could have been stroke, and therefore, the MMAG corrected it towards the primary diagnosis rather than to the final symptom.

That explains the numbers, and that is the complete information on this slide.

DR. GILMAN: Dr. Brooke.

DR. BROOKE: I think what we are seeing here, which is unspoken, is the inbred cynicism of neurologists. We basically sit in a clinic and we become convinced that the only three diagnoses that general practitioners make are multiple sclerosis, stroke, and old polio, and I think that is at the basis of our skepticism about diagnoses, which are coming in from the periphery.

I don't entirely agree that the only thing that

could happen, that would increase or decrease the p-value, it depends a great deal on what kind of mishmash you have there, but it does make a huge difference on what the labeling instructions would be if, in fact--and I am not saying it is--but if, in fact, there are a lot of misdiagnoses, which neither the practitioner nor the MMAG were able to pick up, and that is the problem.

I mean it is not a solvable problem, and we can talk around it for a long time, but we do understand the predicament. You have to understand our cynicism.

DR. GILMAN: Dr. Kawas, did you have a comment?

DR. KAWAS: I guess I just need to say I have been quite confused by this discussion. I tend to agree mostly I think with Dr. Drachman. I don't think it matters how these people got diagnosed as long as they were diagnosed the same way in each of the four groups, and nothing that I have seen here today has suggested to me that that had not occurred.

I mean there is no reason to believe that they are calling stroke something different in one of the treatment groups than they are in the placebo. That being the case, whether it is done by an obstetrician or a neurologist or whatever, as long as the diagnosis is consistently applied, it seems to me the issue is irrelevant for the discussion.

DR. GILMAN: Any other comments from the FDA, the sponsor?

[No response.]

Discussion by Advisory Committee

DR. GILMAN: If not, then, you have all been given a couple of sheets that you already had in your packet. They address the questions that we are supposed to come to grips with now.

There are five of them. The first is the effectiveness of Aggrenox is being supported by a single European study. Based on this single study, has the sponsor provided substantial evidence of effectiveness of Aggrenox for the desired indication?

If no to (1), has the sponsor provided substantial evidence of effectiveness of Aggrenox for any other indication? If so, for what indication?

The third question. Would you recommend approval for Aggrenox for the requested indication?

Fourth. Would you recommend approval of Aggrenox for an indication other than the requested indication? If so, for what indication?

Fifth. Are there any particular safety concerns with use of Aggrenox?

Let's come to grips with Question No. 1 to begin. If I may, I think I will just briefly summarize my own position in this to get a start maybe.

We have about a single large trial that had

multiple concerns that we have been talking about all day today. My own concern is that this medication was devised in a fixed dose combination without attempts to find clinically optimal doses for this indication.

There was a change in the primary endpoints over time with initially stroke, death as the two primary endpoints, and then later a third was added. Yet, the randomization initially was based upon those two endpoints.

There is some question about the safety committee looking annually at the endpoints. I think that is still somewhat of a question, but my feeling is that the committee was looking, blinded, to which case was in which group.

There is some question about the addition of the 2,000 cases to the originally prescribed number of 5,000, but I come away with the conclusion that there is convincing evidence Aggrenox is more effective than either of its components for stroke, but not for the composite of stroke or death.

So, I would be comfortable with the recommendation that it be utilized for stroke as the indication, but I am not very comfortable with the wish the company has expressed, that it be written up as indicated for stroke or death.

Let me see what my committee thinks.

DR. PENN: I agree.

DR. DRACHMAN: When it says for the desired indication, would you like to be very explicit--

DR. GILMAN: Yes.

DR. DRACHMAN: I mean death is not an indication. I mean that is a desired thing to avoid. So, how does that read, what is it?

DR. GILMAN: That is a good point.

DR. TEMPLE: Stroke isn't a desired outcome either.

[Simultaneous comments.]

DR. GILMAN: Stop. One person at a time.

DR. TEMPLE: It would be prevention or reduction of risk or some words like that.

DR. GILMAN: So, the company wants it to be indicated to reduce the combined risk of death and nonfatal stroke in patients who have had transient ischemia of the brain or completed ischemic stroke.

My suggestion is that it be indicated to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke because, to my mind, what the data tell us is that this medication works better than either of its components for that purpose, and I personally came away thinking that that is a reasonably robust p-value, particularly for, as Dr. Talarico said, for such a serious problem.

DR. DRACHMAN: Then, should it say, does it say somewhere thrombotic ischemic stroke?

DR. GILMAN: I think that would be a very good idea, yes. We don't want to use this for hemorrhagic stroke.

DR. DRACHMAN: Right. Does that include hemorrhagic ischemic stroke?

DR. GILMAN: Well, that has not been defined in the trial, as I understand the trial. There is no look with CT to determine whether blood was present consistently.

Is that correct? Let me ask the company, the sponsor.

DR. HAEHL: That is correct.

DR. GILMAN: That is correct. Thank you.

DR. KONSTAM: Can I just comment on that? I mean I am thinking about this. This is the first time we have talked about this. I mean the endpoint defined was stroke. What we are saying, at least some of us are agreeing that stroke was reduced, and I could justify that as the indication, that the total frequency of stroke was reduced.

Now, it is conceivable that there were a few more hemorrhagic strokes. We don't know that.

DR. GILMAN: We don't know that.

DR. KONSTAM: But if they were, they were, you know, far outweighed by the number of thrombotic strokes.

So, I mean I personally would be comfortable just saying reduction in the frequency of stroke.

DR. DRACHMAN: I wouldn't. This is going to be the very first question my residents are going to ask me. They will say should we do a scan, see whether there is hemorrhage in the stroke, and if there is, do we give it.

DR. KONSTAM: That is something different, I guess. That is I guess for which patients, what is the population for which it is indicated. In other words, the indication will be to reduce subsequent stroke. What is the population for which it is indicated?

There, I don't know. I mean I assume that people with hemorrhagic strokes were not permitted into the trial, right? They were not.

DR. HAEHL: They were not.

DR. GILMAN: Did they all have CT scans to ensure? No. They did not.

DR. TEMPLE: It means no deliberate hemorrhagic stroke, but they don't know.

DR. HAEHL: Patients with hemorrhagic stroke were not supposed to be included, and in 80 percent of the patients included a CT scan was there.

DR. GILMAN: But in order to be sure you are not dealing with an initial hemorrhagic stroke, you need a CT scan in 100 percent, not 80.

DR. GILMAN: Therefore, from the remaining 20 percent, we assume that they didn't have hemorrhagic stroke from the clinic, but we have not a CT scan.

DR. DRACHMAN: But should that modify the wording of the indication? Should we put that right in the indication and the labeling?

DR. GILMAN: Dr. Talarico.

DR. TALARICO: The labeling does call for reduction of combined risk of death and not for the stroke in patient or have transient ischemia of the brain or completed ischemic stroke.

DR. GILMAN: That would be just fine.

DR. DRACHMAN: That is all right, but ischemic stroke may be hemorrhagic.

DR. GILMAN: What you mean is that sometimes an ischemic stroke will cause hemorrhage into the surrounding brain tissue because of damage to the blood vessels even though the basic mechanism is ischemic.

DR. DRACHMAN: Right, emboli typically do that or may do that.

DR. GILMAN: I think that what will happen is that if this drug is approved, the FDA will come to grips with the labeling with the company, taking in the light of what we have said, what we have deliberated about here.

DR. BROOKE: Could we take a step backwards. I

hate to do that, but I am convinced that there has been interesting effect shown by the combination of aspirin and dipyridamole. The question is whether it is a good thing to combine them in one drug.

Now, obviously, the advantage is convenience, but isn't there a severe disadvantage? The dose of aspirin was argued about for a long time. When you have a combination drug, you have set the ratio, so that it is inflexible, nobody can see whether you need less aspirin, more dipyridamole, and is that not a disadvantage?

I think that what I have been convinced of this afternoon is the combination of those two drugs is advantageous for the disease which has been tried. I am not sure I have been convinced that combining them in one tablet has been shown to be a great advance to mankind.

DR. GILMAN: I tend to agree with that position, which is why I think it is a pity that some dose finding studies were not carried out independently, looking at different doses of aspirin and of DP.

Dr. Grotta.

DR. GROTTA: Well, I mean but the fact is, is that this combination is better, and somebody else can do a study of a different dose combination and find out if that is better than this one, but we do have a result that is positive, that seems to provide an advantage to our patients

over what we have available now.

I mean I agree it would be nice if we had 10 different studies of different combinations and to choose the best one. I also feel very uncomfortable with us changing the characteristics of the patient population and the study characteristics upon which we are basing any approval.

I would be very careful about doing that. This was a study carried out in patients with suspected ischemic stroke or TIA, and I don't think we should be any more restrictive than that in deciding which patient population should be studied just because we have certain clinical assumptions.

The data indicate that when patients are included with TIAs or suspected ischemic stroke, that the combination reduces the incidence of stroke. So, I really wouldn't change and be more restrictive than that.

As far as the death issue is concerned, to me, unless you are willing to take the indication of death away from aspirin 50 mg, I don't think that we should--I would argue that we should include death because the drug contains aspirin 50 mg for which there is already an indication that it reduces the incidence of death, and the clinicians out there are going to be very confused when you approve a drug that has aspirin in it, at a dose that has already been

approved to reduce death, and now you say that this drug doesn't.

I think we are being inconsistent and the study was not powered to look at the death endpoint really, and I don't have a problem--I disagree--I don't have a problem with the endpoint or the indication as stated.

DR. GILMAN: Let me respond. First, that this committee was not the committee that approved aspirin for the indication of death or stroke.

Second, the data that we have been presented showed no beneficial effect with respect to the endpoint of death. That being the case, I think it would be rather illogical for us to approve it for benefit with respect to death.

Dr. Temple, do you want to comment?

DR. TEMPLE: Well, we actually thought you would come to this, and we are agonizing about it ourselves. It is very unclear whether to focus most on the individual study results which show no benefit on death or on the fact that it contains aspirin, which already has a claim, which I would say we probably still think is legitimate even though it wasn't shown in this study.

So, I don't have any advice for you except it is really hard, and we love to listen to what you say, and we will be undoubtedly agonizing about it more.

DR. GILMAN: Dr. Califf.

DR. CALIFF: Let me just try to summarize my feelings about this. We start from a base of one out of three endpoints with a fairly dramatic result for that endpoint in terms of a p-value, and then there are a list of things which raise the level of uncertainty from that fairly dramatic p-value - the three endpoints, the multiple looks, the resizing based on looking at the result, the elimination of some patients after randomization due to a problem with the site, the fact that there are no minority patients, which we are labeling this drug for use in a population which had not to some extent been studied, and I personally think that a nonfatal measure endpoint in a disease which is often fatal, looked at in isolation, is a fatally flawed endpoint.

Without any mathematical way of taking all these things into account, I guess that I have to agree with what everyone else has said, is that it looks like substantial evidence, but I would be also in favor of saying death or, because I am really stuck on the point that we can't look at a nonfatal endpoint in a disease which is often fatal.

The issue of dose ranging, if we think we have a problem with sample size looking at a single dose when we are looking at hard endpoints, if you want to do dose ranging for a drug like this, you are going to be talking

about hundreds of thousands of patients.

I am just glad we actually have some combinations to look at now, because in most of the rest of medicine, we have got multiple drugs approved for indications with no knowledge at all about how to combine them. At least this is a start.

DR. GILMAN: Thank you.

We have heard from the sponsor. Please, this is for the committee's deliberation now with all due respect, please.

Dr. Van Belle.

DR. VAN BELLE: With respect to the mortality, I would be inclined to do two things. One is pass the buck to the FDA ultimately because it is a policy issue, as well, but I would also say that from these studies, you would be able to argue that the results are not inconsistent with a mortality reduction. I don't think that they contradict that.

So, then, the question comes up how seriously are you going to take the aspirin data by itself from other studies and imply the effectiveness to this particular study.

So, my inclination is let the FDA handle it, so that it can come up with a consistent labeling effort and that this committee would simply say that the results are

not inconsistent with the effects of aspirin.

DR. GILMAN: Dr. Konstam.

DR. KONSTAM: I am just trying to think this through myself. I guess I have a problem. Well, let me just say that there must be some kind of imaginative language that needs to be used in combination products, because this is an issue that is specific for the fact that it is a combination product.

I have trouble saying that by definition because it contains aspirin--you know, the labeling is going to be for this particular combination product--and therefore to say, well, here is a combination product, and it reduces the incidence of death or stroke, when that has not been shown, boy, I guess you could market aspirin plus ginger root, you know, and say it is for reduction in death or stroke, because anything containing aspirin has shown that, so we didn't even have to do any of this.

We could have just said, well, as long as the dipyridamole is not having any adverse effect, we can market it for the combination of death and stroke if that is the logic. So, I guess I am going to have trouble with that. I mean I guess I am going to have to say that I can't get past saying that the specific combination is indicated for what we found in this study, and that is reduction in stroke in the population defined, and them some additional wording to

say that, by the way, you know, we know aspirin is indicated for blah-blah-blah, and this thing contains aspirin.

You will have to work it out, but I think that is my feeling.

DR. GILMAN: Dr. Katz.

DR. KATZ: I don't know if this is terribly relevant, but you couldn't mark it ginger root and aspirin unless ginger root had an effect, as well, by the combination policy, so it doesn't necessarily address the aspirin issue, but you can't just add aspirin to anything.

DR. KONSTAM: But then you have to ask then, okay, following that logically, well, then, what is this combination product approved for.

DR. KATZ: No, I agree. I agree.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: If I understand your last suggestion, you were saying focus for the combination purposes on what was shown for the combination, and then perhaps somewhere else in the indications, remind people that aspirin is indicated for that. That is not out of the question. It doesn't have to be a one-liner. It can be longer than one line and explain more.

I forgot before, the matter of what the right dose is, that is a somewhat tricky question here. For example, if the doses for people with coronary disease and MIs is

larger than 50 mg a day, you have the problem suppose someone has both and the physician wants to use a somewhat larger dose along with dipyridamole because he is convinced that dipyridamole provides a benefit, well, I mean you could do it, you could do a baby aspirin to the combination, but my question was, is the controlled release product available or going to be available as a single entity or only in the form of this combination?

It is not available? What is your plan?

DR. HAEHL: It is now not available. We have concentrated all our development on the combination product, however, if there is a population which is in need of that, then, we are certainly prepared to discuss that with the FDA.

DR. TEMPLE: Obviously, that problem is complicated, too, because the only combination data we will have is with the 50. Nonetheless, in response to what was said before, combinations pose that problem, and they always do.

The other thing is regrettably, we often don't see good dose finding when it takes 7- or 8,000 people per study to find even one dose works, so we are often devoid of good dose response data, although Rob is working on it in some of his studies.

DR. GILMAN: I would like to have seen at least a

couple of doses of aspirin with dipyridamole.

Are there any new points about this first question for us?

DR. PENN: I was just going to go ahead procedurally and propose something to vote on. Is that in order at this moment?

DR. GILMAN: That is perfectly acceptable.

DR. PENN: Since I agree basically with your position, I would vote no on Question 1 and tie that to a vote yes on Question 2, there is a specific indication which would be stroke. I don't know whether procedurally we are allowed to combine those two.

DR. GILMAN: Dr. Katz.

DR. KATZ: Yes, I think procedurally you can pretty much do anything you want, I mean as long as it is clear what you are trying to tell us.

But I just want to make a gratuitous comment. There has been considerable discussion about who should this be indicated in or what the actual effect is, is it stroke. I just want to remind people--and you may already be taking this into consideration in your votes--but I just want to remind folks that there is another critical phrase in the question, which is substantial evidence, and that embodies the question of is one study enough.

So, even though you might be thinking about that,

what I am hearing is a focus on what is the claim as opposed to is there substantial evidence.

DR. PENN: I didn't mean to imply that because I think there is substantial evidence.

DR. GILMAN: I thought there was substantial evidence also.

There is a motion on the floor which is that we say no to Question 1 and give some language for Question 2.

Is there a second?

DR. TEMPLE: Can I just ask for a clarification? A no could mean that there is no substantial evidence for anything or that there is no substantial evidence for including death. So, however you phrase it, make sure we know what you are voting.

DR. GILMAN: If you wish, we could discuss Question 1 and then go on to Question 2. I think what is important is that we deliver the message that seems to have at least the majority of the committee

DR. TALARICO: Can you separate the two?

DR. GILMAN: Separate the two?

DR. PENN: Then, I can withdraw my motion and say that I do not think there is substantial evidence for the combined indication, and make that as a motion, well, we can vote that question, I guess. We just vote the question, just call for the vote on the question.

DR. GILMAN: Is there a second to the motion?

DR. DRACHMAN: What motion?

DR. GILMAN: The motion was that the answer to Question 1 will be no, there is not evidence that this single study supported the indication that the medication is useful in stroke and/or death.

Is that right, Dick?

DR. PENN: Yes. Yes, that is what I intended.

DR. BROOKE: Stroke or death?

DR. GILMAN: Stroke and/or death, the combined endpoint.

DR. BROOKE: Isn't it stroke and death? I think it may be effective in stroke.

DR. CALIFF: In the composite of stroke.

DR. GILMAN: Let's call it in the composite of stroke and death.

Was there a second?

[Second.]

DR. GILMAN: There is a second. All right.

Discussion?

[No response.]

DR. GILMAN: All right. All in favor of the motion, please so signify.

[Show of hands.]

DR. GILMAN: Seven.

All opposed?

[Show of hands.]

DR. GILMAN: Three. Seven to three.

DR. TEMPLE: So, yes means no, right?

DR. GILMAN: Those in favor of the motion. The motion was that the answer to Question 1 is no.

DR. TEMPLE: Just making sure.

DR. GILMAN: But we are going to modify that response by going to Question 2.

DR. PENN: And the motion of Question 2 is the committee agrees that there is substantial evidence for the effect of the product on stroke.

DR. TEMPLE: How should someone who thought there was evidence for both vote?

DR. PENN: They have a choice.

DR. TEMPLE: Well, no.

DR. PENN: The people who voted, they already indicated, three people have indicated they think we are all wrong, you know, of the 7 that voted that way are wrong, but they have included their clear indications of why, and they do not want to confuse physicians about this.

DR. TEMPLE: Let me suggest something different, that if you believe it should be approved for both stroke and death, you would want to support this, not vote against it That will just confuse everything.

DR. GILMAN: Dr. Grotta.

DR. GROTTA: Well, you could amend your motion to reflect what Dr. Van Belle suggested, and that it doesn't exclude an effect on death, in other words, that the studies have shown that the drug reduces the incidence of stroke, and does not exclude an effect on death.

Then, I think that you would not have that dilemma for those three people who voted yes on No. 1.

DR. PENN: I would be pleased to amend it in the way you have stated it.

DR. GILMAN: Would you restate the motion then.

DR. PENN: The motion, once again, is that there is substantial evidence to support the effectiveness of this product for stroke, and that there is not enough evidence to include in the indication death.

Isn't that what you were saying?

There is inconclusive be acceptable?

DR. VAN BELLE: It is not inconsistent with.

DR. PENN: It is not inconsistent, okay, I am sorry, I chose the wrong word. Is that all agreeable, then, not inconsistent with the three people that voted the other way?

DR. LACEY: Not inconsistent, I am not sure I understand.

DR. KONSTAM: Can I restate it? I think the

motion would be that there is data supporting the prevention of stroke without regard to the death question is really I think what we are saying. So, you would not prejudice your vote against this motion if you felt that there was a combined indication, there was sufficient data for a combined indication.

It is really focusing on the stroke indication independent of the combined question, right?

DR. GILMAN: That is a little different from what Dr. Van Belle said now.

DR. CALIFF: I think it is quite different because I can't accept--I mean I will have to accept it if is a majority vote, but I would opposed vehemently--I mean you just cannot ignore informative censoring. O'Neill used the word, I couldn't think of the right word, but, you know, we will be rewriting the textbook of what we have learned about clinical trials in the last 10 years to say it that way.

I think the way it was stated before is fine.

DR. PENN: Using inconsistent I think would--

DR. GILMAN: It is not inconsistent with an effect on death.

DR. BROOKE: Do you feel you have to have death in the phraseology?

DR. GILMAN: I don't think that Dick particularly cares, but we have three votes that may go the other way on

this question unless that is included.

DR. PENN: Yes, and I have no problem with stating what the fact is, at least I think what the facts are from what was presented to us.

DR. BROOKE: It is like telling children not to stuff beans up their nose. The first thing they do is they go and do it. If you mention that it is not inconsistent with prolonging death, the person who reads the insert will think, oh, good, it prolongs life.

DR. KONSTAM: Maybe we could ask the agency if we just went around the room and each of us said what we felt about this, would that not be sufficient information for them? They are all nodding their head.

DR. PENN: We have to vote, I thought.

DR. GILMAN: We are supposed to give guidance.

DR. KATZ: I think what is most critical is that we get clear, if you can give us clear guidance on what we should do, I think the vote is, you know, it is a tradition I guess. I don't think there is anything in the law that says you have to vote.

But we would definitely like to get a clear picture of what you think the indication ought to be.

DR. TEMPLE: Well, no, there is two things. One, what do you think there is evidence for, and then there is a lot of nuances of exactly how to say it.

DR. KATZ: When I say evidence, that is what I mean, what you think there is evidence for.

DR. GILMAN: Well, folks, we have seen some evidence here that does not tell us that this medication will prevent death. I am sorry, but no matter what any other trial says or what the FDA has said before, the data do not support that claim.

DR. TEMPLE: Well, you actually voted on that. Three people thought maybe it did, and the rest didn't, so that one you voted on, that is clear. But the question here is we need a clear understanding of whether the committee thinks there was evidence for a different claim.

DR. PENN: That is a misinterpretation of that vote. I thought that the people who objected wanted consistency with other data, not just the data that was presented to us.

In other words, they thought that the aspirin labeling was all right, and that because we had aspirin that they would go along with that, and they didn't want to confuse physicians about it.

DR. TEMPLE: You may be right, that isn't--the question says whether there was substantial evidence supporting that claim, but you may be right about why people voted the way they did.

DR. BROOKE: Just because aspirin used on its own

has an effect on survival, doesn't mean that when it is used in combination with another drug that it has the same effect. I mean there is numbers of examples of drugs that don't work well together. I mean as far as death is concerned, I am not talking about stroke.

DR. GILMAN: Claudia, do you want to comment?

DR. KAWAS: There have been a lot of things said today, and I just thought I would run through the list of the ones I am not concerned with and end up with the one I am concerned with, which is exactly what we are debating.

I mean I know there were discussions about multiple looks with regards to safety, and that personally didn't concern me. It looked to me like--it was essentially as safety monitoring committee, and didn't affect the integrity of the study.

There was concern about the diagnosis of the events and the inclusion, and as I said before, I think that those were taken care of by the randomization process, and there doesn't seem to be any appearance of breaking the blind which would affect that.

So, as a trialist, I am not concerned about that, although as a neurologist, like many of the people here, I can say I am very concerned about accurately diagnosing strokes.

I was also taken with the discussion about the low

dose of aspirin, but I think that the consensus of the scientific community supports that even if the data doesn't, and here is another place where the data doesn't support things, and that is the aspirin and the risk of death. Most of the previous studies really haven't shown that aspirin has an effect on death even though we keep talking about it like it is clearer in the previous studies than it was in this one.

In regards to the questions that the FDA presented to us, I believe that this is a single study that meets a lot of their criteria. I mean specifically, it is certainly large since we have heard repetitively it is significantly added to the number of patients exposed in clinical trials to both of the drugs.

It does have some consistency between groups, and I didn't find that a problem, as well as multiple studies or pairwise comparisons that were satisfactory in endpoints.

The issues about generalizing to other populations isn't any different from any other drug we have on the market since most of our studies have not been adequately studied in other racial groups, even the ones done in the United States, much less the ones done in Europe.

So, the things that do concern me come down to the primary endpoints. In particular, the interim analysis wasn't prespecified, and increasing the sample size didn't

bother me because I think that doesn't change the results, but I do have some concern about how the endpoints were decided, and I think that is the crux of the discussion we are having, because it makes it hard to know how many corrections or pairwise comparisons we should be making.

The data, to my mind, suggested that there was a role for this combination, better than placebo, to prevent stroke, and that there was a clear additive effect, and that is part of the consistency of the study where the estimates really looked very consistent to me.

The data does not show, however, to my mind, that there is an effect on death, and the problem is earlier in the day, you know, Dr. Temple told us that how we indicated this or interpreted this was to some extent are taste, and I don't know what my taste is in this because I understand both sides of the argument.

I mean death is very much embroiled in cerebrovascular disease. Overall, despite the way I voted a minute ago, I do think probably death needs to be factored in, but there is not data that convinces me that this delays death.

That is why I don't know quite how to vote on all these convoluted suggestions that everybody is giving me with double negatives and triple, or whatever, but I do think that we just saw a factorial design that showed me

that there was a role for this combination as compared to placebo in prevention of stroke.

I am glad that the FDA uses us as an advisory committee, and they get to figure out the real answer.

DR. GILMAN: Dr. Talarico.

DR. TALARICO: Probably it might be easier if we go back to the question as questions rather than making into making motions, because the first two questions address just whether you are convinced that this study has shown enough evidence of effectiveness of Aggrenox for the desired indication, which is the combined endpoint of death and stroke, and the answer can be yes or no. Then, if not, then go to the next question because otherwise it becomes very difficult.

DR. GILMAN: I understand. We want to be as helpful as we can.

DR. TALARICO: The discussion was very informative, but I think if we can come to the vote in terms of question, it might be easier for you.

DR. GILMAN: We are getting a mixed signal now. Would it be most helpful to the FDA if we were to vote or if we were to go around the table and just everybody respond to Question 1 and then Question 2, and so on?

DR. TALARICO: The discussion is very informative, but eventually the vote has to come to the question as it is

posed.

DR. TEMPLE: But the question has to be clear. For example, if there were someone--Rob may not be such a person--who thought that the stroke thing was well done and at least they ought to get that, then, you don't want a no answer on No. 2 just because they thought it also ought to get death. That would be a confusing answer.

So, as long as you clarify those and say how people who think various things should vote, then, voting is fine or the recent discussion was very helpful, too.

DR. GILMAN: Well, then, just to reiterate, in Question 1, the three no votes were based upon their view that death ought to be included as an indication for the reason that there was some evidence suggesting that it may be helpful even though the data were not significant.

Is that correct, the three no votes?

DR. VAN BELLE: As one of the three, it just seemed to me that from the discussion earlier this morning, there was some degree of arbitrariness as to whether death is included in a labeling issue or not, and so I was just responding to Dr. Temple's comments earlier this morning that death is often included, and we have also heard some other aspects to that effect.

What I am saying is that when I look at the data, the data are not going to be inconsistent with that claim.

There clearly is no proof in these studies that death is delayed or reduced. That is not the case. But the results are not inconsistent, so it is really a question of power, and we have heard before that death as an endpoint requires much larger studies, and so you are just not going to get that.

So, I see it as somewhat more of a policy issue rather than a scientific issue.

DR. GILMAN: Yet, the question is based on this single study, has the sponsor provided substantial evidence of effectiveness of Aggrenox for the desired indication, substantial evidence.

Dr. Drachman.

DR. DRACHMAN: Just so we don't lose sight of Dr. Brooke's point, we will use aspirin for headache, yet, in this particular mode, the number of headaches in the mixed drug was greater than for placebo.

So, if we are thinking about something for which there is no evidence, meaning the alteration or elimination of death or reduction of death, the fact that aspirin sometimes works for a headache, sometimes may prevent death, may not provide substantial evidence here for either one.

Is that clear?

DR. TEMPLE: No, I had a flash.

DR. DRACHMAN: Let me say it again then, Sid. We

believe that aspirin by itself may reduce the amount of death in stroke. We also do believe that aspirin in another setting is very useful for relieving headache.

Here, in this study, as I recall the data, there were more headaches in the combined drug than in the aspirin or placebo drug, meaning that the combination is not necessarily equivalent to the sum of its parts.

DR. GILMAN: Well, that is because the headache came from the dipyridamole.

DR. DRACHMAN: Well, we don't know that.

DR. TEMPLE: This is 15 mg of aspirin. It is not relevant to headache.

DR. GILMAN: That is another point, small amount of aspirin.

DR. TEMPLE: I had a flash. See if this helps. In Question 2, say, has the sponsor provided substantial evidence of effectiveness for either reduction of the risk of the stroke or the reduction of risk in stroke and/or death. Then, you get both groups, one or the other.

Does that make sense?

DR. PENN: No. I think we should have a clear vote that we think that it works in stroke and get that over with. The phrasing of how we indicate the situation on death, we are argued about and we have given you clear indication that--not how confused we are--but that we don't

think that there is substantial evidence in this particular study.

DR. KONSTAM: But you want people who voted yes to No. 1 to be able to vote yes for No. 2, as well, and I think that Bob's suggestion permits that. So, I think it is just a tactic to do that, and I think it would work.

We already voted no, 7 to 3, on Question 1. So, those three people have carved out their viewpoint. What I think we want to say is we don't want to keep those three from voting no on 2, if we think that there is a stroke indication in there, and Bob's suggestion would do it.

DR. PENN: Why would you vote no on 2?

DR. KONSTAM: I think he doesn't want a 7 to 3 vote in favor of No. 2, and then in the end of the day, not being able to figure out what that 7 to 3 vote meant, when, in fact, the three people were convinced that this agent is worthy of an indication. Right?

DR. BROOKE: If you couple death and stroke, some of the people that voted for stroke will not vote for it. You will lose the 7, as well as the 3.

DR. KONSTAM: He is the one we are advising.

DR. PENN: In fact, that is the case, I would not vote for something that couples it.

DR. DRACHMAN: Why don't we just separate them?

DR. GILMAN: One person at a time. Dick?

DR. PENN: I am sorry I interrupted that way, but I wouldn't unless somebody puts a very convincing argument it vote for a motion--

DR. KONSTAM: You are not being asked to. You are being asked to vote yes for No. 2 if one of these is acceptable to you, and then in the discussion, you can tell which one. We will go around the room, and we will be able to tell which one of the two, and we will give a yes vote, and it wind up with a clear message that there is an indication here, and give them the input about which one we think it is. I think we are just trying to get over a hump here, aren't we?

DR. TEMPLE: This was really to do what you wanted to do, get a vote on stroke.

DR. KATZ: Don't we already know that 7 folks want this to be approved as a treatment for prevention of stroke and that 3 people want it approved for stroke or death, don't we know that already?

DR. KONSTAM: I think we have already voted on it. I think we have done it.

DR. GILMAN: We know that.

DR. TEMPLE: No, the 7 who voted on the first one just said they didn't want it for stroke and death, and I am not sure where Rob is going to come out, for example.

DR. HOUN: But then the 7 people, why don't we

find out from them if they don't agree for stroke and/or death, what do they think there is substantial evidence for? So, we just focus on the 7. The 3, I think have voted--is that true that they vote there is substantial evidence for the desired indication of decreased risk for death and nonfatal stroke?

DR. TEMPLE: Which must include stroke.

DR. HOUN: It is the 7 we want to know, if they don't believe, what do they feel there is substantial evidence for.

DR. GILMAN: Rather than dealing slavishly with Question, let's just go around the table for the 7.

DR. DRACHMAN: Stroke.

DR. CALIFF: Stroke.

DR. GILMAN: The evidence is substantial for reduction of stroke, yes, but not for any other indication.

DR. LACEY: I echo that.

DR. KAWAS: Stroke.

DR. KONSTAM: Stroke, and I would just like to explain the vote a little bit. I think that I would agree with stroke. I take the argument around the concern about not having a combined endpoint and the possibility that by not including death in the combined endpoint, perhaps we are biasing it, but I don't believe that is going on here, because I don't think that there is any adverse effect on--

there is no adverse effect on mortality, and my guess is that at least components of this have a beneficial effect on mortality, so I am not concerned about that.

So, I am left saying that it does reduce the incidence of stroke, and I guess it would be worthwhile, I think, us spending a minute saying why it is that we believe this single trial provides sufficient evidence to support that, because I think the statistical reviewer are argued against that, so I don't know if enough of us have spoken to this specific question, what is it in the data set that really is driving us to say yes, so I will just speak for myself about it.

We have some very low p-values. I mean the specific p-value that I focus in on is 0.008 for the combination compared to aspirin alone in the prevention of either fatal or nonfatal stroke, and I guess that would have to be corrected down for the fact that we have a couple of different endpoints at the beginning and there was more than one look, but I think given all we know about this, I am willing to accept that as very strongly positive signal that I will accept the one trial.

So, that is the summation of my feeling. That was a yes for stroke.

DR. GROTTA: I would like to say just one thing. Again, it reiterates the point. My understanding is, is

that there are three drugs out there that are approved for the combination endpoint of stroke and death. There are three drugs out there--well, what is the indication for clopidogrel? Is it just stroke?

DR. CALIFF: Clopidogrel is stroke, death, MI, all three.

DR. TEMPLE: And in a very mixed population, however.

DR. GROTTA: Okay, and aspirin, as well.

DR. CALIFF: But a very similar data set in terms of its actual effect on stroke.

DR. GROTTA: And Ticlid is also a combined endpoint approval, it's not just stroke.

DR. TEMPLE: That is true, and actually some of the data came from noncardiovascular deaths.

DR. GROTTA: So, all I am saying is that the clinician has three drugs out there that are approved for more than stroke. This drug comes out, and we have an indication for stroke. The clinician is going to see that, when, in fact, the data shows that this drug is superior to aspirin for the prevention of stroke and in the combined endpoint of stroke and death, is at least as good. There was a statistically significant effect of this combination on the endpoint of stroke and death. It just wasn't statistically significantly better than aspirin or

dipyridamole.

So, the fact of the matter is, is that this is why I have trouble with eliminating the death issue from this, that you are going to confuse clinicians by this, and not only that, it doesn't really reflect--I mean we heard a very articulate summation of the data a minute ago by Dr. Kawas, and it seems to me that we just want to state what the data shows, what were the results.

Well, the results are that the drug is superior to aspirin or dipyridamole for prevention of stroke, and it is at least as good as aspirin for preventing the combined endpoint of stroke and death. So, maybe that is what we should say, but that is why I have trouble just limiting it to stroke. I don't know how I can say--I have said it three times now, so I don't think I can say it any more than that.

DR. KONSTAM: There is a really good point that is coming up here, which I don't think we have really touched on directly is the equivalence question. I mean if we were able to derive from the data set that the combination is equivalent to aspirin, therefore, no worse than aspirin in preventing some larger endpoint such as mortality, then, I think that would be sufficient to warrant that indication, wouldn't it?

DR. GILMAN: If you look at the data, there is no significant effect upon death as a marker.

DR. KONSTAM: I understand.

DR. GROTTA: Nobody is talking about death. You are confusing the issue, no one is talking about death. We are talking about the incidence of stroke or the incidence of the combined endpoint of stroke or death.

Nobody has suggested that there be a statement in there that says that the drug prevents death per se. It is the combined endpoint of stroke or death over which there is an indication for all the other drugs.

DR. GILMAN: But that has not been demonstrated in this study.

DR. TEMPLE: Yes, it has. Let me just make an observation. I must say I am guilty of it. We are so focused on the combination policy, which is what is the contribution of each component to it, that we have neglected the fact that the whole thing has the desired low p-value effect on stroke and death.

DR. GILMAN: But because it is a combination product, we are focusing on whether it is better than two other ingredients.

DR. TEMPLE: Well, one could separate this conceptually by saying can you show that there is a contribution of a valid kind of each component of this thing to something, and one might conclude that that is shown by stroke. A number of people have said that.

You then can sit back--this is a labeling thing, I must say we have not dealt with something like this, so I am out on a limb here--but one can think of what the whole drug is for without necessarily representing or requiring that each component be shown to do that. Those are separable issues potentially which we would obviously need to think about.

DR. GILMAN: Dr. Katz.

DR. KATZ: The fact that the whole combination has shown an effect on the composite endpoint largely, if not entirely, is due to the fact of its effect on stroke. So, I mean I think the question is, is it misleading--I don't know about the data for the other drugs out there--but is it misleading to tell people in labeling this has an effect on stroke or death, when, in fact, there is no evidence that is has an effect on death.

I mean I think we have to deal with the potential misleading nature of such a claim, and as Bob has said, it is very tough, it is hard to know what to do with this in the context of the fact that one of the components already has that indication, other drugs out there like this have that indication. It is a very tough call, but I think the question of misleadingness is worthy of thought.

DR. TALARICO: If people are concerned about misleading, the labeling can address the issue by showing

exactly what were the results in strokes and what were the results in death. So, it is not going to be just the indication for death and strokes.

DR. KATZ: I should say we have regularly done that, where there was a triple component endpoint, we have given the actual results with each one. Now, of course, we stick that in the clinical trial section that people may or may not read, but it could be in a more prominent place if that was thought important.

DR. GILMAN: Dr. Califf.

DR. CALIFF: Dr. Grotta couldn't have made his part of the argument as well. I mean he really said it quite well, and I can't do it any better, but the other thing for me again is that I think you are seizing on a p-value for an endpoint that you can't accurately measure, and that p-value that you are looking at is counting a denominator which is not a real denominator. It is influenced very much by the deaths which are unaccounted for, and that, combined with Dr. Grotta's reason, it is really both of those that are impacting the way I feel about this.

DR. GILMAN: Again, I think Dr. Katz said it very well, the data on death or stroke in fact were carried by the very robust effect upon stroke.

DR. CALIFF: The strokes that you think you are

measuring being unable to account for all the patients that were randomized. This is a well-described phenomenon in composite endpoints where there is a significant mortality in the trial.

DR. BROOKE: Censoring data is a problem, but we have to deal with the data that we have got. We can't imagine what it would have been if we had the censored data. Committees like this are accused of paternalism, and it is probably true.

I mean maybe the best way to do this is to say, look, this drug is safe, clients are the ones that decide whether they want it or not. It will fall or stand in the marketplace, and if it is not a good drug, then, eventually, nobody will buy it.

But I still believe there is a last vestige of academic integrity around here, and the data that we have presented showed an effect of the combined treatment, which was additive, on stroke and, of course, the results on stroke was robust enough that it carried over into a combination.

But I think it would be a little dishonest--I don't see what is wrong with voting one on stroke and one on death, and you were halfway around, and I thought that was a good idea. I was one of the 7, and I would vote for stroke, but I wouldn't put death in the flyer.

DR. GILMAN: Dr. Van Belle, you are the one person who has not spoken on that issue.

DR. VAN BELLE: Well, I will certainly vote for stroke, and again, as I said, it is not a principial thing with me in spite of the academic concerns on my left here. I think it is a matter of the FDA's setting up a labeling system that will not confuse practitioners, so I think it is a practical issue rather than a philosophical issue.

DR. GILMAN: Dr. Penn.

DR. PENN: I would just like to make one last point on this. We are often in a situation where we have to deal with a scientific presentation and we are limited by what is presented to us in that scientific realm.

On the other hand, there is a fairness issue here, and that is that we are penalizing the company for getting an equal right to market its drug the way that other drugs have been marketed for the extra indication of death.

So, we have to indicate that to the FDA, that we think there is something wrong here. The science is pretty clear to us, but there is a fairness issue to the company that has to be dealt with in a very positive and strong way, and to say maybe in the labeling, something to the effect that there is the same amount of information on this drug as the others for the indication, the combination indication, is a way of handling it at least in part.

It still penalizes the company because they can't advertise in the same exact same way, but this is not an uncommon problem that our hands are sort of tied by what has been happening in another realm, that death has been thrown in inappropriately when they didn't have the data because they didn't do large enough studies in any of these cases.

DR. GILMAN: Let me ask the FDA now, have you heard enough?

DR. TEMPLE: Can I say what I think I heard? I didn't hear anybody who, despite the concerns about multiple endpoints and all that, didn't think that an effect on stroke had been shown.

The closest to a negative view of that would be from Rob Califf, who thinks that you really have to take the combined endpoint and look at that, but he seemed satisfied that that was okay anyway, but may want to clarify that, but I didn't hear any other reservation about the stroke endpoint. There is a vigorous debate about what you should do about death, and we obviously have all heard that, and we will have to be imaginative, which since we are bureaucrats, is difficult, but we are going to work on it.

DR. GILMAN: To summarize, it appears that 10 members agree that this drug has been shown to effective in stroke, and 3 believe that it should be labeled as helpful for preventing death or the combined stroke/death

combination. Only 3 believe that.

Do you want anything further on No. 2? Have we done enough? We have done 2.

No. 3. Would you recommend approval for the requested indication? I believe the answer is yes--no, sorry. It is late in the day. The answer to that is no.

DR. KATZ: I think the next two questions sort of complicate things. I think they are basically equivalent to what you have already voted on, unless you thought there was a safety problem, which is the last question, but if you don't think there is a safety problem, I think you have given us your view on the matter of approvability.

DR. GILMAN: Thank you. Let's just skip down to 5, and I don't believe there are safety issues of particular concern, are there, members of the committee?

[No response.]

DR. GILMAN: All right. I believe we are done. I can't believe it, but we are done.

[Whereupon, at 4:50 p.m., the proceedings were 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