would have made a decision to stop the trial on the basis of excess of adverse events.

DR. GILMAN: But again, how would you determine what was excess?

DR. PATHY: That really wasn't the role of the MMAG.

DR. HAEHL: The definition of excess, in order to decide whether the trial should continue was limited to the interim analysis. The safety information, the yearly safety information to the ethics committee was given in its totality to compare what was reasonable as an overall incidence, and then the ethics committees would intervene or not, and they did not.

DR. GILMAN: But, again, how do they determine what was reasonable?

DR. HAEHL: We, as the company, did not propose to them when they should intervene or not.

DR. GILMAN: There are a number of questions. So, Dr. Brooke had his hand up first, then, Dr. Califf, then, Dr. Grotta, then, Dr. Katz.

DR. BROOKE: I want to be absolutely clear that I understand this. A variable that was being used as an endpoint was also being used as a safety assessment?

DR. GILMAN: Could we hear a response?

DR. HAEHL: The incidence of the endpoint stroke

at the predefined interim analysis was used in a randomly allocated treatment group design to decide whether the study could continue or not.

DR. BROOKE: I don't want to be aggressive about this, but is it true, then, that a variable that you had planned on using as an endpoint was also used in an analysis of safety? Is it yes or no?

DR. HAEHL: The answer is yes.

DR. CALIFF: I am not saying this is easy, and I am not actually sure how to deal with it, this is a common problem, but my understanding then of what happened was that you had an ethical committee that was reviewing for safety on a regular basis, looking at the primary endpoint, admittedly not knowing which group was which, but with the option if they were concerned about something for unblinding and doing something, and that is not being called an interim analysis every time they looked, is that correct?

DR. STREET: That is correct, because there was the one decision point built into the protocol based--

DR. CALIFF: That was a built-in decision point, but every year when they looked, if they had been concerned, I guess the question I would raise as a matter of policy is if there is only place to make a decision, why would you look at the other times if you are saying there is no way they could make a decision based on that data.

DR. HAEHL: As we do in any of our large trials, that we inform the ethics committee about the conduct of the trial, and we would expect the ethics committees, both individually in the centers, but also if we have a central ethics committee, to interfere with the trial if they don't feel confident with the safety of the trial anymore.

It is I would say standard procedure, and as a matter of fact, in Europe, it is requested by the ethics committee that you inform them on a yearly basis.

DR. CALIFF: That may be another point to come back to among the committee and maybe with Bob Temple's help, but this is a major issue of multiple looking and including the primary endpoint in the safety, and I don't know how to deal with that.

DR. GILMAN: Dr. Grotta.

DR. GROTTA: Well, I mean I could understand if your safety is looking at death, and death is combined in your endpoint, and even strokes, that the safety committee needs to look at it. I guess what is bothering me is whether the company was aware of these differences among the groups, as well.

So, maybe you could clarify a little bit about how much information about group differences on these important endpoints, namely, death and stroke, was known outside the ethics committee and by whom.

DR. HAEHL: Dr. Bertrand, he has referred to the company and even not the statistician didn't know the treatment allocation for the safety updates.

DR. GILMAN: That didn't answer the question.

DR. GROTTA: Were you aware of the group differences?

DR. GILMAN: In other words, were you notified about the number of deaths and the number of strokes in these groups?

DR. GROTTA: In the different group, even though you didn't know the group identifications, the safety committee didn't know the identification of the groups either, they just knew that Groups A, B, C, and D had different rates of death or stroke.

So, my question is who besides the ethics committee or safety committee in the company knew that information?

DR. BERTRAND-HARDY: Yes. The answer yes, we were informed about the number of events in a group. I mean the person working in the study.

DR. GILMAN: That still didn't answer the question. The question was who in the company knew about the results of the ethics committees.

DR. BERTRAND-HARDY: Just the person involved in the studies, that means the little group working in

Brussels, and the ethics committee, and that's it, no more persons.

DR. GILMAN: Which little group in Brussels?

DR. BERTRAND-HARDY: I mean what we call the TSU, called the technical support. That mean myself and three other physicians, and, of course, the statistician, and the members of the coordinating committee.

DR. GILMAN: Dr. Katz, I think was next, then, Dr. Drachman.

DR. KATZ: I guess maybe the fundamental question we are sort of dancing around is--and we should ask the statisticians this question--does the fact that they were looking periodically under the rubric of safety at an efficacy endpoint, even though there were no formal stopping rules, the way there was for the one formal interim analysis for death and stroke, should we be concerned that the testing at .05 at the end of the study inflates the Type I error, the sort of thing that we usually worry about?

I mean does this maneuver affect how we ought to think about the results? I think this cuts right to the chase.

The concern is because the ethics committee on these safety analyses is blinded to the treatment group, and they are making assessments on death, on stroke, and on bleeding based on whether there appear to be extreme

differences, they don't know what the nature of that difference is, for all they know it can be higher in the placebo group than in the active treatment group, so they don't know it.

But I think if I understand the issues correctly, it surrounds the fact that the study went on for three years, so there were like three safety looks and one efficacy look, and under the sort of if you follow the Peto Haybittle rules, which it appears they did, with a p-value of .001 or more extreme for stopping, then, I think that my own view of this methodologically would be that there would be no necessity to adjust p-values at the end for multiple looks.

If this had been like a 8 or 10-year study, it would be a different story. So, it may be a tempest in a teapot from the perspective of statistical adjustment, and it certainly seems, in terms of knowledge of the outcome because of the safety monitorings, nobody knew which treatment group was which.

DR. GILMAN: Let's stick with the same point for a moment.

Dr. Grotta.

DR. GROTTA: What we are going to hear about in a moment is that the sample size was increased during the study from the original number by over 1,000 or more

additional patients, so decisions were made during the conduct of the study, and I guess the question then comes up is were those decisions influenced by the group differences and the magnitude of group differences that were being seen during the course of the study.

I suppose if no changes had been made in the study, it would be a little easier to accept the fact that group differences in the endpoints were known by the statisticians.

DR. STREET: It is quite correct. They did re-estimate the sample size, and the group rates were used to rerun the simulation program that had been originally used to design the study, and instead of a 35 percent reduction between the best and the worst treatments, and with the assumption of the other treatments being halfway between, they found a 20 to 25 percent difference between the best and worst treatments at the interim analysis.

They plugged those rates into the computer program without knowledge of which treatment group was which, but simply on the overall test of homogeneity of these treatments, and that was the principle.

After this was done, and it was also done in another fashion, again still blind to the exact identity of the groups, the statistician concluded that 7,000 patients would be required or 1,750 per group.

His recommendation to the steering committee following the interim analysis in November of '91, the steering committee acted on that and said they agreed with it.

Later, in March of the next year, this was presented to the ethics committee, and the ethics committee reviewed the existing data on aspirin. Again, from the meta-analyses, they concluded that the efficacy of aspirin in stroke and TIA patients had not been adequately proven. They agreed to continue the trial as originally constituted, and agreed at that time to increase the sample size to 7,000 patients per recommendation of the statistician.

DR. GILMAN: Dr. Drachman had a question next.

DR. GROTTA: This is just in response to that response.

So, therefore, this really turned out to be a demonstration more than an experiment, and that you found a difference, and then you adjusted your sample size to show that that difference really was true.

I guess I need to know is there precedent in clinical trial design, an accepted clinical trial design, to adjust your sample size mid-trial, knowing that your differences weren't as great as you had initially hypothesized them to be as opposed to starting over again with a larger sample size.

DR. HAEHL: When we initiated ESPS-2, the situation was such that we had no information other than speculation what the contribution of dipyridamole in this four-arm setting would be, what the contribution of low-dose aspirin would be, and therefore, any assumption for sample size calculations were based on speculation.

And because this was the case, the statistician included in the protocol a planned interim analysis in order to prevent--that we are performing a trial which involves a large number of patients and exposes them to medication, however, because based on wrong assumptions, non-established assumptions, fails, just fails to show a true benefit.

I think that was the rationale for us how this trial was designed, and therefore, the interim analysis had to be in. The other consequence would be that we would have potentially discontinued the trial just falling short of showing an existing benefit, and we would not have the results as we have them on the table today.

DR. GILMAN: I think Dr. Grotta's question perhaps ought to be addressed by Dr. Katz, Dr. Temple, or both.

DR. KATZ: No, I mean you have just said that the plan to reestimate the sample size was prospectively designated in your plan for the interim analysis. That may be, and that is all well and good.

The question is, is it an appropriate thing to do.

The fact that it is prospective doesn't automatically make it so. So, I would ask the statistician, Dr. Van Belle, how you feel about what increasing the sample size on the basis of a look, which is blinded to some extent, but you do know A, B, C, D, and as Dr. Grotto suggests, that you could guess, for example, that the difference in Group C, if that had the largest difference compared to some other group, might have been the treatment you were interested in, the combination.

What does this maneuver do under these circumstances to the Type I error at the end?

DR. VAN BELLE: Let me make several comments. One is the issue of whether there was one interim analysis or more. I think that is really one of the key issues here.

I get the impression, and this is the impression that the ethics committee had its own rules for looking at the data without any kind of an interim analysis. I would think that if there had been an extreme imbalance, whatever that might mean, that they might have asked for an unblinding of the data, but as far as I can tell and from what I have heard today--and maybe the company can also explicate that--it seems that the ethics committee did not explicit rules for when to stop the trial or when to ask for unblinding, so that is one issue.

The other issue is the one that is raised now,

what about the interim analysis affecting the sample size. I think I have seen that done more than once, and it would affect the p-value undoubtedly in some sense, but I would not know how to actually model that. I think it is a very complicated question, and I don't think it is very fruitful either.

I think I would just take the added sample size as being reasonable and particularly in view of the results, I am not too concerned about that aspect. I am more concerned about endpoints, whether they were prespecified or not, and also I am concerned about the number of interim analyses that were actually done, and I get the impression that there was only one.

DR. KATZ: Can I have a follow-up question?

DR. GILMAN: All right, please.

DR. KATZ: As far as the first point you addressed, what increasing the sample size on the basis of this interim analysis does to the p-value, it might be fairly important in the analysis of this trial, because there is some question as to whether or not even the nominal p-value for the comparison of the combination of the components is significant by the usual rules.

I mean obviously we will get to that, but the point is if it does do something to the p-value, and we can't quantitate what it does, it might actually I think be

fairly--at least where they got the combined endpoint of mortality and stroke.

DR. VAN BELLE: I don't know. My impression would be that under any reasonable scenario, the effect on the p-value would be reasonably small.

DR. GILMAN: I would like to stick with this question for a moment. Dr. Temple, can you comment?

DR. TEMPLE: Well, it almost has to be relatively modest. Even a full Bonferoni, which would be very conservative in this case, would only double it.

My impression is that Gordon Land actually has looked at this question fairly recently and has published on this very question, because there is naturally a desire to expand the population sometimes.

I don't know those data--there may be people in the room who do--but the conclusion was that the correction is real but modest, fairly small for expanding it. Obviously, it isn't a whole separate study, most of the data are already locked in, so how much impact could it have.

We may need to look into that, but I believe it has been actually addressed, probably with modeling.

DR. GILMAN: When you say real but small, can you give us an order of magnitude?

DR. TEMPLE: Well, the most conservative thing you could do is say I have got two studies here, and if you did

that, you would say the nominal p-value has to be doubled. That is a Bonferoni. Well, that is obviously absurdly overconservative, because 80 percent of the data are already locked in, so they are not independent. So, it has to be considerably smaller than that, but I am well beyond my limits.

DR. HENNEKENS: If I may make a comment, I agree with Bob that Gordon Land and Dave DeMets are publishing on the small corrections that one can make at the end, however, it is not uniformly agreed upon in clinical trials. Peto's position is quite the opposite, that says that if you have an extreme enough p-value to start with in terms of safety and efficacy monitoring with one look at year for several years, there is absolutely no need to make any correction.

Having said that, as a chair of several data monitoring boards, we routinely in the middle give advice to the investigators about whether to increase the sample size or not, and we have not taken the view that the p-value needs to be corrected based on those interim looks, because then it becomes a catch-22, because what is the net gain if, in fact, you are telling them they have to correct for something, they have to get an even result.

But there is a big philosophical debate between Land and DeMets and Peto on this issue, but I think Bob's point is the most important one, that even if you did it,

the correction would be quite small.

DR. GILMAN: Dr. Drachman.

DR. DRACHMAN: I think you may have answered this, but maybe you would clarify. The ethics committee knew membership in groups, but did not know which group was which or did not know who belonged in which group?

In other words, they were told that these patients are Group A, but we don't know what drug it is, or they were just given all the patients without any assignment by group, which was it?

DR. GILMAN: I believe he said it was by group.

DR. BERTRAND-HARDY: By group.

DR. DRACHMAN: They knew the groups, but they didn't know what the drug was?

DR. BERTRAND-HARDY: They knew the groups. I mean they knew it was Group A, B, C, or D, they knew that.

DR. STREET: It needs to be pointed out that those A, B, C, and D were not uniformly applied across each event. They were randomly permuted in every table, so they were simply nominal levels, but you could not correlate from adverse events back to efficacy events using this.

In fact, I gave the study report to a statistician, I said can you decode this, and he said no. I said can you tell from the adverse events what the efficacy groups are, he said no, so I tested it myself.

So, this random permutation preserved the blindness to that degree, but they were grouped with nominal levels.

DR. GILMAN: The end results were stroke or death. Why could that not be done? If you have A, B, C, D groups, you know there are two deaths in A, three deaths in B, four deaths in C, five deaths in D, you can assume that you are looking at some endpoints, right? And therefore, you are looking at efficacy, as well as adverse events.

DR. HAEHL: In this respect, it is true.

DR. STREET: That is, of course, true, but you don't know which of the treatment groups. That's all we have.

DR. GILMAN: I understand. The point remains that the examination of safety also deals with the endpoint of the study.

DR. HAEHL: In a study like this, it does.

DR. GILMAN: Dr. Brooke.

DR. BROOKE: When one is wrestling with a problem, I was once taught that you put it in language that your grandmother can understand, and I have a question here, because I work in a lab, as well as in a clinic, and sometimes I have an experiment which I know should come out the way I want it to come out, and then my lab tech comes to me and says it is not working the way you wanted it to work,

and I say, well, put it back in the refrigerator until it does.

This change in number that is the result of an analysis, does that come under the same heading like the study isn't going quite the way we want it to, let's increase the numbers, because if that is in fact true, that is a bit of a problem.

DR. GILMAN: Is there a grandmother in the room? I mean can we hear a response from the company perhaps, the sponsor.

DR. HAEHL: My answer would only be that is a hard endpoint which we would not have impact on just by, to stay in your picture, to put it back in the refrigerator, and as we have mentioned, the majority of the data was locked, so it was the extension in order to get the power for a true result, but I don't think that the study and the measures here are able to change direction and influence the direction.

Dr. Easton, you wanted to comment on that.

DR. GILMAN: Stick with this point for a moment.

DR. EASTON: I was struggling with what you are struggling with and thinking that in the Canadian and American ticlopidine study, the trial was extended by adding additional months on to the trial on the recommendation of the DSMB. In the CAPRIE trial with clopidogrel recently, it

started out at 15,000 patients, and it ended up at 19,000 patients based on a look at the blinded overall group event rate that was going on in the trial and adjusted upward.

So, certainly, those adjustments take place regularly.

DR. GILMAN: Let's stick with this point. Do you want to comment on this point, Dr. Califf?

DR. CALIFF: Yes. I mean Dr. Easton just made the point I was going to make. I mean there is a methodology to do this that has been pretty well worked out based on either control group event rates or blended event rates prospectively planned.

I sort of agree and disagree with Dr. Hennekens, that the penalty, if there is one, and having sat through a number of debates about this meaning specifically devoted to this topic, the penalty is not huge for doing this, and probably will not have a major impact on the interpretation of this particular data set, but as a matter of policy, I think there is almost unanimous agreement that this is bad policy to continue your experiment having looked at the results part of the way and then adjusting the size of the experiment to confirm a result that you have already seen. It is not good methodology.

DR. GILMAN: Dr. Temple, will you address that question?

DR. TEMPLE: I don't agree with that. I don't think that is true any more than taking interim looks is true. These changes can introduce some bias, and it is all about multiplicity. These are all variations of having multiple endpoints, multiple looks, multiple subsets. It is the same conceptual problem, and it is not that it is evil, it's that you may have to make some correction and adjust the alpha level.

As Rob says it is perfectly true if you do it without breaking the code in any way, so that you are just looking at total events, the correction is very small. I used to think it was none, but I am told by statisticians that there is a very slight one, and that is the cleanest, but it is not as efficient.

So, if you want to make another one, you can do it, but you have to pay what the appropriate price is.

DR. CALIFF: But since we don't know the price, this could be like a scud missile, you are getting closer and closer, and you keep redesigning and redesigning, and eventually, you have engineered the experiment to get the result you want.

DR. TEMPLE: But you can't really do that. I mean if you have 8,000 people, they don't go away when you add another 1,000. You can't make it come out the way you want, but you do increase the possibility that you will have a

favorable outcome when there shouldn't have been one, and you can correct for that.

I believe there is a recent--I probably wouldn't understand it anyway--but I believe there is a recent analysis of this by Gordon Land that suggests what the nature of the correction might be, and one would have to do that, I think. I don't agree with Charley, I think you do have to consider the correction.

DR. GILMAN: Can you address that point?

DR. HENNEKENS: Yes, I would like to address that point. You know, theoretical speculations are out there, but the p-values here for the combination versus placebo is less than 0.001 on stroke. For the combination versus aspirin it is 0.006. For the combination versus dipyridamole it is 0.002.

So, while I take the point that there is this debate about whether or not to do so, with the robustness of these p-values, I really think it would be unfortunate if this trial, we are giving the impression that, well, gee, I don't know about this because if you make a correction, you are going to get a qualitatively different answer.

You will not. These are quite robust findings for the combination versus placebo, aspirin, or dipyridamole on stroke.

DR. GILMAN: Dr. Grotta.

DR. GROTTA: Just a question and then a comment. So, the possible increase in sample size at the interim analysis was prespecified. I mean when the study was designed, it was recognized that at the interim analysis, some increase in sample size might occur based on the data?

DR. HAEHL: No.

DR. GROTTA: It was not?

DR. HAEHL: No, the sample, that the trial should be reassessed, that is the formulation. At that time, in the protocol, there was no specification by what means the trial would be influenced.

The primary aspect was to discontinue should the results go to the extreme. The other option that was seen by the statistician was to adopt a sample size for the outcome.

If I may, I would like to add an information which you will see later, is that because of this issue, the first 5,000 patients which were included in that have been analyzed separately, and just to anticipate, the result is the same as for the totality of the patients. So, this is an additional step in addition to correcting for p-values to ensure the homogeneity of the two populations.

DR. GROTTA: Well, my comment is that, you know, I am a pragmatist, and so I think that we do need to make clinical trial execution somewhat flexible as long as we

don't violate basic principles, so I mean this notion of increasing sample size doesn't really bother me that much, but I just think we need to be crystal-clear and have it read it into the record that if this drug is approved, that the precedent has been set, that in the course of a trial, particularly if it is prespecified on the basis of an interim analysis that it is valid to increase the sample size to be more certain of the endpoint.

DR. GILMAN: May I just ask you to clarify, prospectively, when did you plan to do your one interim analysis, and what did you plan to be the outcome of that analysis?

DR. HAEHL: The interim analysis was planned with the protocol, and the outcome of the interim analysis was to consider the further conduct of the trial in both directions.

The primary idea was to discontinue the trial early should there be excessive or unexpected efficacy.

DR. GILMAN: And if there were inadequate power, then?

DR. HAEHL: And the statistician at that time--and I think we have also to consider that this trial was not initiated today, and the protocol was not written today, under today's guidelines and rules--and the statistician interpreted this, that he would also be requested to

consider the power of the trial and the adequate sample size because when he did the sample size calculation at the beginning, he was left with assumptions which were not established in literature in the prior experience.

DR. GILMAN: Was it planned for an interim analysis when you accumulated 5,000 patients?

DR. HAEHL: What was the exact definition, when we accumulate 5,000 patients or was it after a certain time period?

DR. BERTRAND-HARDY: That was when we accumulate at least 1,600 patients followed for at least two years or 3,000 patients followed for any time.

DR. GILMAN: Then, why did you, in fact, carry out this interim analysis with 5,000 patients?

DR. BERTRAND-HARDY: A little bit more. There were 4,000 patients included in the interim analysis.

DR. GILMAN: I thought it was 5,000.

DR. HAEHL: I think we have to clarify. When I mentioned the 5,000 patients, it was after the trial was concluded in order to see the impact of the increase of the sample size, an analysis was performed, not only on the total patient population, but also on the first 5,000 patients in order to reflect the original sample size.

DR. STREET: In fact, the sample size--

DR. GILMAN: Wait a minute now. Wait a minute

now. So, you did two interim analyses then.

DR. HAEHL: No.

DR. GILMAN: No, you did one.

DR. HAEHL: Then the trial was concluded, and the complete analysis was done. The question came up what is the impact of increasing the sample size, and above all the things that have been discussed here, we addressed this question by looking into the effects of the first 5,000 patients recruited into the trial as a subgroup.

So, that is an analysis for robustness if you want, and that was performed.

DR. KATZ: The 5,000 comes in because that was the original protocol specified for the trial.

DR. HAEHL: Yes, yes, we wanted to post hoc mimic the situation had we continued the trial as it was planned in the very beginning without interim analysis and without the consequence of the interim analysis.

DR. GILMAN: Thank you. That clarifies that situation. It wasn't clear from the books.

Dr. Drachman.

DR. DRACHMAN: Would you show us the data both at the time of the interim analysis right then and with the 5,000? Let's see what you have got.

DR. STREET: I don't know that we have the slides prepared for the interim analysis, which I want to remind

you it was performed with 3,994 patients on an average of 12 months follow up, many who had not even reached two years, and so when the trial was continued, we found, as you have seen, increasing benefits over time between the two treatment groups. So, I think that is why it appeared somewhat that the effects were smaller than they were in the final analysis.

So, I do not have that, but I was going through in the course of this, if we could jump ahead, please, to one of the robustness analysis slides.

DR. GILMAN: If you can't show that, can you show a comparison between the 5,000 and the 7,000?

DR. STREET: Yes, that is what I am getting here.

DR. KATZ: Which outcome did you look at in the interim analysis as being primary, or was there one that was primary?

[Slide.]

DR. STREET: In the interim analysis, they viewed the composite endpoint of stroke or death at the interim analysis.

DR. KATZ: That was prospectively?

DR. STREET: Well, to get the history of that, when you read the protocol--let's go back to the original wording of protocol, because there seems to be a bit of confusion on this, and one needs to set the record straight.

The stopping rule was clearly specified. That is the 0.001. That is for a global test of homogeneity between the four treatment groups, and that was going to be done by the statistician on the endpoint of stroke or death.

There was also a provision which was broadly worded, that said the interim analysis might be the basis for a new assessment of the rationale of the trial by the steering committee.

Now, that doesn't say anything specifically about an increase in sample size, however, the minutes to the steering committee meeting, which took place in 1990, I think in October of 1990 or thereabouts, a year before the interim analysis, do mention that this sample size would be increased--I am sorry, not increased--that it would reevaluated. That is the first explicit mention of sample size increase, and that was one year prior to the actual analysis.

So, that is the record, and it is true what you are saying that adjustments are very difficult to provide when you don't have a clearly specified rule. In fact, in frequenter statistics, you really can't make that adjustment, but in making any reasonable assumptions, you know that the impact is small, and the bottom line is really over here in the first 5,002.

We were very fortunate that these results--up here

you see the planned primary efficacy analyses for stroke. I am concentrating on stroke, which is where we have efficacy.

The primary analysis, the main effects which we had prespecified and were planned in the protocol, 0.001, less than 0.001 for aspirin.

When we come to the comparisons of Aggrenox versus its components and versus placebo, we will see a 0.002, a 0.008, and frankly, one, 10^{-6}, one in a million here for Aggrenox versus placebo.

We come down to the first 5,0002, and here we have the same level of significance, comparable anyway, across all the most important comparisons in the trial, so all I can say is it would have succeeded on the original plan.

It also succeeded even more on the final plan because many other endpoints could be investigated adequately. So, I believe that is a direct pragmatic answer to a thorny technical question.

DR. GILMAN: Dr. Robie-Suh.

DR. ROBIE-SUH: I had wanted to ask about the interim analysis when the sample size was increased. What were investigators told, if anything? Did they know that the sample size had been increased or were they just continuing until someone told them to stop?

I guess sometimes one thing that I think about in increasing sample size is the penalty shouldn't be a whole

lot if the patient population and all the other things sort of stay the same and we just go along, but, you know, people are kind of curious, investigators.

DR. STREET: I have no knowledge of that. I know that the basic decisions were taken by the steering committee and by the ethics committee.

DR. HAEHL: I remember that the decision was taken, and the decision to increase the sample size was, of course, communicated to the participating investigators.

DR. GILMAN: Did that answer your question?

DR. ROBIE-SUH: Was any reason given to them?

DR. HAEHL: Yes, the reason was given that the sample size, as calculated, or that the previous sample size would not be adequate.

DR. GILMAN: But it proved to be adequate.

DR. HAEHL: It proved, but as Dr. Street has mentioned, the interim analysis, of course, didn't have the complete data as we have at the 5,000 patient level right now.

DR. STREET: It has approximately 4,000 patient years of follow-up at that time, and in totality, we ended up with 13,000.

DR. GILMAN: Dr. Konstam had a question.

DR. KONSTAM: I just wanted to make sure I understood something that you had said a moment ago, when

you said that at the interim look it was prestated that the primary analysis would be stroke or death.

DR. STREET: Number one, that is correct.

DR. KONSTAM: Is it stroke or death, or stroke or death? In other words, did the define the combined endpoint as the thing that they were looking at?

DR. STREET: The statistician viewed it as the composite endpoint of stroke or death.

DR. KONSTAM: This was defined in the protocol?

DR. STREET: It is clearly indicated in the statistical appendix.

DR. HAEHL: To be very clear, in the protocol, the endpoint, the primary endpoints are stroke firstoff, second primary endpoint, death. In the analysis plan--

DR. KONSTAM: The primary endpoint was stroke, do I understand?

DR. HAEHL: No, we had two primary endpoints.

DR. KONSTAM: Two primary endpoints.

DR. HAEHL: Yes, the two I mentioned.

DR. KONSTAM: What are the two?

DR. HAEHL: Stroke and death.

DR. KONSTAM: Death.

DR. HAEHL: And in the analysis plan, the statistician included the combined endpoint, and that is probably not up to date, but that is how--

DR. KONSTAM: Was it planned to share the alpha between these two primary endpoints?

DR. HAEHL: I can't answer you about alpha, I have to get assistance.

DR. STREET: No, it was not planned in the protocol to split the alpha, but when we took our proposal to FDA at a pre-NDA meeting in August '97, we took our full analysis plans down there, and we proposed a Bonferoni home adjustment for the two planned primary endpoints of stroke and death, and we also adjusted per request of the statistician for the 0.001 interim analysis that was spent, the 0.001 that was spent.

So, no, the protocol did not specify, but we had, we felt, in our composite review of these data, we wanted to bring it up the standards as best we could of how it would be viewed today.

DR. GILMAN: Dr. Drachman.

DR. DRACHMAN: Had you looked at stroke alone at the interim, would it have made it then? In other words, you now show us your stroke data for 5,000. What was it like when you did the interim analysis?

DR. HAEHL: I am sorry, we don't have the data right here. If that is necessary, we have to get it.

DR. GILMAN: Could you get that today or is that not possible?

DR. HAEHL: I would have to consult and tell you later whether we can get it today.

DR. GILMAN: Thank you.

Dr. Temple.

DR. TEMPLE: If I remember the slide you showed, and if you applied sort of ordinary O'Brian-Fleming rules, it probably would not be make it. It was very encouraging, I imagine, but it wouldn't have made a 0.001 value. That is for a three look, though, isn't it.

DR. HENNEKENS: It is exactly right, it does not achieve a stopping boundary with 4,000 person years of observation, and even if the effect size, as large as it is at the end, it doesn't make a 3-standard deviation.

DR. TEMPLE: I should say as an aside, when anybody comes to us, we strongly urge that nobody stop trials for endpoints that can change. Death doesn't change, that is a good endpoint, but stroke can be re-evaluated, and endpoints committee can say something different, so we discourage doing that unless there is a perceived ethical compulsion to go ahead and do it, but it can lead to trouble.

DR. HENNEKENS: And actually just speaking on the stopping rule, as chair of a number of data monitoring boards, we routinely review the data and give advice to the investigators about whether to keep the study going or not.

We don't expect that they need to adjust anything, but we are not giving them any information about what we are saying in the deltas. We are talking about event rates in the placebo, either achieving or not achieving the expectations.

So, it is quite common to extend the trial and increase the sample size, and not have to spend anything at the end of the study about it. I think the thorny issue comes when you are looking at the comparison at the time and then making that--and it is not clear whether that was going on here given the fact that everyone was blinded.

As I understand it, if treatment A was the combination for stroke, it might not have been, treatment C might have been the combination for death. So, it was very hard to unravel this.

DR. GILMAN: Dr. Konstam.

DR. KONSTAM: I understand this debate about how many looks there were and was there one, so let me just ask, in terms of the safety looks, how many of these safety looks were there that took place?

DR. GILMAN: I think it was one a year, wasn't it?

DR. HAEHL: How many safety, was it three or four?

DR. BERTRAND-HARDY: Four.

DR. HAEHL: Four.

DR. KONSTAM: I think one of the things that would

be useful for us internally or among the statisticians to ask let's take the worst case, which is that these safety looks actually were interim looks of some sort, what would be the penalty and what would we wind up with.

My own suspicion is it won't kill it, but I think it would be worthwhile really asking that question.

DR. VAN BELLE: If they had stuck to what was specified in the protocol that they would work at the 0.001 level of significance, so basically, the expenditure--you are worried about the Type I error, namely, accepting effectiveness when there is none, that is really what we are looking and that is what we are worried about.

So, my judgment is that that would have been a minimal effect.

DR. GILMAN: Any other questions? Should we let Dr. Street continue? Please, go ahead.

DR. STREET: I will go on to the next concern, which you have already expressed, and that is what are the primary efficacy endpoints.

[Slide.]

Again, I think the best approach is to quote directly from the protocol where the record is unambiguous. There will be two primary efficacy endpoints: one, strokes; and two, total mortality.

These were to be the strokes confirmed by the

MMAG, that is, the Morbidity and Mortality Assessment Group, and all-cause mortality. The MMAG, however, though blind to treatment, they did assess the cause of death as one of their functions, but still our analysis will be based on all-cause mortality.

[Slide.]

In addition, there were four secondary efficacy endpoints.

DR. GROTTA: Can I interrupt and ask a question?

DR. STREET: Yes.

DR. GROTTA: This is an important point to those neurologists among us who do clinical trials. What information did the group, MMAG, have on which to base this judgment? How much evaluation was done by a local neurologist? How certain can we be of this primary endpoint stroke that you are resting your claim on?

DR. HAEHL: That is an ideal question for Dr. Pathy, I think, as chairman of the MMAG.

Would you like to comment, and we have a slide for that on the basis of what?

DR. PATHY: Yes, we have a slide.

[Slide.]

This just summarizes what the MMAG saw as its key areas of concern

Could I go to the next slide, please.

[Slide.]

These give the causes of death, but it is the next slide I need really.

[Slide.]

Yes. The MMAG, of course, was supplied with all the Trialist data, supplied with CT scan or MRI scan information if that were done, supplied with all the clinical background data, was supplied with all investigational data which would include ECGs and echocardiograms were they done. ECGs were invariably done, of course.

We made certain definitions about stroke having come to the conclusion the patient had a stroke, so anyone dying, as I mentioned earlier, within 30 days following endpoint stroke, we wrote the cause of death as stroke in the same way as anyone dying of a myocardial infarction within 30 days of that infarction, we designated the cause of death as myocardial infarction whatever may have been a symptom, such as cardiac failure, and the same for stroke. Even though the person may have developed an interim chest infection, we did not call the cause of death a chest infection, but a stroke if the patient died within 30 days.

DR. GROTTA: I am sorry to belabor this point, but that just doesn't quite cut it for me. I mean the main effect of the drug is on nonfatal stroke.

DR. PATHY: Yes.

DR. GROTTA: So, convince me that the nonfatal strokes that were called nonfatal strokes really were nonfatal strokes.

I realize the study was carried out in Europe, probably not all these patients were seen by a neurologist. Was there a standard neurological examination at least that had to be carried out in everybody that was called a stroke, so that the central adjudicating committee had a neurological examination to go by?

What was required to call somebody a nonfatal stroke?

DR. PATHY: Thank you. Yes, we had to have the detailed neurological assessment of those patients before al members of the MMAG had to unanimously agree that this was a stroke. There were three neurologists on the MMAG, and it required unanimity among them on the basis of the clinical data, the neurological data often amplified with, of course, a CT scan or an MRI.

DR. GROTTA: Sometime before the end of the day, would it be possible to produce the case report form that had to be filled out on an endpoint stroke for me to look at?

DR. PATHY: I think we could get hold of that.

DR. GILMAN: Just to amplify one of Dr. Grotta's

questions, was it a neurologist who saw the patient and collected the clinical data or what sort of physician would that have been?

DR. PATHY: No, it would often be a general physician, by no means always a neurologist.

DR. KONSTAM: Maybe this requires a cardiologist to ask this question. Do you have set criteria? In other words, you said unanimity of agreement among three neurologists, but were there prespecified criteria or some sort as to what defines a stroke? Do we have them for MIs, for example?

DR. PATHY: Yes. Obviously, it depended. We divided them between TIAs and strokes. We wrote definitions much more precisely for TIAs because we found that this is where there was a greater degree of controversy, about strokes defined as an acute neurological deficit lasting for more than 24 hours.

DR. GILMAN: Did you require that there be a physical sign of the deficit or would a symptom alone suffice?

DR. PATHY: No.

DR. GILMAN: For example, if numbness occurred on one side of the body, but no neurological abnormalities could be found on examination, would that qualify?

DR. PATHY: If the person had an acute homonomous

hemianopia, but then there would be physical signs, but that would qualify.

DR. GILMAN: That's not my question. That would be a physical sign.

DR. PATHY: Yes.

DR. GILMAN: My question is, if a patient had a symptom, but had a normal examination, and the symptom continued for days, would you consider that to be a stroke?

DR. PATHY: No, they had to have positive clinical findings.

DR. GILMAN: Thank you.

Dr. Katz.

DR KATZ: When were these determinations made by the committee, after all the data were in at the end of the trial, or were they made in real time?

DR. PATHY: Yes, the MMAG met about three times a year, therefore, there may be a longer or shorter interval between reviewing the Trialist data depending how near the death or the stroke, the endpoint was to the meeting, but we met regularly approximately three times a year.

DR. KONSTAM: Did the committee principally have a confirmatory function? I guess the question, would there be ever a circumstance where you would identify or define a stroke that was not categorized by the investigator as a stroke, would that ever happen?

DR. PATHY: Yes, it would particularly in terms of TIAs.

DR. KONSTAM: In other words, they were called TIA by the investigator, and you reclassified as a stroke?

DR. PATHY: Yes, that's right.

DR. KONSTAM: Can you give us an idea of what percentage of the total strokes might fall into that category?

DR. PATHY: I can't off the cuff I am afraid.

DR. KONSTAM: Let me just follow then in that case. Did you keep track of investigator-defined strokes, was that something kept track of in the study, as well, or not?

DR. PATHY: We, of course, didn't know the investigator at the time that we arrived at a decision.

DR. KONSTAM: Maybe it's for the sponsor. Was there a designation by the investigator that there was a stroke that had occurred?

DR. STREET: Yes.

DR. KONSTAM: Which then was confirmed by the endpoint committee? If that is the case, I would just be curious to have a look at how the data look vis-a-vis the investigator-defined endpoint as opposed to the endpoint, committee endpoint. It would be worth looking at.

DR. STREET: Yes, we have that data.

DR. GILMAN: If you have those data, maybe you could show them to us.

DR. STREET: If we go back to the summary of robustness slide, please, this is a bottom-line look at it, but in addition to the MMAG-confirmed strokes, there were a number of others which we can easily retrieve the numbers that were rejected by the MMAG.

[Slide.]

We put them into a separate category here and analyzed to see what the results were from including all of the strokes without regard to MMAG, and based on the clinical diagnosis of the neurologists, we found exactly the same results.

DR. KONSTAM: I am curious the other way, too, in other words, strokes that were not considered strokes by the investigator, but were defined by the endpoint committee as a stroke. I would be interested in those events.

DR. STREET: I am not aware of that data.

DR. KONSTAM: The reason I bring it up is because I think there is the potential for those being softer events in my mind.

DR. STREET: The ones that went from TIA to stroke, you say?

DR. KONSTAM: Yes.

DR. STREET: I was not aware of those.

DR. GILMAN: Dr. Drachman.

DR. DRACHMAN: Really, just a brief comment. Whether or not the GPs were very reliable, this was blinded, wasn't it? Bad as the diagnoses were, they were equivalent on all sides.

DR. GILMAN: Dr. Katz.

DR. KATZ: Just to sort of nail this down as much as possible, since it seems to be the endpoint of most interest, if a patient who died met that endpoint, and the death certificate arrives at the MMAG because you were also looking at cause of death, and it said patient had had a stroke, would that patient have been called a stroke with no other additional information for the patient?

DR. HAEHL: Dr. Pathy.

DR. PATHY: We needed a good deal of information, for instance, if it was sudden death for which there was no cause known, and the Trialist had labeled it as stroke, we would disagree with that. We would just label it sudden death, and all sudden deaths, that is, deaths occurring within 24 hours from unknown cause, and they would then be in the analysis, would be regarded as a vascular death.

So, merely to have a death certificate without any confirmatory evidence, that is, somebody had identified by examination the appropriate neurological deficits, no, that wasn't accepted. It may also go under unknown if the was

completely absent, just a diagnosis was not an acceptable piece of information to reach a conclusion.

DR. GILMAN: Dr. Street, let's see if we can get through one more slide.

[Slide.]

DR. STREET: Now we come to the controversial four secondary endpoints, which are transient ischemic attacks, which were clinical diagnoses by the investigator, and generally not reviewed by MMAG, MI, which was reviewed by MMAG, other vascular events. All first other vascular events went to MMAG.

This was a composite of four endpoints. All of these were prespecified in the protocol. They consisted of pulmonary embolisms, deep vein thromboses, peripheral arterial occlusions, and retinal vascular accidents of which there were very few.

Finally, the protocol identified another composite endpoint called ischemic events, and this was stroke, MI, and sudden death.

[Slide.]

Now we come to the analyses, the types of analyses performed. I think we have already mentioned numerous robustness tests, which I will describe in a moment. These were designed to show that the efficacy results were not sensitive to various assumptions about the analysis or the

subgroups.

We took these analysis plans to FDA at a pre-NDA meeting, and confirmed these planned robustness tests, as well as our plans for exploratory subgroup analyses to check general consistency of results across numerous demographic and disease characteristics, some of which are listed here.

I just want to say generally, the subgroup analyses confirmed the primary efficacy of stroke, was consistent within limits of chance across most subgroups.

[Slide.]

The statistical analysis plans, I won't go into much detail here other than to say that these were conducted exactly as stated in the protocol. The primary analyses were conducted exactly as stated in the protocol, that is, two-year follow-up, intent-to-treat population, Gehan-Wilcox and survival analysis was chosen in the protocol in preference to log-ran, but the results are consistent for the log rank, and also the plan was to have a factorial analysis of these effects. I will say more about that in a minute, just so that we get the jargon straight.

I think I already said that last point.

[Slide.]

First, we have the factorial design. Now, the principal advantage of this design is its ability to evaluate the effects both of the individual components and

their combined effect in one experiment with fewer patients.

In statistical jargon, we have the main effects of each of the components, extended release dipyridamole and aspirin, and all this really means is you are going to be comparing the 3,300 patients who received dipyridamole with the 3,300 patients who didn't receive it. That constitutes the main effect of dipyridamole.

Similarly, we compare half the patients on aspirin with the other half not on aspirin. That doesn't complete the analysis, but it gives you, addresses two key questions that we had prespecified, do they each work, and finally, the interaction effect of the two drugs, and this is important because they may not be additive, they may be sub-additives or super-additive.

DR. GILMAN: Can we interrupt for a second? Dr. Van Belle has a question.

DR. STREET: Yes.

DR. VAN BELLE: The question I have is this, strictly speaking, a factorial design, and it is a little bit of a trick question because if I were a member of an HMO, I would say just give them dipyridamole plus aspirin, and you don't have to prescribe Aggrenox. That would be the interpretation of a strictly factorial design.

So, what is your response to this issue?

DR. STREET: Well, I would say extended release

dipyridamole. It proves that the effects are additive, and it is nothing but a combination of the two, a literal combination of the two ingredients, but you couldn't give them--

DR. GILMAN: I think the point is that extended release dipyridamole is not accepted or is not distributed here in this country.

DR. VAN BELLE: No, no, my point is much more simple. My point would be instead of giving people one drug, the Aggrenox, just give them dipyridamole plus a baby aspirin. That would be the interpretation of a strict factorial design.

DR. HAEHL: However, in the factorial design, it was not dipyridamole, but it was dipyridamole extended release.

DR. GILMAN: Assuming extended release were available, then, your point remains.

DR. STREET: It is truly the combination in one capsule.

DR. KONSTAM: I would like to understand this a little bit, and just have Dr. Van Belle or others comment on it, because I am not sure I understand.

I guess the issue with regard to a factorial design or what's the design, really relates to what kind of correction has to be made, if any, I mean to me the question

is what kind of correction is going to need to be made for the fact there are multiple cells.

Well, that is the question I am going to have. I mean to me, if you are doing a factorial design to ask two discrete questions, and there is no anticipated interaction between the two drugs, and you are not actually looking at four individual cells, but you are simply asking two questions across the population, it is sort of like two trials that don't have anything to do with one another, you are just doing them together.

In that circumstance, it seems to me I don't have any problem making no correction. This is a different scenario where there is interaction expected, and therefore what is going on in each of the individual cells is relevant, and in particular, you are looking at the combination and asking the specific question about the combination relative to the other cells.

So, I guess my question is, what, if anything, does all of that, how does all of that impact on your correction for multiple looks, multiple comparisons?

DR. VAN BELLE: I don't think there is any issue there. The test would be, first of all, a test of the overall effect, so basically, you would use it for the two main effects and the interaction, and that clearly was significant, so then you would go back and look at the

individual main effects.

That was not the point I was raising, I guess. The point I was raising, and it is somewhat of a technical point, but should the extended dipyridamole become available in this country--which it isn't I guess at this point--then, what would be the advantage of prescribing Aggrenox over dipyridamole plus one baby aspirin.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: There is never an advantage of using a fixed combination over the two components other than convenience. That is the only advantage there could ever be, and all this study can show really is that the two components each contribute to the claimed effect, and a person who read this and said, oh, I am going to take dipyridamole and a baby aspirin would be within their rights. As a company, they are hoping to gain something from marketing the combination, because it is convenient.

I do have one comment about what Marvin said. This involves a little history of the combination policy. The basic requirement to market a fixed combination is that you have to show that AB is better than A and AB is better than B, so that each of the two components has to contribute.

When you actually do that, not that we have ever allowed this, if you were making corrections, you would

actually conclude that testing at 0.05 is too conservative, because there is a multiplication of beta error. People have explained that to us, and we have said, well, that is interesting, but never mind.

So, we usually insist that each of those tests be positive at 0.05, but since you have to win on both, you don't really have to make a correction for multiple cells in the sense of preserving alpha, because you do have to win on both. You have to show that each component wins.

DR. KONSTAM: If that was the purpose of the study, I guess.

DR. TEMPLE: Let me continue because you are raising a very interesting question.

A factorial study historically is designed to evaluate the effect to see what aspirin does and see what dipyridamole does, so a classic factorial analysis doesn't do pairwise comparisons, it does aspirin groups and dipyridamole groups, but we have generally said, well, that's nice, but that doesn't make a combination because we don't care whether aspirin works alone, in fact, we already know it does, you really have to show that aspirin works when you add it to dipyridamole.

So, we emphasize the pairwise comparisons, which of course are always less robust than the factorial analysis, and, you know, they are presenting both, and they

have done both.

So, I am not sure what to make of the factorial analysis. It isn't strictly designed or directed at the combination policy, which shows that you have to make a contribution when you add to the other drug.

It may, however, help you believe in the overall observation, in other words, as appeared on an earlier slide, we have identified as something that makes one study more persuasive the fact that something works when you use if alone and when you add it to a combination. The example we gave was ISIS, but where aspirin and streptokinase worked alone against placebo, and also added to each other, and that was a kind of internal replication. So, one might think that something like that is going on here.

But the factorial study, the factorial analysis strictly doesn't really address the combination question, because it could be driven by the aspirin alone component and the dipyridamole alone component.

DR. HENNEKENS: Bob, but in the interest of sort of making an even playing field, they have got ESPS-1 that shows that the combination reduces the risk of stroke in patients with TIA and stroke, and the rejoinder to that is yes, but we don't know which of the components works.

It may be just aspirin alone, the dipyridamole studies are too small, they haven't showed anything, we want

to know that it is not only that both components work, but that the combination is better than both, and the only way to do this is a 2 x 2 factorial, and that was the state of knowledge.

DR. TEMPLE: There is nothing wrong with the study, the study is fine. The question is which analysis is the most telling, whether it is the factorial analysis, which draws from both, for example, dipyridamole versus placebo, and dipyridamole plus aspirin versus aspirin, and it gets part of its strength from something that is not relevant to the combination or not as relevant, namely, the comparison of dipyridamole with placebo.

So, it is the pairwise comparisons, that is, the combination versus A and the combination versus B, that is the most relevant to the combination policy. We have had these conversations for 30 years.

DR. HAEHL: And we will show you both.

DR. GILMAN: Well, now, we have made it through one slide, Dr. Street. Go ahead.

DR. STREET: I want to move back a slide. I haven't finished with this, no. I wanted to also say, of course, the design allows six pairwise comparisons of which we made five.

We took Aggrenox versus each component, we took Aggrenox versus placebo, and then we took dipyridamole and

patients who ceased treatment. Some continued treatment all the way through until month 24, some died while on treatment, and here are the percentages of patients in the aspirin/placebo groups, somewhat lower than the percentage who ceased treatment in the Aggrenox and extended release dipyridamole groups. So, we see a little higher treatment cessation here.

Dr. Rakowski will give a further discussion of these data later, but what I want to emphasize at this point is that just because they ceased treatment doesn't mean they weren't followed to the end, nor were they excluded from the analysis. Everything we did was intent-to-treat analysis, and we followed all patients to the best of our ability.

At the conclusion of the trial, there were 108 patients lost to follow-up for stroke and 44 for death. We then performed further follow-up of these patients, and we were able to reduce the numbers down to 28 lost to follow-up for stroke and 15 for death. So, we do have complete follow-up regardless of the treatment cessation rate.

[Slide.]

Now we come to the first result of the study and the primary result of the study, first graphically, and then analytically. This depicts the stroke-free survival over the two years, and we see that roughly 10 percent of patients had a stroke on the combination versus roughly 13

percent on the components. On placebo, we are down to about 16 percent strokes.

If you translate that into the number of patients who were spared a stroke per 1,000 treated over a two-year period, this comes out to be 59 spared on Aggrenox, 30 on aspirin, and 26 on dipyridamole. These are comparisons with placebo, so roughly 59 to 30, you are roughly sparing twice as many strokes on Aggrenox as on aspirin. This is just a rough view of it.

[Slide.]

Let's take a look at the primary factorial analysis. I call it primary because this is the per-protocol analysis. In the 3,300 on dipyridamole versus the 3,300 not, we have a 19 percent relative risk reduction, the p-value 0.001.

With aspirin, 21.2 percent consistent with what we have heard earlier, also even more significant at less than 0.001. For the interaction, we have virtually nothing, which is consistent with these being additive effects or each of the treatments makes an independent contribution to the combination, but let's look at that more specifically in terms of the pairwise comparisons on the next slide.

[Slide.]

Here, we have the ones that are clearly of greatest interest to this committee, and that is, Aggrenox

versus aspirin, Aggrenox versus extended release dipyridamole. Both of these showed large relative risk reductions of around 22 and 24 percent respectively, and each was highly significant at 0.008 and 0.002 levels respectively.

Looking at Aggrenox versus placebo, we see approximately a 37 percent risk reduction, and as I quoted to you earlier, this 0.001 is quite misleading. It is really 1 in 1 million, and we just chopped it off at 0.001.

Likewise, I am not going to pay much attention to these comparisons of dipyridamole versus placebo, and aspirin versus placebo, but both significant. I will focus on the key points.

[Slide.]

To move on to the robustness analyses, and these have been of some concern also. The primary analysis p-values are summarized here. When we did a Cox-adjusted analysis for all significant predictors of stroke, we came up with the same results. When log rank was done it was also the same stratified by center, when we studied investigator-diagnosed strokes, ignoring MMAG, and so forth, and finally a worst-case analysis where we imputed strokes to all the people who were lost to follow-up, again totally consistent results.

[Slide.]

So, my conclusion is that we have answered three of the questions that were posed at the outset, that is, low-dose aspirin effectively prevents stroke, extended release dipyridamole also prevents stroke and to a roughly comparable degree, and Aggrenox exhibits the additive benefits of its components, and these results are highly significant and robust.

DR. GROTTA: On the Cox analysis, did it consider the concomitant use of anticoagulants, antiplatelet drugs, that were frequent in your population, although matched among the different groups?

DR. STREET: No, it did not. It was only based on baseline characteristics, baseline risk factors.

DR. GROTTA: You will later show us that the concomitant use of antiplatelet drugs or anticoagulants among your population didn't contribute to these results?

DR. STREET: No, I would have to construct such an analysis because we believe the ConMed data which only indicated whether or not it was used. We had no information on dose duration or indication, were not sufficient to make a meaningful analysis.

DR. GILMAN: This is of concern because more of the patients who received Aggrenox had carotid endarterectomy, some of them had added on aspirin, we don't know what dose, we don't know what percentage of these

folks, so that is a question that has arisen in at least my analysis of this.

DR. STREET: I think what we can do is we will-- can we bring that back to you after the break because it would require a little work?

DR. GILMAN: Please, yes. We appreciate that, yes.

[Slide.]

DR. STREET: Summarizing the secondary endpoints, this is a very important slide I believe to ESPS-2. I have got the four prespecified endpoints, I have stroke across the top. Here, everything is put in terms of odds reductions just for consistency of presentation. Results are similar to risk reductions.

What I want to note is that the effect on TIA was roughly the same size as one would hope as that on stroke, and it was also of comparable significance. We see the effects of both components, their additivity, in the small group of 148 patients who had other vascular events, deep vein thromboses, and so forth, we see a similar effect, 40 percent on dipyridamole, 34 percent reduction aspirin, and fully 62 percent on the combination.

Ischemic events, which include stroke, MI, and sudden death, are naturally the mirrors of the stroke results because the stroke results dominate that endpoint,

it is not just completely distinct information.

Finally, for MI, we see aspirin 21 percent risk reduction, not significant. Similarly, 23 percent risk reduction on Aggrenox, also not significant as one might expect in a study like this, because these would be very low-powered comparisons.

[Slide.]

In conclusion, I guess I have really stated the conclusions. We have two very important endpoints which are distinct from the stroke endpoint, which internally confirm the reality of the efficacy on the stroke endpoint, and acute MI showed a positive trend on Aggrenox and on aspirin.

[Slide.]

Now, I turn to patient survival, the other primary endpoint, and we already looked at this curve, and I tried to tell you the numbers saved per 1,000 treated, and now I have them in front of me. There were 11 per 1,000 on Aggrenox, 13 on aspirin, and 9 on dipyridamole, all closely comparable.

[Slide.]

The factorial analysis showed nothing of significance, small effects both of dipyridamole and aspirin, and no evidence of interaction.

[Slide.]

Pairwise comparisons, again, nothing statistically

significant, but I would like to draw your attention to two lines, that is, Aggrenox, which is our drug, 9.2 percent relative risk reduction, comparable to that seen on aspirin in mortality with an 11 percent reduction, neither effect significant.

[Slide.]

So, for the death endpoint, to conclude, no statistically significant risk reductions, roughly 10 percent risk reduction on Aggrenox, is comparable to that of aspirin alone, and I say that these risk reductions are comparable to those that have been shown earlier today--well, maybe they haven't been--in meta-analyses of placebo-controlled studies of aspirin in this type of patient, stroke or TIA patients.

[Slide.]

Now we come to the nonfatal stroke or death results. The lesser magnitude in statistical significance of this than the results for stroke, result from diluting the substantial additive effect which we saw on stroke with the modest equivalent effect on reduction on death between Aggrenox and aspirin.

So, what we see is the same general pattern of curves here with Aggrenox superior to the other curves, but not by as clean a line, all of them superior to placebo. This is the dipyridamole in orange. It takes a little

longer to get into the act.

Now, I just want to caution you about the label. When I call it a primary factorial analysis, it is a primary method of analysis, not a primary endpoint. When we look at this, we do see some very strong effects on our composite endpoint. We have a 14 percent relative risk reduction on dipyridamole, highly significant at 0.003; similarly, 12.2 on aspirin, 002, with again no evidence of interaction.

[Slide.]

Taking a look at the pairwise comparisons, we have Aggrenox versus aspirin, 12 percent reduction, not statistically significant, 0.084; Aggrenox versus dipyridamole, 10.3 percent. 0.079.

But I think the most impressive line of this table is for our compound, and that is Aggrenox versus placebo where we are seeing a full 24.4 percent on the combination, and this is statistically significant at the 2 in 100,000 level, 0.00002.

So, we do have, though not significant contributions, we do see a nice additive effect as earlier seen in the factorial analysis.

[Slide.]

So, for nonfatal stroke or death, I will just restate it because it is very important to the debates that are ongoing. Highly significant efficacy of both

dipyridamole and aspirin were shown in the factorial analysis, and we saw additive efficacy in Aggrenox.

The pairwise comparisons showed a 24 percent risk reduction on Aggrenox versus placebo, but only favorable trends on Aggrenox versus its components.

So, this brings me to my conclusions.

DR. GILMAN: Just before you do that, Dr. Street, could I just ask, isn't it the effect on stroke that really carries the day for this?

DR. STREET: Yes, definitely, no question.

DR. GILMAN: So, you are showing essentially the same thing with effect on stroke as you are on nonfatal stroke or death, but it is all stroke.

DR. STREET: But it is diluted, but it is diluted by the lesser effect. You are combining a sensitive endpoint with an insensitive one, and one that normally requires meta-analyses, such as Peto performs, to see effects.

DR. GILMAN: Yes. So, the effect is on stroke, and not upon death, and when you combine the two, you still get highly significant effects because of the robustness of the effect on stroke.

DR. STREET: Yes, you get highly significant effect in the primary factorial analysis, establishing they both work in that indication. They also are completely

consistent with additivity.

So, from that analysis, one would tend to draw the conclusion that yes, Aggrenox inherits the benefits of both components, but I just want to make it clear because it is very easy to get confused between all the various analyses I have presented today.

[Slide.]

Finally, just a word on the efficacy conclusions, and I will stop. I have shown that Aggrenox is significantly more effective than aspirin alone and dipyridamole alone in reducing the risk of stroke in TIA and ischemic stroke patients.

Moreover, we believe that this conclusion is based on reliable, well-controlled, and generalizable evidence, and satisfies the FDA requirements or guidelines for approval of single study NDAs.

First, it is a large multicenter trial, the largest single stroke prevention trial in TIA and stroke patients ever conducted, with 59 centers. It had a factorial design which was able to demonstrate the effectiveness, not only of the monotherapies, but in view of the absence of interaction throughout the efficacy data, additive effectiveness of the combination.

Another requirement is the results, I think are very statistically persuasive in that they stand up to just

about any reasonable test we throw at them, even a worst case analysis, and consistency is seen across subgroups, although not shown directly in my presentation, it is even longer than it is.

Finally, I want to reemphasize that we saw on distinct endpoints, OVE and TIA especially, very strong effects, which to me have an internal confirmation, if not an external confirmation.

I want to thank the committee for your attention.

DR. GILMAN: Thank you for that clear presentation.

Dr. Brooke.

DR. BROOKE: That is a very interesting result, and I wonder. It's odd that you are having such a positive effect on stroke and yet death is not affected. It would suggest that they are being killed by something else.

But I wonder, we always have a problem. You would think that a neurologist could define death, but we always have a terrible trouble with defining death, and I wonder how you define death in your study.

The reason I ask is that neurologists sometimes take patients with strokes who would have died and put them on artificial life support in intensive care where they may survive for weeks or sometimes months.

I wonder how that figured into your endpoint

definition.

DR. HAEHL: I have to admit I was talking about administrative issues, so I cannot answer your question at the moment. So, could you please--I hear Dr. Pathy is willing to answer your question.

DR. PATHY: There were no patients on life support machines that was reviewed by the MMAG.

DR. GILMAN: Dr. Grotta.

DR. GROTTA: Again, as a neurologist, I want to be reassured about the validity of the strokes as endpoints. I also want to be reassured about the validity that the patients that were put into the study really did have TIAs or minor strokes, and maybe we could address that for a minute.

What percentage of your patients had CT scans to exclude other diagnoses, such as cerebral hemorrhage or other conditions that might mimic a stroke, and what were the time periods that those CT scans were carried out, and who made the diagnosis of stroke or TIA, and what were the criteria or definitions of TIA or stroke that a patient had to meet in order to get into the study, recognizing, as with the previous question, that this randomization should take care of this to some extent, but nevertheless, you know, junk in, junk out, you just want to be sure that these were stroke patients and that they, in fact, did have strokes.

DR. EASTON: Speaking as a neurologist, it isn't junk in and junk out. What came out is actually very positive. It would strike me, though, Jim, wouldn't it, that if you are putting in migrainers, they are benefiting, too. If you are putting in brain tumors, they are benefiting, too.

In other words, it would seem to me that that would take things in the other direction. We can find out precisely sort of how that was done, but I would think this would be an especially germane question had it gone the other way, but here actually, whatever it is they are treating, it certainly works.

DR. HAEHL: And there have been analyses done, and it doesn't quite answer your question as to how that was established, whether Rankin scale or other gradings of the qualifying stroke that influenced the result, and it did not.

I wanted to come back to your earlier question. You were interested to see the case report form for the assessment of stroke as an endpoint, and I have overhead copies produced of that in the meantime.

DR. GROTTA: Good, but I would still like the question answered about whether CT scans were done on these patients, when they were done, and what the definitions were of TIA and stroke for inclusion in the study. I recognize

what Dr. Easton said, and it is true. I would be more concerned if it were a negative study, but nevertheless, I think it is still relevant to know who was put in the study.

DR. KATZ: Just to sort of follow up on that, right, generally speaking, we would think that any heterogeneity of diagnosis would tend to obscure any drug effect if there was one, so I don't think it is that so much, but you have got to remember if the drug is approved, labeling has to be written. I don't think this is really going to be a big problem, but if they are giving it to migrainers, and it is helping them, then, the drug would be labeled for preventing stroke and migrainers, so you want to know who you are dealing with, so I think Dr. Grotta's point is well taken.

DR. HAEHL: We will come back if that is acceptable to you after the break and bring you the definitions of the entry criteria. Are you interested in the case report forms issue?

DR. DRACHMAN: The stroke or death, is the death merely bath water, in other words, was that merely thrown in? Were there stroke or cancer, stroke or acne, would the data have been just as positive for both or those, or how do you remark that? Do you regard that as being part of the real answer, should we view it that way, and just say stroke?

DR. HAEHL: We have a significant result for stroke, and we have an endpoint which is very much related with the outcome of stroke, and that is death, and it has been established for aspirin, that aspirin does have an impact on death, and therefore in the situation where you have an approved dose of aspirin in your treatment regimen, we felt that it is consistent to investigate and to test whether the results of ESPS-2 actually add up to this prior experience and are consistent with the prior experience, and as you have seen, it is, and we think that is different than just bath water.

DR. GILMAN: But it is not different. It is not true. There was no change with respect to death. There is no significant effect upon death.

DR. HAEHL: There is no significant effect on death as opposed to stroke, however, the trend observed is consistent with the individual trends in aspirin trials, and is consistent with the summary, and we can show a slide to that.

DR. GILMAN: We are seeking statistical evidence for the allegation that there is an effect upon death.

DR. HAEHL: Yes, which is also true for aspirin.

DR. PENN: The fact that we don't have good data for aspirin does not help us in this case. I mean just because maybe a mistake was made in labeling aspirin does

not help us say that we should make the same mistake in this labeling.

It seems to me your statistics, if anything, are diluted by adding death as was clearly outlined to us, so what is the compelling reason to this committee to include death? We need a very strong reason other than somebody else included death in an aspirin study that there was only a trend in.

DR. HAEHL: The question for us is if we were to administer aspirin 50 mg daily in patients after TIA or stroke, we would expect from the label a reduction or an impact on mortality.

Now, if we take that same tablet together with dipyridamole, and we have compelling evidence I think from the results presented that there is consistency between the aspirin in Aggrenox and the aspirin which you can buy individually, we would find it very strange and not to say confusing for both the patient and the treating physician that one formulation would reduce mortality and the other wouldn't.

DR. GILMAN: We are not getting a clear answer to the question. You are making presumptions not based upon the data. The data do not show a beneficial effect upon death.

DR. HAEHL: The data did not show a significant

benefit, they showed a trend which is consistent what has shown for aspirin trials individually.

DR. GILMAN: We have a lot of people that want to speak. Bob Temple, Robert Califf, Marvin Konstam.

DR. TEMPLE: The aspirin labeling at least partly reflects results of meta-analyses of controlled trials that do show a small benefit of aspirin on survival. So, when that labeling was written, that was taken into account.

It does seem an interesting dilemma that this product contains aspirin, and therefore one would imagine it would have the usual aspirin effect even though the study didn't show anything. I don't have the answer to the dilemma I should tell you.

DR. CALIFF: My reasoning and for feeling quite difficult than obviously most other people on the panel about this is for a different reason, which is that you cannot ascertain the effect of a drug on stroke if a large number of people died and you don't know why the died, because you have a lot of people who are likely to have had a stroke, who are dead, and therefore you can't assess whether they had a stroke or not.

So, the normal course of events in cardiovascular trials now is to prospectively declare the composite as the primary endpoint, because when you say we are assessing the effect of a drug on stroke, but we are going to ignore

people who are dead, you can't do that.

DR. GILMAN: You mean because they died, they didn't have an opportunity to have a stroke.

DR. CALIFF: Well, they may have had a stroke and you don't know it.

DR. GILMAN: But the committee did look at the cause of death and ascertained it as closely as possible.

DR. CALIFF: But the cause of death is--well, I don't want to say silly--but what did all those people who had sudden death die of?

DR. GILMAN: We have heard a variety of causes.

DR. CALIFF: That's my point, you know, one of the main ones of which would be occlusion of an artery to the brain.

DR. KONSTAM: To me there is two separate things going on. One is I think at the end of the day, we are going to have to grapple with are we going to prove it and specifically for what, and so that is when this really is going to come up, and Bob spoke to this dilemma before, which is that you have a combined endpoint, and the combined endpoint is positive, but death is not, so we will have to deal with what the wording is, but I think Rob's point is that it is important to look at this combined endpoint, to look to see that the combined endpoint is, in fact, positive, because if it weren't, you would be worried that

there is some fluky reason why the strokes were positive. So, I think it is very important to look at that endpoint.

But I have to say I am confused about why deaths--and maybe Bob said it--why deaths is not positive. This is where I think I would like the sponsor's help, because it isn't that the numbers of events were small because the number of death were actually substantial, so you can't say, well, okay, but the number of events was substantial.

I guess I share Rob's lack of interest in general in cause of death, but I actually would like to see it here, and I would like to see a table showing cause-specific deaths across the different groups, because I am just wondering whether there is not some signal in there, that there is something negating the anticipated positive effect on death.

Several people have said it, and I guess I concur, I would like to see that. Are we going to see it?

DR. EASTON: I can make a copy of the table that I was reading before the panel, or just give them this.

DR. KONSTAM: Does it show it across the different treatment groups, because you mentioned the numbers?

DR. GILMAN: Could you use the microphone, please, Don.

DR. HAEHL: We don't have this provided. We would have to take a copy.

DR. GILMAN: It is really going to be important that all of us hear what you are saying and what you are reading, so could you just read it into the record.

DR. EASTON: I would just say that if you would like copies of that, I would certainly see that that gets taken care of. What it lists them is by the four groups, then, the summary.

DR. GILMAN: We have something to show. Good.

Let's look at the overhead.

[Slide.]

DR. FARRELL: I am Dr. Farrell. This is just a table produced from the clinical trials report showing mortality. Qualified stroke are the individuals who died within the first 30 days. The endpoint of stroke are those individuals who died of failed stroke, and then I continued on in the table those who died of myocardial infarction, cardiac failure, sudden death, vascular events, infection, bleeding, and other causes, just to show that there appears to be no difference for any form of mortality.

DR. KONSTAM: I guess the striking thing is that there are a lot of noncardiac--well, there aren't a lot of noncardiovascular deaths, are there?

DR. FARRELL: No.

DR. KONSTAM: So, if you added up all the cardiovascular deaths, there is still nothing, right, there

is not even a hint of an effect in either of the treatment groups on cardiovascular death.

DR. CALIFF: Just a point here, if I may, on that issue. You have two endpoints, one of which is much more common than the other in the population. Even if the treatment had the same effect on both, you have got for the less common endpoint, a higher probability that you will see--

DR. KONSTAM: I am not sure that is true, Rob, though.

DR. CALIFF: It is definitely true.

DR. KONSTAM: No, no, the first statement that stroke is much more common than death. I mean it isn't in this population. It is just not true.

DR. CALIFF: So, how many stroke endpoints were there?

DR. KONSTAM: I mean the fatal and nonfatal stroke, it is running about, you know, a little over 200 per group, and the death is running a little 200 a group. That is the point, it is not a major difference.

DR. CALIFF: You are right.

DR. GILMAN: Well, we settled that.

Dr. Temple.

DR. TEMPLE: This is a good question, and I certainly don't have an explanation, but it is not

unprecedented. The aspirin trials, all of which were able to nicely show reduction in MIs, were uniformly unable to show improved survival for reasons that have never been quite clear.

The most striking example I know of is Charley Hennekens' study which reported--of course, this is only one study, and there is a British study that sort of went the other way--reported a 50 percent reduction, 50 percent reduction in nonfatal MIs and fatal MIs, but there are only a few, and survival was dead even, so to speak, which really makes just no--it just makes no sense.

It could mean in his study there was at least a hint that there were more sudden deaths in the treated group, and maybe that was it, but you never could figure it out, but the aspirin history is if you take an overview, you find a smaller effect on deaths, but the individual studies, which are plenty large enough to show MIs, never show it and I don't think anybody knows why.

DR. HENNEKENS: I think Dr. Temple makes an important methodologic issue in all the cardiovascular trials, and in the aspirin areas we see 30 to 40 percent reductions in the nonfatal events with aspirin and 10 to 15 percent reductions in deaths.

Furthermore, in the trials that accumulate a sufficient number of endpoints--and our trial did not, our

trial was stopped early, because of the MI finding we didn't have enough deaths. We needed about five times the number of deaths to really find anything. But they come later, as well, and I think this is a problem, and if we look at the aspirin data right now, now there are four primary prevention trials - the HOT study, Tom Meade's thrombosis prevention trial, the British Doctors' trial, and the U.S. Physicians looked at an aggregate.

There is a p less than 1 in 100,000 benefit on MI of a third or more, and yet, there is still no significant effect on deaths in primary prevention. In secondary prevention, 30 to 40 percent reductions in the nonfatal endpoints of MI and stroke, 10 to 15 percent reductions in death, which was significant, but they are not nearly as significant or extreme both in magnitude or statistical significance, and I think that this is not that surprising in that context in my view.

DR. GILMAN: Dr. Grotta.

DR. GROTTA: I guess I don't have as much trouble at least understanding why the drug doesn't have an effect on death that is all that obvious. In stroke patients at least, the major determinant of whether a patient dies of the stroke is the severity of the stroke. Patients who don't have very severe strokes generally have a much lower mortality rate.

I remember--maybe you could clarify this--but I remember in a presentation of these data at a meeting, although I have not seen this published, that the drug did not have an effect on the distribution of stroke severities, so that you are reducing the absolute number but not adjusting the severity of stroke.

So, maybe that is an explanation for why we don't see a major impact, that we can reduce the number of strokes, but not reduce mortality in this population.

DR. HAEHL: There was a nonsignificant minor shift towards minor strokes over the treatment groups and away from major strokes, and that will be shown later.

DR. ALBERS: I just want to say from the clinical point of view, I think that what the stroke patients are most concerned about is winding up with a disabling severe stroke, but death in general is thought to be less severe an outcome than winding up severely disabled in a nursing home, and when the severe strokes were looked at, there was a substantial benefit, and I think that may mediate a little bit of the death issue.

DR. GILMAN: Dr. Konstam.

DR. KONSTAM: I would like to just pose a hypothesis about what it is, which is that I guess it is only a percentage of cardiovascular events that are fatal, so you are collecting a number of cardiovascular events in

the course of a study, and some minority of them I guess are going to be fatal, but then there are people dying, and I guess that they are dying in association with cardiovascular events that had occurred years ago.

So, somebody who has had an MI, you know, five years ago, before they entered the trial, is more likely to die during the course of the study than somebody who hasn't, and that is not going to be impacted by your drug, because you drug is not going to affect an MI that occurred before the trial started.

So, I think maybe the hypothesis is that deaths is harder to influence because there are events that have occurred before that you can't influence.

DR. DRACHMAN: What about the dose of aspirin, the reduction of death was with much larger doses, was it not?

DR. GILMAN: Dr. Temple.

DR. TEMPLE: The original six trials that we used to approve the reduction in MI, probably reduction in MI plus death because we used the combined endpoint, mostly five out of six of them I think used doses of a gram per day, and had the same weak to none effect on survival. There is no clear evidence that dose matters.

The disease matters though. If you take people with unstable angina, you can show a nice effect on survival.

DR. GILMAN: Dr. Haehl, did you want to show the form that you used for stroke?

DR. HAEHL: The case report form you requested, yes.

DR. GILMAN: Yes.

[Slide.]

DR. HAEHL: This is a three-page form photocopied out of the case report form to assess stroke as an endpoint during the course of the trial.

You can see the description of new stroke at onset, the description of motor power--well, first of all, the date, the duration of symptoms, motor power, left, right, sensation.

[Slide.]

Other symptoms, etiology of stroke, location of the lesion, if performed, what neurological and other investigations supporting the diagnosis, CT scan, NMR, doppler, angiography or others, and comments, if necessary, and the last page.

DR. BROOKE: These are descriptive features. Was there a true inclusion form where, you know, you had to have four of the five features, or something like that, or was it just purely a description?

DR. HAEHL: No, I am now talking on stroke as an outcome, as an event. That is the assessment of the events,

what was asked for, how did we assess if a patient had a stroke in the periphery.

DR. BROOKE: I am sorry, I misunderstood. I thought you were talking about the inclusion to the study.

DR. GILMAN: This is purely descriptive.

DR. GROTTA: So, how often were patients seen in the course of the study on a routine basis?

DR. HAEHL: Every three months with the exception of the first month. There was one after one month, and then every three months.

DR. GROTTA: So, this form was filled out, then, by the local investigator, and each and every time a stroke was identified at a local site, then, it was adjudicated by the Central Committee.

DR. HAEHL: Right, on the basis of this form and further data.

DR. GROTTA: And other data, such as scans and things like that.

DR. GILMAN: It is 1 o'clock. We have successfully gotten ourself about three and a half hours behind schedule, but that's okay. We are getting our questions answered.

So, let's take about an hour for lunch and resume here at 2 o'clock. Let me caution the committee not to discuss anything related to this drug over lunch. All

discussion should be in public. So, please don't talk about this drug, and there is a place in the restaurant next-door for the committee members.

[Whereupon, at 1:00 p.m., the proceedings were recessed, to be resumed at 2:00 p.m.]

AFTERNOON PROCEEDINGS

[2:00 p.m.]

DR. GILMAN: I think we should proceed.

Dr. Rakowski, would you start, please.

DR. RAKOWSKI: Thank you.

Safety

DR. RAKOWSKI: Good afternoon.

[Slide.]

My name is Ken Rakowski. I am responsible for drug safety and information at Boehringer Ingelheim.

[Slide.]

Members of the committee, one safety question was posed to you by the FDA, and it is all-encompassing: Are there any particular safety concerns with the use of Aggrenox?

This portion of the presentation is intended to try to provide the pivotal information to allow you to assess that question.

[Slide.]

If we could summarize briefly what we do know about Aggrenox, three things would become evident.

One, there are no unexpected adverse events with Aggrenox. This isn't really unexpected in the sense that you have a product with two components, dipyridamole and aspirin, that are well characterized compounds with well

delineated safety profiles.

Two, the expected adverse events are established for the two compounds. This truly is a phenomenon of what you are getting is what you have seen with the components.

I think you will notice that as I go through the subsequent slides with the data, I will show you the similarity of AE reporting patterns between Aggrenox and the appropriate component.

Three, I think the data will hopefully lead you to the conclusion that the benefit/risk assessment is favorable.

[Slide.]

If we start with a somewhat busy slide, but one that I think will put things in perspective, these are the on-treatment adverse events with an incidence in the Aggrenox group exceeding that in the placebo group by 1 percent or more.

I think, cutting through all the data, focus in on the total number of patients with AEs and you will see a remarkable similarity and balance across the groups. The highest number of total AEs occurred in the aspirin group, the lowest number actually occurred in the dipyridamole group.

If we look at headache, you will see some similarity between the experience with the dipyridamole

component and the dipyridamole-alone group and the Aggrenox group, and likewise, that holds true when you look at the gastrointestinal disorders as a whole with similarity between the dipyridamole group and Aggrenox.

If we focus in on the bleeding disorders, however, the parity seems to be between the aspirin group and the Aggrenox group, and likewise, with anemia, there is similarity between the aspirin group and the Aggrenox group.

DR. GILMAN: Before you go on, I am struck that there is almost equal incidence of headache in the aspirin group as the placebo.

DR. RAKOWSKI: Aspirin and placebo are very, very similar.

DR. GILMAN: Pretty close, but--

DR. RAKOWSKI: And when I take you through a factorial analysis, which you can analyze for the contribution of a component to an AE, I will show you that the relationship with aspirin really appears to be a dipyridamole effect.

[Slide.]

If we look at the incidence of most common adverse events associated with treatment cessation, I think, relative to your point, you will find that there starts to be some differences between the groups.

The placebo group had a 21 percent discontinuation

rate, the aspirin group discontinued at 19 percent, but there is remarkable similarity between the Aggrenox and the dipyridamole groups.

The most common events, headache, dizziness, and nausea again seem to be very compatible between the dipyridamole treatment and the Aggrenox treatment group. If you really look at the slide and scan it quickly, you will find there is a consistent pattern that tends to emerge.

[Slide.]

We looked at potential interactions and we looked at drug to disease and drug-demographics interactions, if the committee will bear with me, let me read this because I will be sure I get it right this way.

For the drug-disease interactions, we basically analyzed for baseline TIA and stroke prior to the qualifying event, ischemic heart disease, peripheral vascular disease, previous cardiac failure or myocardial infarction, hypertension and baseline blood pressure, cardiovascular disease, hypercholesterolemia, diabetes, and arrhythmias.

Looking at the demographic interaction analyses that were performed, the areas were analyzed by geographic region, age bracket, gender, weight bracket, type of qualifying event, and the severity of the resulting handicap, and the consumption of coffee, alcohol, or cigarettes.

I think the slide clearly conveys that no clinically significant differences were evident in any of the interactions performed.

[Slide.]

Laboratory analyses were also performed. Laboratory data was collected at baseline, one year, two years. It was analyzed for hematology, indices of renal function, abnormalities of liver function, fasting glucose, cholesterol, and LDL cholesterol.

There were no clinically significant differences or effects demonstrated in any of the groups.

[Slide.]

Relevant to your question, if we look using the factorial analysis method to try to look at the contribution of a component to the occurrence of an adverse event, what you really see here is that, by a factorial analysis, the headaches, the gastrointestinal events as a whole, the nausea, diarrhea, and vomiting, appeared to be related to the presence of dipyridamole in the product.

The bleeding events obviously tend to be related to the presence of aspirin in the product. Ulcers, although didn't show statistical significance, trended towards the expected association with the use of aspirin.

[Slide.]

I think if you ask the logical clinical question

with the use of any antiplatelet agent, it is going to be what is the risk of bleeding with this compound.

This slide presents the incidence of on-treatment events and focuses in on the bleeding events and the ulcers. I think if you really look--again, there is a lot of specific events provided--but I think I would focus in on the overall occurrence of bleeding events, and notice the similarity between the placebo and the dipyridamole group in terms of the event rates for bleeding, and notice the similarity between the aspirin group and the Aggrenox group for the overall bleeding event rates.

Likewise, if we look at the ulcers, you will find the similarity again holds up between the aspirin-alone group and the Aggrenox group.

[Slide.]

Focusing in on the serious adverse events, we start to see a little bit of difference that I think is fairly easily explainable. I think the first thing you need to note is that the total number of serious adverse events actually occurred in the placebo group. In an endpoint study as we discussed this morning, where you have a high probability that your endpoint stroke is going to be categorized and captured as a serious adverse event, I don't think that is unexpected to anybody.

The lowest actual raw number and the lowest

percentage of total SAEs occurred in the Aggrenox group.

When we look at the total number of bleeding events, the numbers get small and we are now into the actual case-specific numbers. Placebo had 11 total bleeding events. There were 17 in the aspirin group and there were 25 in the Aggrenox group. The 25 comprises 1.5 percent as a total rate of the identified codes.

Although the contribution of each of the codes, the numbers are low and the contributions small, but the biggest contribution is made with melena and gastrointestinal bleeding.

Going down to the ulcer group, we see again numerical differences with the Aggrenox group having 7, 5 in the aspirin group. Honestly, you know, when you don't power a study for safety endpoints, it is hard to put clinical significance to these findings in the sense that obviously, there is an uncommon, relatively low rate of overall bleeding events. They are not statistically significant, but there is a numerical difference between the groups, and I think the clinical significance is still undetermined.

[Slide.]

If we look at the on-treatment deaths, focusing just on the gastrointestinal bleeding and ulcers, we again see a numerical difference. What is surprising to me at least in our table is zero for the aspirin group, 5 for

Aggrenox group.

I think to put this finding into perspective and try to balance it, let's look at the total number of deaths across the group, and if you look at on-treatment deaths, and here they were defined as a death that occurred on treatment or within 30 days of discontinuation of the treatment, the highest number of deaths occurred in the placebo group, the lowest number of deaths occurred in the Aggrenox group.

[Slide.]

In conclusion, we feel that ESPS-2 clinical data supports the safety of Aggrenox. There were no unexpected adverse events observed with the combined use of extended release dipyridamole and aspirin.

[Slide.]

The dipyridamole-related adverse events are primarily headache and gastrointestinal and again as I think we all expect with that product, with that component, and the aspirin-related groups are primarily bleeding events as expected.

[Slide.]

Serious adverse events of potential clinical significance other than stroke, as you can see from the GI analysis, are really relatively uncommon.

There were no demographic or disease-related

factors identified. We believe that the data demonstrates the safety of Aggrenox when taken as directed, and I know a lot of contention about the endpoints, but given the benefits that were really explained this morning by Dr. Street, we do feel that it is reasonable to reach a conclusion that the benefit/risk assessment for Aggrenox is favorable.

Thank you very much. I will turn it over to Dr. Haehl.

DR. GILMAN: Let's see if there are any questions for you before you leave.

Any questions about safety?

[No response.]

DR. RAKOWSKI: Thank you.

DR. GILMAN: All right. Thank you.

Dr. Haehl.

DR. HAEHL: Mr. Chairman, we had some questions in the morning where we tried to collect answers. One question was as to the diagnosis of the qualifying event.

A side remark to the qualifying event should be misdiagnosis between stroke and TIA in a randomized trial, placebo-controlled and randomized, we would expect that this would work against the efficacy, showing efficacy, and underestimate a benefit should there be one.

So, we believe that in this trial, the possibly

available or present degree of misdiagnosis like in any trial would not impact positively at least on the result and on the findings.

[Slide.]

This is a photocopy out of the report where it is described how the definitions for the qualifying events were. I can read through that.

TIA, a focal disturbance of the cerebral circulation resulting in a clinical neurological deficit that completely resolved within 24 hours. That was with functional sequelae.

Stroke, a focal disturbance of the cerebral circulation resulting in a clinical neurological deficit lasting more than 24 hours.

RIND defined in between.

These criteria were valid with no upper age limit or limitations in sex, number of previous neurological events, or the specific circumstances of the patient care after the qualifying event provided that neurological and general clinical condition was stable and not evolving.

The diagnosis of the qualifying event was made prior to inclusion by clinical neurological examination for neurological signs by the date of event, the evidence that the CVA had stabilized and by CT scan.

Also, optional disk examination was strongly

recommended to confirm the ischemic origin of the CVA and to exclude other possible causes of the symptoms, such as tumor or intracranial hemorrhage.

The CT scan was performed in order to confirm to confirm the qualifying CVA. An absence of CT scan abnormalities was not regarded as an exclusion criterion, and as an additional information, 80 percent of patients had such a CT scan.

The next question was did the qualifying event have impact on the outcome.

[Slide.]

Here, we have those patients with qualifying stroke, and you have the odds reduction in the factorial design for dipyridamole versus no, with 14 ASA with no, with 26, and then compares Aggrenox with placebo with 37, and if you take the group which had as a qualifying event TIA, then, these numbers are comparable, certainly not different.

[Slide.]

Just for your information, the composition of the Ethics Committee that accepted the changes or the increase of sample size.

[Slide.]

The next question is the interim analysis, and there I would like to ask Dr. Street to present that.

[Slide.]

DR. STREET: This is from the ESPS-2, November 1991 interim analysis report. At the time, there were 3,994 patients followed for an average of 10.6 months, and here is the statistician's summary statement from the report.

For what concerns survival, no statistical test is presented as agreed upon by the protocol. The signification level of 1 per 1,000 is never reached. The overall impression that can be derived from the study of the survival functions for the endpoint is that the four groups are different, and no two groups seem to cluster as being identical.

Now, let me show you the data which he presented at that time.

These are the numbers of endpoints, and these endpoints mean here the composite of stroke or death, and it shows them both at 12 months and 24 months, and down below here you have some estimation of the size of the groups.

Now, the 4,190 versus the 3,994, that is a little hard to explain, but it is the survival analysis. That is how it was taken into account. Very few patients had reached the full duration of study, and this is the kind of presentation that was made on all the tables. They were tr, 1, treat, 2, treat, 4, and so forth, and those were randomly permuted between each and every figure.

So, his conclusion was simply this group seems

better than this, and none of them seemed to be clustering, so that is the conclusion he drew from the study. Then, he re-ran his sample size program and reestimated the same sample size. That is nature of the information.

Conclusion

DR. HAEHL: With this, I would like to come to our conclusion.

[Slide.]

Members of the committee, we have reviewed a lot of information and we have made an attempt to provide you with a broad understanding of both the science and our rationale for the development of Aggrenox.

We certainly do realize--and that was reflected by the agenda this morning--that an important NDA like this one necessarily also has to raise important and relevant questions, and we do hope that with the data presented we could show that there are clear answers to those questions.

Therefore, to complete the remarks I would like to propose to you our perspective relative to the data presented, and I would like to propose the following conclusions, and I would also like to have the pointer back.

[Slide.]

Aggrenox represents a therapeutic advance to the secondary prevention of stroke that builds on the vast clinical experience with its components.

The findings, both ex vivo and in the clinic, are consistent with additive beneficial effects of aspirin and dipyridamole.

[Slide.]

ESPS-2 provides compelling evidence of the safety and efficacy of Aggrenox that can be generalize to general practice.

ESPS-2 is robust and eliminates concerns regarding chance or bias as a basis for the findings.

ESPS-2 meets the requirements for a single trial to support approvability of a product.

[Slide.]

The factorial and pairwise comparisons support the conclusion that in the second prevention of stroke, Aggrenox is significantly superior to aspirin or to extended release dipyridamole alone and has a favorable benefit-risk ratio.

[Slide.]

This is reflected by the fact that with Aggrenox, 59 stroke events per 1,000 patients treated for two years versus 30 events prevented per 1,000 patients treated for two years with aspirin versus 26 events prevented per 1,000 patients treated for two years with dipyridamole.

[Slide.]

Mr. Chairman, after the discussion of this morning, I take a big breath, and still I would like to

propose to you the conclusion that based on the positive trend for a mortality benefit, which in our opinion is consistent with the aspirin label and on the basis of the inclusion of an FDA-approved daily dose of aspirin, it is appropriate from a scientific and regulatory perspective to afford Aggrenox the same label indication as aspirin.

[Slide.]

And ESPS-2 establishes Aggrenox as first line therapy for secondary prevention of stroke and its labeling should describe its superiority to aspirin.

[Slide.]

With this, I would like to thank the panel again for giving us the opportunity to present, for listening, and to give us your advice, and my colleagues and I continue to be happy to answer any questions.

Thank you very much.

DR. GILMAN: Thank you, Dr. Haehl.

Any questions from the panel for the sponsor?

[No response.]

DR. GILMAN: Is the sponsor content that you have presented all the data that you wish to present to us?

DR. HAEHL: Yes.

DR. GILMAN: Thank you.

I will break up the flow now by asking that we turn into a public hearing, an open public hearing, so that

those people who had come here particularly to address the panel can have an opportunity to do so.

We will wait to hear the FDA's presentation and hear from the public.

Dena Van Husen, Senior Vice President of the National Stroke Association, Englewood, Colorado.

Open Public Hearing

MS. VAN HUSEN: Thank you, Mr. Chairman, members of the committee. My name is Dena Van Husen. I am the Senior Vice President of the National Stroke Association. On behalf of our entire organization, I thank you for the opportunity to talk to you today briefly about stroke.

The National Stroke Association devotes 100 percent of its resources to stroke. We have been providing educational information to stroke survivors, caregivers, the general public, stroke at risk, and a broad variety of medical professionals since 1984.

Our mission is to reduce the incidence and impact of stroke by changing the way that a stroke is viewed and treated. Our efforts cover stroke prevention, treatment, rehabilitation, and research.

I am here today to encourage you to accelerate the approval of all compounds that are found safe and effective for preventing strokes, treating strokes, helping in stroke recovery.

The National Stroke Association strongly supports the development of new medications because there are so few options available for treating stroke.

As you know, over 730,000 Americans experience a stroke each year in the United States. That is one stroke every 45 seconds, and 160,000 people die from their strokes annually. There are 4 million stroke survivors in the United States. One-third of stroke survivors are left with very serious impairments, and everyone who has a stroke is at greatly increased risk of having another stroke.

Stroke is devastating to the individuals and families both emotionally, financially, and strokes can affect anyone. Strokes can no longer be written off as a disease of the elderly. One-third of strokes happen to people under age 65. As the baby boomer population ages, stroke is expected to become even more prevalent.

May is National Stroke Awareness Month. In three days, the National Stroke Association will launch one of its most significant public education efforts ever. Former President George Bush, who has atrial fibrillation, which is the leading risk factor for stroke, will tell the nation through public service announcements to "Be Stroke Smart."

Research and identification of new drug therapies is pivotal in the management of stroke, and we honor the researchers who dedicate their days to finding new

breakthroughs for stroke.

Should the Advisory Committee find any compound submitted for approval to be effective and safe, we encourage the committee to recommend its rapid approval, so that it can be made available for those at risk of stroke and to those who may experience or survive one.

Thank you.

Now I would like to turn the podium over to Dr. Phil Gorelick, who is the Chairman of the National Stroke Association's Prevention Advisory Board.

DR. GILMAN: Dr. Gorelick.

DR. GORELICK: Mr. Chairman, ladies and gentlemen, I am Dr. Phil Gorelick, Director of the Center for Stroke Research in Chicago.

My professional and research interests are the prevention of primary and secondary stroke. I administer NIH funded research projects on stroke prevention and have particular expertise in the efficacy of antiplatelets in secondary stroke prevention in African-Americans.

Today, I speak on behalf of the National Stroke Association, a not for profit agency whose mission is to reduce the incidence and impact of stroke by changing the way stroke is viewed and treated. Through my comments today, I hope to lend support to the rapid approval of compounds which will enhance stroke treatment options.

I am affiliated with the National Stroke Association through its Stroke Center Network, its Professional Advisory Council, and I am Chair of its Stroke Prevention Advisory Board. Over the past several months, I led the Stroke Prevention Advisory Board in the development of the National Stroke Association Consensus statement on primary stroke prevention.

I am here today to remind the committee of the devastating costs to patients and families from secondary stroke. My commitment to stroke prevention stems from my professional experience with the staggering neurologic damage imposed by stroke.

Each year, more than 700,000 of our countrymen suffer stroke. Approximately 160,000 of them die, the remaining 540,000 survive with varying levels of impairment. Stroke is the third leading cause of death and the leading cause of adult disability in our nation.

There are a myriad of factors which place individuals at risk for stroke. These factors range from those which are potentially modifiable, such as hypertension, to those which are potentially manageable, such as diabetes.

Through identification and management of risk factors for stroke, the incidence of this devastating condition can be diminished. Given our understanding of the

impact of stroke on our society, we face an imperative to develop and implement strategies for identification and management of all stroke risk factors.

A substantial risk factor for stroke is stroke itself. Individuals with a personal history of stroke and transient ischemic attack are at extremely high risk for subsequent events.

Because this population is relatively well defined, we have the opportunity to offer aggressive intervention strategies for secondary stroke prevention. Because this population is at risk for progressive neurologic damage resulting in progressive physical and cognitive dysfunction, we have a medical and ethical imperative to offer the most effective interventions available.

Research and identification of new and promising pharmaceutical agents is a critical part of our ability to offer patients effective treatments for stroke. Based on my knowledge of the expanding population of stroke survivors and my understanding of the opportunity to offer medical interventions to preserve neurologic function, I am an advocate for the development and rapid approval of compounds to prevent recurrent stroke.

Thank you.

DR. GILMAN: Thank you, Dr. Gorelick.

Mark J. Alberts, M.D., Asscciate Professor of Neurology, Director, Stroke Acute Care Unit, Duke University, Durham, North Carolina.

DR. ALBERTS: Thank you, Dr. Gilman.

Good afternoon. My name is Mark Alberts. I am an Associate Professor of Neurology at Duke University Medical Center in Durham, North Carolina, and Director of the Stroke Acute Care Unit at Duke Hospital, however, I am here today representing The Stroke Belt Consortium.

The Consortium is a diverse, multidisciplinary group of people, organizations, and companies dedicated to improving public and professional education about stroke in the Stroke Belt area of our nation.

Let me disclose that I have not participated in research involving Aggrenox, nor do I have any financial ties with Boehringer Ingelheim. However, I am a consultant to Boehringer Ingelheim, and the company has provided educational grants to the Consortium.

The Stroke Belt defines a region encompassing the Southeastern portion of the United States where stroke incidence and mortality has significantly exceeded the national average over the past 50 years. The highest age-adjusted stroke death rates for this region have been recorded in South Carolina, Georgia, and Mississippi.

The Consortium includes physicians, health care

providers, pharmacists, representatives from the pharmaceutical industry, managed care groups, minority groups, legislators, NIH, CDC, and other interested parties. The Consortium strongly believes that there is a need for concentrated efforts aimed at lowering the cerebrovascular disease health risks in this population.

The overall goal of this Consortium is to educate the public and the medical community about the risks of stroke for patients residing in the Stroke Belt region. People in these states are at a greater risk of stroke in part due to higher incidences of hypertension, heart disease, and diabetes and higher rates of smoking and obesity.

In addition, these states have a higher than average population of African-Americans and older patients, older adults, populations that are recognized to be at increased risk for stroke and for dying from a stroke.

The Consortium is committed to working with all groups in the Stroke Belt to improve methods for preventing, diagnosing, and treating stroke. As such, the Consortium has led to the formation of several different state-based programs and organizations to improve public and professional education about stroke. These include the North Carolina Heart Disease and Stroke Prevention Task Force, as well as the Florida Stroke Partnership Council.

Also, the Consortium has funded dozens of pilot grants and demonstration projects aimed at furthering public and professional education about stroke and its prevention and treatment. Examples of such projects include sponsorship of church-based educational programs, including stroke warning signs in the mailing of utility bills, and conducting an education survey about stroke awareness in the Stroke Belt region.

The Stroke Belt Consortium applauds the efforts of the FDA Advisory Committee in considering the approval of Aggrenox for the secondary prevention of stroke. As you know, each year, more than 700,000 Americans have a new or recurrent stroke and the risk of developing a subsequent stroke is in the range of 8 to 10 percent per year.

Despite educational efforts, most patients, even those with family members who have experienced a stroke, do not know the risk factors for stroke, and as such, they are unlikely to alter daily behaviors, such as smoking and poor diet, that increase their risk of having a stroke. Therefore, it is even more imperative that new therapies for the prevention and treatment of stroke be made available in this country, especially in those regions of the country, like the Southeast, where the risk of stroke is elevated significantly.

I believe that the development of new therapies,