review them, unless you want to take questions now.

DR. ROSEN: I think we should just take questions for you first, Dr. Egan. Thank you for an eloquent presentation.

DR. KREISBERG: Dr. Egan, that was a spectacular analysis. In all of the studies that were used for the determination of adverse effects, it is remarkable that men are underrepresented. They represent 30 percent. Yet, all of the completed suicides were in men.

Do you think that the composition of the study group underestimates the risk of suicidality?

DR. EGAN: I guess that is a possibility. If you looked at the studies that were a little bit more gender balanced, such as RIO-lipids or RIO-diabetes, in real lipids it is interesting. We often saw an increase in almost every type of adverse events, and whether that was because of the gender imbalance I am not sure. We did not do a separate analysis by gender for that study alone.

DR. ROSEN: Dr. Gilman and then Dr. Wang and then Dr. Woolf.

DR. GILMAN: I have a series of questions. I hope you will bear with me for just a moment or two.

I thought it very frustrating to go through the material, both the FDA material and the material from the sponsor, because there was a lack of specificity, so let me see if you have any--or the sponsor has any--answer to this series of questions.

First, the symptom of dizziness. Dizziness is a terrible symptom because a physician, a neurologist, never knows what a patient means when the patients complains of dizziness. It can mean lack of balance when walking, of a sense of vertigo--that is, a spinning of the environment.

It can mean nausea. It can mean loss of vision. It can mean weakness in the legs. It can mean sweating. In other words, dizziness is a non-descriptor of what the patient is perceiving, so you have to drill down and find out what exactly the patient is experiencing.

I found nothing in here to explain this further except an occasional mention of vertigo, which means a spinning of the environment or of the person.

Do you have any more information, or does the sponsor?

DR. EGAN: Probably the sponsor could clarify this better. The basic methodology for assigning terminology to these adverse events is to take the verbatim term, which then gets translated through several different layers. So it goes from there to an actual adverse-event term, to a preferred term, to a high-level term, to a high-level group term, to a primary system organ class.

So, you are right, a lot can be lost in the translation. And we also had a problem with language where angina was often reported, but it was frequently to describe sore throat instead of the angina that we are more familiar with.

So, it was a confusing process, because, yes, it is not unique to Sanofi. It is a difficult

problem.

DR. ROSEN: We might ask the sponsor if they have some additional data for just a brief response.

DR. BRADLEY: My name is Walter Bradley. I am Professor of Neurology at the University of Miami. I have some conflicts; that is, my time is compensated for the department by the sponsor, and I receive reimbursement for my travels.

I have looked at a fair number, but not all of them, of the case-report forms and other information of that nature that has dizziness and, as you well know, it covers all sorts of different disorders. There are a number. True benign positional vertigo. There is one of Meniere's disease. But the vast majority of them are uncategorized and it is impossible to know what they are.

DR. ROSEN: Thank you very much.

You can finish your line of questioning and then we can move on.

DR. GILMAN: Yes, please. The second

question has to do with the tremor. Once again, the word tremor doesn't mean a great deal without more description. For example, cerebellar disease causes a proximal tremor so that there is a tremor on reaching certain other disorders, such as central tremor called a distal tremor, tremor at rest usually is associated with Parkinson's disease, tremor on action may be anxiety-related.

So, the word tremor by itself is only a teaser. It doesn't tell you what is going on. Do you have any more information about that?

DR. EGAN: Again, we were just using the preferred terms that were assigned by the sponsor, so I can't tell you the methodology that they used to assign those terms. But I am sure they can.

DR. ROSEN: A brief comment from the sponsor?

DR. BRADLEY: Again, I have looked at a fair number of those. We looked particularly at cases that were unilateral because of the possibility that those were parkinsonism, and the majority of those, in fact, although classified

under tremor--the terms used were actually jerking of the limb, not actually tremor--although it fell under the rubric of tremor when classified according to the standard methods.

There were whole body tremors. They were bilateral tremors, and it did not again appear to be specific. I could not get the sense that this was benign essential tremor that was being activated.

We did look specifically to see whether there was any association with anxiety, and, in fact, there was no tying up between the cases that had anxiety or tremor and vice versa.

DR. ROSEN: Thank you for that clarification.

DR. GILMAN: I won't go on too much longer.

Under "cognitive disorders," there were many terms including amnesia, memory impairment, disturbance in attention, et cetera, et cetera, lethargy, syncope.

Were there any objective measurements

made? Did anybody do a Mini-Mental State examination so they would have some sort of measurement of what exactly this meant, or is this only a symptom that a physician or an individual on the site recorded?

DR. EGAN: That's correct. This would have been recorded by the investigator at the investigator site. Now, one of our concerns was, yes, we actually--if you type up a table with all of the neurologic adverse events that were listed by preferred term, it encompasses 3 pages.

So, that is why we said we had a great deal of difficulty getting a grasp on what they all meant, because so many different terms were used. Part of this may have been because that is how the patients were reporting it. It may have been just difference in investigators.

A lot of these people did not have neurological consultations, did not have any kind of complementary investigation, so getting a firmer diagnosis is difficult.

DR. ROSEN: One of the issues of querying

with adverse events is that you have these broad terms which are difficult and require further investigation.

DR. GILMAN: I appreciate that. However, there is no substitute under those circumstances for doing an objective test, and then you would know what you are dealing with.

For example, Mini-Mental State exam can be done in five minutes or so, and you get a number. So you know what you are dealing with. The patient may have the symptoms but be cognitively intact. We just don't know from this data set.

Thanks. I am through.

DR. ROSEN: Dr. Wang.

DR. WANG: You showed us your date on possible effect modification of the risk for adverse psychiatric events by age, gender, and weight loss.

Do you have similar data on how the relative risks might vary by baseline BMI?

DR. EGAN: Yes. I mean we--are you talking about a psychiatric adverse event like

baseline BMI?

DR. WANG: Yes.

DR. EGAN: I think we did do that analysis and I am sorry--I am not sure if Todd or Lee remember the--I mean you are right because, typically, people in the higher BMI categories, a BMI of over 40, tend to have more depression.

I know from the sponsor's analysis they said that that was not found. But we will get back and get that information to youo. We did it for suicidality, but that's, you know--

DR. WANG: It is pertinent also because I think, you know, in your briefing material you sent us, it looked like there was also a suggestion that there was greater efficacy.

DR. EGAN: Efficacy in that group.

DR. WANG: So, that would change the risk-benefit profile, but anyway, that would be helpful.

DR. WOOLF: This series of studies were done under the FDA guidance of September '96. They met the criteria for weight loss, but there was

another criteria that they did not meet, and that is--and I am quoting from the memo of 9-24-96 that said, in order to obtain an adequate estimate of the safety of weight control drugs for long-term administration, generally, about 1,500 subjects are expected to complete 12 months with 2- to 500 of these completing 24 months.

According to the adjudicated data that we received a couple days ago, only 975 patients, in fact, completed the 20 mg dose. In the unadjudicated data, I think there were two less. So, in point of fact, it appears that only two-thirds of required patients, by FDA guidance, this is what it says in the data received from the FDA.

Actually, we completed the full year and I would like to know whether obviously that is correct, because I think that has a huge impact on whether we can proceed or not.

DR. EGAN: I think the number was actually closer to 1,100 who finished approximately 12 months of treatment on rimonabant 20.

DR. ROSEN: Comments from the sponsor?

DR. DURRLEMAN: Yes, maybe two points of clarification that came up earlier today concerning the gender difference in the risk for suicidality or depression.

We have performed this analysis and, as presented in the briefing package of the FDA, we noticed that the risk for men is 1, basically. So, really the increase in symptoms of suicidal thoughts is mainly toward women as presented in the FDA briefing package.

We also have performed the analysis of risk for psychiatric symptoms and suicidality for BMI categories, and, in fact, as we go to higher BMI class, the risk is smaller and smaller. As far as the duration is concerned, in our original NDA, we had the numbers as presented. We have a number of ongoing studies that we are going to propose and present for the duration of exposure.

DR. ROSEN: Can we just clarify the number again? I am not sure we have clarification on the completion, the number completed and adjudicated

for one year.

DR. GURAL: Total patient exposure for one year at 20.

[Slide.]

As you can see in this slide, and I will point, 20 mg exposure up to one year, it is 1,134, two years of exposure, 441. In the smokers, which is an additional population, although not intended for the indication, there is an additional 183.

DR. WOOLF: There is a 300-patient discrepancy here, or 200-patient discrepancy between the data that you were telling us here and that the FDA analyzed.

DR. ROSEN: Is that from the completion, from what we have December 2006 to March of 07?

DR. GURAL: I am sorry, could you repeat your question?

DR. WOOLF: The document that we received a couple days ago from the FDA had 975 patients completing the RIO studies on the 20 mg dose out of a total of 2176, and yet you have got 250 patients more, so were they included in the data set that

the FDA was able to analyze, or where did they come from?

DR. GURAL: These are from the completed four RIO studies as identified here in the footnote.

We will validate the number for you.

DR. CIRAULO: I will try to get several questions in. Let me just say I am worried about the use of this drug in a population that has not been discussed today, and that's the schizophrenic populations who develop metabolic syndrome from atypical antipsychotics.

I am especially concerned because I didn't hear much about the schizophrenia study although it was in some of the background material. So I just want to throw that out there.

I am also concerned that some of the anxiety symptoms--and they were talking about suicidality--but some of the anxiety symptoms may indeed be psychotic panic especially, as you pointed out, the role of the system, the cannabinoid system and anandamide, in reducing

psychosis.

So, I am wondering about how carefully--the comments made earlier--how carefully those were queried, how skilled the people who were making those queries about psychological symptoms were.

So, I think that my general feeling is I would agree that there is an underestimation of the severity of the psychiatric risk associated with this drug.

DR. ROSEN: Any comments from Dr. Egan?

DR. EGAN: Yes, I was just looking for a slide that we do have. We do have a slide prepared on the psychotic and dissociative events that occurred, which you are right, they are--we didn't discuss this, but we are concerned about evidence of psychosis, and you can see the imbalance here where 2.7 percent of rimonabant users versus 0.5 percent of placebo--and this is just the RIO study, so we haven't factored in the schizophrenics--experience a dissociative or psychotic disorder, and we had 1 percent developed

aggression.

So, yes, you are right. One of the populations we do have tremendous concerns with are the patients on atypical antipsychotics who tend to gain a lot of weight and would likely seek out a drug like this.

DR. ROSEN: Dr. Carpenter.

DR. CARPENTER: A question regarding the European data, which I think is very helpful in terms of seeing an experience in current practice, and that is, do we have any sense of the denominator? Do we know roughly how many scripts of each of those compounds have been written since approval or since marketing?

DR. COLMAN: No, I don't have that specific data for the other two compounds. Roughly 100,000 have been written for rimonabant. We do have something called--and I hesitate a bit to mention it--it is called data mining, which does take into account the use of the various drugs. And what I can tell you is the signal for suicidal ideation is about 2 1/2 fold higher for rimonabant

versus sibutramine, and that does take into account the extent of use. So, that is about the best I can give you right now.

DR. ROSEN: Michael, did you have a question?

DR. PROSCHAN: Yes. A lot of this suicidality discussion seemed to hinge on--well, some of it hinged on that smoking study 4796. I was just looking at your slide 49 where it shows that smoking trial with kind of a big confidence interval. We can't actually see how big it is because it keeps going. And yet that trial had very large sample sizes and the total number of events was fairly high. And so I would expect that confidence interval to be narrower than it is and it doesn't seem to match figure 7 in document you sent us although I just realized, as I was looking at this, that 7 is actually risk difference rather than the odds ratio.

Is that the correct length of that confidence interval?

DR. EGAN: Yes. I can probably sort out

and find the exact confidence interval for you and, actually, this is interesting in and of itself. And she chose 5 mg here thinking it was more or less giving something away, because we expected to see some events on active treatment, and we were willing to concede that in order to put that in the analysis. So it wasn't done to deceive anyone. We thought we were actually helping the sponsor and doing a very conservative analysis.

DR. PROSCHAN: Yes, that was interesting because earlier the sponsor objected to that use of it, use of the 5 mg, because it is an active dose. But, like you said, you would expect that to make it look even, you know--

DR. EGAN: Better for them.

DR. PROSCHAN: Yeah, less of a problem.

DR. ROSEN: Dr. Egen, if you remove that one study, do the confidence intervals go to 1 with the removal of the smoking study?

DR. EGAN: I did mention the sensitivity analysis. It is not included obviously in the obesity study. I think I mentioned it was 1.93.

Sensitivity analysis first ignoring the second randomization revealed an odds ratio of 1.7. That confidence interval was 1.0 to 2.8, p-value of 0.0283. And then excluding the studies with a second randomization, the odds ratio is 1.6 with a confidence interval of 0.89 to 3.03 and a p-value of 0.1077.

DR. ROSEN: Thank you.

Any other questions from the Committee? Dr. Burman first, and then Dr. Gilman.

DR. BURMAN: I would like to focus on the question of whether psychiatric-disease screening, a history of psychiatric disease, can be used to predict who is going to get future psychiatric problems from rimonabant.

It seems, if I understood correctly, that there is a discordance between the sponsor's result on this and your results, but I don't know that I understand why there is such a discrepancy.

Do you have a possible explanation?

DR. EGAN: I think that they limited their analysis to depressed mood disorders and

disturbances. What we looked at were people who had a baseline history of depressed mood disorders and disturbances, and then looked at the number of people from that group who developed a psychiatric adverse event. Again, that was a composite. It wasn't just that they went on to develop depressed mood. They went on to develop a psychiatric adverse event.

What we found was 32 percent of those with a baseline history went on to develop a psychiatric adverse event, and only 17.6 percent of those who did not have a baseline history of depression went on to develop a psychiatric adverse event.

But if you looked at the total number of psychiatric adverse events, I believe there were 1,235 of them, all but 153 of them occurred in subjects who did not have a baseline history of depressed mood disorder.

DR. GILMAN: Let me ask you about seizures now. I would like to cycle back to that again. On the FDA's page 41 and on the sponsor's page 99, this is taken up and I just wanted to ask you about

the type of seizure, because it is not clear here. As I make out this table, there are three patients on placebo who had seizures and eight that were on drug that had seizures.

I know there have been two experts who have adjudicated these case report forms and concluded these are seizures, but that does not satisfy me much. I wonder if there is any descriptor that would help us understand what is going on. Is there a specific kind of seizure? Is it psychomotor?

DR. EGAN: It was all--it could have been a petit mal. It could have been a focal motor. It was not limited to grand mal.

DR. GILMAN: The problem with petit mal, it's a disorder of children, and when people say they have petit mal, they probably mean it's a partial complex seizure. Petit mal is a very specific entity seen in children, not adults generally unless they have had it from childhood.

I an troubled by this table. I don't think the data here are very good as reported, at

least by other than sponsor or the FDA.

DR. ROSEN: We have a brief sponsor clarification.

DR. GURAL: We have with us Dr. Mattson, who did do the blinded evaluation of all the potential cases for seizure. Dr. Mattson.

DR. MATTSON: Thank you.

I have the same conflict as Dr. Bradley. I am here on behalf of the company, the sponsor.

In response to the kind of seizures, most of them were convulsive that we considered likely seizures, and the basis for that diagnosis was the usual things like tongue biting, mouth biting, incontinence, and reported convulsive movement.

There were a few in whom they could have been complex partial seizures or they could have been a dissociative episode. We considered those possible and included them as being seizures.

There were about a quarter that did not conform to what one would consider a description of an epileptic seizure as is very common in people with a diagnosis of seizure coming to an epilepsy

center. About a quarter of them are not epilepsy.

But most of them were convulsive as you would expect in an adult population. In children or in the elderly, we often have partial presentation. So, most of them were convulsive.

DR. ROSEN: Thank you.

DR. EGAN: Your concern is a valid one. This was a retrospective analysis and there often wasn't very much information that was recorded.

DR. ROSEN: Dr. Hirsch.

DR. HIRSCH: I don't know who to ask the question. We hear a lot about the smokers and their adverse effects. I just want one or two other questions about the group. I gather they didn't stop smoking, apparently, but without giving details of that, I do wonder did they lose weight.

DR. EGAN: I don't know that. I don't even know if it was measured, I honestly don't know.

DR. HIRSCH: I wonder whether the ones who did stop smoking gained weight. I would be interested in knowing anything you can easily tell

us about it.

DR. ROSEN: Briefly.

DR. SEBILLE: Marie Sebille, Clinical Development, Psychiatry, Sanofi-Aventis.

We have investigated the efficacy of rimonabant in smoking cessation. You have seen the program we have conducted with three short-term studies for smoking cessation and one long-term study for evaluation of maintenance.

We have evaluated weight in these studies as main secondary endpoint. And the objective with rimonabant was to see to what extent the drug was able to reduce the usual weight increase that is observed in abstinent smokers. So, the objective was not at all to evaluate a weight decrease in this population but to prevent, try to reduce, the weight increase.

What we saw is actually the drug was effective to reduce the weight increase observed during the smoking cessation process.

DR. ROSEN: Michael, did you have another question? Unless there is any other questions,

this will be the last--oh, there is one more, I am sorry.

MS. COFFIN: Melanie Coffin, Patient Representative. I am curious. It goes to the population. Most of the group studied was caucasian women that were middle-aged. So, I am wondering should we be concerned for women in child-bearing years?

DR. ROSEN: Good question. Child-bearing age, the issue of approval.

DR. EGAN: I think that Dr. Davis-Bruno touched on this earlier about the teratogenic effects. Did you want to comment, Karen?

DR. DAVIS-BRUNO: I will comment briefly because I wasn't going to discuss the repro effects.

There are repro effects. There is also maternal toxicity concomitant with those reproductive effects seen in rats and rabbits, so that will be a review issue for the labeling.

DR. ROSEN: Good. Thank you.

DR. PROSCHAN: I just wanted to, you

know--because someone mentioned the sensitivity analysis without that smoking trial and it looks like certainly if you go by the risk difference, it looks like it is going to make a huge difference whether you include it or not because that confidence interval is very small for that smoking trial. And so I think it will have a huge difference there.

I don't know about when you look at the odds ratio, but at least for the risk difference.

DR. EGAN: I think Dr. Sahlroot would like to comment about that, please. He is our chief statistician.

DR. ROSEN: Great.

DR. SAHLROOT: Todd Sahlroot, Staff Team Leader.

Getting back to the--before I get to the risk difference, the odds ratio--that study did have a tremendous variance, the smoking study, not because there were 12 overall events but because one arm there were zero events, so that really does inflate the variance and the weight is inverse to

that.

So, there was a very small weight attached to a very large odds ratio. So, I don't have the exact data in hand, but I believe we did do that analysis and the odds ratio. When you remove that study from the total studies, the odds ratio came down. It was not as low as 1.3, which is what I think the sponsor had, but it was between 1.3 and our original odds ratio of 1.9.

The lower bound of the confidence interval, I think was below 1.

DR. PROSCHAN: Right. But the risk difference is what I am talking about. It looks like it would make a big difference whether you take it out or leave it in for that measure of the treatment effect.

DR. SAHLROOT: Yes, it would make a bigger difference there, because the confidence interval I believe was tighter, so, yes, that's true.

DR. ROSEN: Thank you.

Paul, you have one final question and then I think we are going to go to break before we deal

with the questions.

DR. WOOLF: A question for Dr. Mackie in slide 30. You had pair-fed mice, who were fed the same amount of food as the rimonabant mouse, but they lost more weight. Now, calories in equals calories out. Did they either burn more calories or did they waste more calories?

If they burned more calories, is this an increase in BMR, and would that translate that into potential weight loss in humans?

DR. MACKIE: This is the graph that was being spoken of. Basically, the observation is that the pair-fed animals lost less weight. The mechanism of this is not clear and I think is not too relevant for human use. It was just a motivator to look for an effect that may be peripherally mediated, which sort of led towards the adiponectin/adipocyte line of reasoning given that the adipocytes express CB1. But, if it's ground fat or something, it is not essentially meaningful for humans.

DR. ROSEN: Thank you very much.

I would like to bring this part of the session to a close. We have a 10-minute break and then the Committee will convene to discuss the questions and take a vote on each of the two questions.

The sponsor has asked me to recognize Judy Jones to come to the microphone, please, and declare your conflicts, as well as who you are, what you do, and give us a one-minute clarification of the European data sets.

DR. JONES: Thank you very much. My name is Dr. Judith Jones. I am President of the Degge Group, a drug safety consulting group.

A number of years ago I was head of the FDA's Drug Safety Group. I want to correct and put in context the data that was presented on the European data. It is very difficult to compare numbers of spontaneous reports but, in this particular case, it is critical.

The rimonabant program is the subject of stimulated reporting through both the postmarketing risk management plan you heard about earlier and

also a patient support program. Thus, the company is actually going out and getting reports so that, in part, explains the larger number of reports.

The second thing is that the reports come from the EUDRA [?] Vigilance program, and EMEA has not completed entering all the data for the older drugs.

Thirdly, the proportion of events that are seen are explainable by virtue of the fact that the two other drugs have other types of adverse effects, cardiovascular for sibutramine, and gastrointestinal for orlistat.

So, it is important to realize that you can't take those numbers literally.

[Break.]

Committee Discussion and Questions

DR. ROSEN: I will just remind the panel that we are not going to discuss diabetes as an indication for approval since that is a separate--and not piggybacked onto the weight-loss question for approval.

I am going to start with Dr. Jules Hirsch

to at least begin the discussion, and the first point that is raised is, please discuss your level of concern regarding rimonabant and psychiatric adverse events, in particular depression and suicidality, and neurological adverse events in particular, seizures, and the reasons behind your thinking on these issues.

I will then just entertain raised hands or we can go around the table and discuss the issues related to safety.

Dr. Hirsch, i would appreciate it if you would start, and please identify yourself one more time.

DR. HIRSCH: Yes. I am Jules Hirsch at Rockefeller University in New York. Your chairman is very kind letting me comment first. I unfortunately have to leave early, so I am glad to give you what comments I can.

I know it's our job here to tell what is good and what is bad about what the sponsor has presented us and what we are dealing with. There is much good about the rimonabant and all the

things you have heard today.

The greatest good I think is that people are trying to do something pharmacologically about obesity, which I needn't remind this audience about the extraordinary prevalence of it and its chief comorbidity, type 2 diabetes, and it is refreshing to hear about new things in this connection.

What also is good about it is the drug does lead to weight loss, there is no question about that. Now, I have a lot of other problems. However, having said that, the first problem I have with it is that, when I examined the weight loss curve, I note it seems familiar to me. It is exactly the same sort of weight loss curve that sibutramine gives and orlistat or Zenecal gives.

What happens is the weight comes down, the majority of it, about 5 percent more than placebo effect in the first 6 or 8 months, and then it sort of flattens out, but if you look carefully, just before a year or two, the inevitable is happening. The weight is beginning to come back, and that happens with both of those drugs.

It seems to me--I didn't do the statistics on it--it looks as though we are headed in exactly the same direction with this drug. It is rather surprising to find the similarity of all of these curves because presumably the mechanism whereby this has occurred is a totally different thing with endocannabinoids, a very new and wonderful area. One would have anticipated something different. But perhaps what is happening in all of these cases, something else leads to the weight loss rather than a correction of a fundamental aberration that caused the obesity.

I feel strongly that we are learning more about these aberrations from the study of the drugs but that none of them is attacking fundamental causes including this one, in my opinion.

I have other problems with this also. I am delighted that some of the type 2 diabetes, the carbohydrate intolerance, and other problems are ameliorated during the weight loss, and I understand the statistical techniques of linear regression that help one evaluate just exactly what

percent of the variance in the carbohydrate intolerance is associated with, and related to, the weight loss, and what isn't, and that there is an independent effect.

I would doubt that very much, however. I think if one really wanted to know about that, the study that has to be done is that rimonabant has to be given to people specifically for that examination, and maybe that is being done or will be done, and great efforts made to maintain no weight loss, but exactly the same weight in a group of obese individuals, and study what happens with carbohydrate intolerance. Without such a study we may not really know that.

So, I am worried about any notion that this drug is better than others because of the good things that it does specifically with these comorbidities.

The problem with the whole thing, as I see it, is, number one, the number of people who are going to lose weight is fairly small. Apparently, about half of the people who are given the drug

will lose some weight, 5 percent or so of their body weight.

About a quarter of the group will lose the wanted 10 percent or so but, even in these circumstances, it is not much. Remember that we were presented several times with data that showed that when you tell people you are going to lose 17 percent of your body weight, which was picked because of what some drugs and stuff do for this, that people find that very disappointing. And this group will find it disappointing, too, those who are put on rimonabant.

You are telling a 220-pound woman that she has a sort of 1 in 4 chance of getting down to 200 pounds if she sticks with the program. Well, that is not going to make anyone very happy, but that is what we are getting out of it.

That is what people can expect and what is going to happen. Now, the question is, on the other side, what are the dangers with it. Well, I am not going to go into any great detail with this because you have heard it just as I have, and at

least I think everyone will agree there is a reasonable suspicion that we had better learn some more and watch this whole affair very carefully before we lunge into massive use of the drug for the benefits that I have mentioned.

Now, in order to take care of that, we were presented also with a wonderful new idea. It is called risk management action plan, and I think that is novel and is very interesting and exceedingly important. We are in desperate need of techniques for handling the Phase IV.

We know that only a fraction of adverse effects are usually reported now. We need new techniques for doing it. I worry, however, about the statement that the help of 20,000 physicians will be enlisted, each of whom will study I think 20 or 200, or whatever, patients and these data will be pooled and the patients will be managed in a special way.

If the sponsors really feel that can be done, I am sort of surprised, because it shows some lack of understanding of the sorry current state of

our health-care management in this country generally, that such a program could possibly be undertaken without the kinds of duress and so on that would probably be not suitable or legal or whatever in these circumstances.

In any event, the idea is a wonderful one, but I don't think we can do that, or I don't believe that can come about unless I misunderstood it completely.

Given this whole situation, therefore, I have come to the conclusion for myself that if I am asked to make a statement about this, I am glad the drug is available. I hope that lots more good work will be done, but I wouldn't in any way suggest that it be approved at the present time for use.

DR. ROSEN: Thank you, Dr. Hirsch.

So, in answer to the question, because I know you have to leave, 2a. Do you believe that the currently available data sufficiently characterizes its safety profile?

DR. HIRSCH: No.

DR. ROSEN: Thank you.

I think what we will do is we will go around the room and discuss Item No. 1 first and then come back for a vote on Item No. 2, and then go to the second question.

Paul, would you mind starting the discussion on Item No. 1 again, your level of concern about the safety issues, particularly the neurologic issues?

DR. WOOLF: Again, I am Paul Woolf. I think there is concern, and I am concerned about what we don't know and the dangers that we can fall into. We have a first in class. We have a whole bunch of studies that are in progress and particularly the stress, as I said before, that it did not appear that the sponsor had the requisite number of patients to meet the target of 1,500.

By the way, that number was reconfirmed less than four years ago at a committee meeting that I was participating in that agreed that 1,500 was the bar that needed to be reached for a one-year trial.

So, we don't have enough patients on here

for a long enough period of time to know what is going to happen down the road, and we have enough concerns. If the drug could cause a 30 percent weight loss, I think we would all be jumping up and down and throwing our hats in the air and say this is marvelous, and we might be willing to overlook the concerns.

But as Dr. Hirsch pointed out, this drug has about the same efficacy as the other two approved drugs. By the way, I think it's ironic that Aleve, the over-the-counter drug actually went to market today.

DR. ROSEN: I guess I could query you then as part of the voting, do you believe that the currently available data characterizes the drug's safety profile?

DR. WOOLF: That's up to the --

DR. ROSEN: I am sorry.

DR. WOOLF: Given what I said yesterday, I am not.

DR. ROSEN: You are not.

DR. WOOLF: I would vote no.

DR. ROSEN: You would vote no.

[Comment off mike.]

Okay. Go ahead, Eric.

DR. COLMAN: We received an e-mail last night from the company that was unopenable, and I was just approached by someone from the company who said--and I think I understand this; correct me if I am wrong--that the company sent us information to correct a table, and it now appears that the table that they sent us was not correct.

Is that correct? No?

DR. ROSEN: I think we are going to have to have you show us the table.

Paul, if you change your mind, we will go back and query you again this.

DR. GURAL: To answer your question, here is the exposure information from the long-term exposure in the Phase III for both one year and two years in the obesity trial plus the information on one year from the smoking trial. The combination of both the 5 and the 20 mg exceed the numbers of 2,000.

DR. ROSEN: Paul, do you want to talk about the guidance again, or Eric--

DR. WOOLF: I am just quoting. The indication was for the 20 mg dose, and I don't think you can adequately compare the 5--lump the 5 and the 20 mg together and say we have enough. We are going for 20 mg indication, do we have 1,500 patients who have been on the 20 mg dose? If it's 1,495 I could care less. If it's 1,100, that makes a difference

DR. ROSEN: Eric, can we get guidance on that? In the guidance it was 1,500 for the approved dose, is that correct?

DR. COLMAN: The original guidance was a little vague. It said 1,500 patients, but some people meant--does that mean 1,500 patients randomized or 1,500 complete? Does that mean every active dose or just the top dose?

I can tell you that internally, we never had any major issues with the number of patients that were studied in the rimonabant trials.

DR. ROSEN: So that settles that.

Paul, I will just query you again, you are not changing your mind?

DR. WOOLF: No.

DR. ROSEN: Okay. I would like to move to Dr. Gilman, please, if you can start the discussion.

DR. GILMAN: I will directly address the question. My level of concern regarding rimonabant and psychiatric adverse events is very high. In other words, I am very concerned that, first, there is a high dropout rate for various reasons. Second, there is a high proportion of people who develop suicidal ideation on high dose versus lower dose versus placebo. Therefore, I think this is a drug that needs further understanding with respect to what it does to people's psyche.

With regard to the neurologic problems, I am mostly concerned about epilepsy, less concerned about multiple sclerosis. It seems to me the data on multiple sclerosis are not definitive; that is, it could be that the events observed are within the natural course of frequency of multiple sclerosis

that we would expect without rimonabant. I don't see any direct tie to them except for that one case in which it appeared to exacerbate its symptoms. That is a possibility.

But with the seizure history, the seizure disorders, I went through these tables very carefully actually and I am struck that many of the patients who had a convulsive disorder did have a history of a previous epileptic episode of some sort even though the data we have are very sketchy.

There are probably three of those cases that did not have a history of previous epileptic seizure or frontal meningioma or an astrocytoma or some other cause for a seizure disorder.

So, it looks as if a previous history of a seizure does constitute a risk factor, at least in this group that were reported. All the same, seizures occurred more frequently in the rimonabant treated group 8 cases than in the placebo group 3 cases. So, I have concern about the neurology with respect to seizure disorders.

For the rest, I have already said it is

very unclear what these patients were experiencing, what do they mean by dizziness, what memory impairment do they have. I don't think we have adequate information despite the very large number of cases exposed. It's a huge number of cases with grossly inadequate data. What do they mean by memory disturbance? Is there anything objective about that?

What do they mean by lethargy? These are words, but they are not documented with anything that one can quantify. So, I am concerned about that.

DR. ROSEN: So, in querying you, do you believe that there is sufficient safety profile for rimonabant?

DR. GILMAN: I am concerned about the quality, not the amount of safety data.

DR. ROSEN: So, would you vote that there is or is not adequate safety data?

DR. GILMAN: Is not adequate, it's safety data.

DR. ROSEN: Thank you. Dr. Kreisberg.

Dr. KREISBERG: I am sorry that Dr. Hirsch said most of what I wanted to say, but I will paraphrase it to say that I am concerned about the relatively low frequency of adverse events that occur in the population that has been studied when you consider this might be extrapolated to a much larger group of patients who would be eligible for the drug.

Some rough calculations that I have made based upon only the psychiatric and neurological adverse effects, recognizing that some of them might be rather trivial, the absolute increase in risk is such that the number that you need to treat for harm is 6, and the number you need to treat for benefit of a 5 percent weight loss is about 4, and for a 10 percent weight loss is about 6. So it looks to me that the number needed to harm and the number needed to treat are pretty well balanced based upon the information.

DR. GOODMAN: Would you mind repeating that? This is Dr. Goodman speaking. Would you mind repeating that? I just wanted to hear that

again.

DR. KREISBERG: The percent of patients who have adverse neurologic and psychiatric events is about 12 percent higher in the rimonabant group than it is in the placebo group, and the number needed to treat, which is 100 divided by 12 is roughly about 8. So the number needed to treat for harm, the NNH, is about 8, 6 to 8.

If one looks at the absolute increase in weight loss as you use the rimonabant 20 mg dose, 5 percent versus 10 percent, the number needed to treat to achieve that particular benefit is somewhere in the neighborhood of 4 to 6.

So, overall, the relationship between the number needed to treat for harm and the number needed to treat for benefit is about the same.

DR. GOODMAN: I thought that was a very important point. I wondered whether the company--we could hear whether the company agrees with that and also whether or not it makes a difference whether you include or exclude the smoking-cessation study. I have some concerns

about us lumping the smoking-cessation study together with the obesity.

DR. ROSEN: I think this is such an important point I would like some clarification from the sponsor on that.

DR. GURAL: Could you please repeat the question, please?

DR. ROSEN: Basically, what we want to know is, if you calculated, as Dr. Kreisberg said, as the number needed to harm versus the number needed to treat for effective weight loss, it comes out about the same. The question, really, is have you done that and, if you haven't, why haven't you. And, if you have, what is your interpretation and does it include the smoking-cessation study which seems to be a bit different than the other ones in terms of the risk association.

DR. GURAL: Let me see if I can answer that question. We looked at the number needed to treat for 5 percent and 10 percent weight loss and, as Dr. Kreisberg said, it is about 5 to 6.

Now, as I showed this morning, for the

neurological events, the serious ones, the ones that require discontinuation, were very, very few. Most of the neurologic events were transient. Most of the patients continued. They were not medically important, did not require hospitalization.

What we did do for number needed to harm was to look at depression. And, when you do the depression, it is about--I think it is 1 in 60 or 70. So, for depression, it is about 70. For the number needed to benefit--and this is only obesity--it is about 6.

You get comparable figures also for diabetes, in diabetes in terms of A1C reduction because A1C reduction is something that has been associated with clinical benefit. So we would say 5 to 6 and about 60 or 70 for the depression.

DR. ROSEN: Is that excluding the smoking cessation?

DR. GURAL: Yes; it is.

DR. ROSEN: Dr. Goodman, you can have the floor.

DR. GOODMAN: Yes; I just wanted to follow up on that. I am a little concerned about lumping all the psychiatric side effects in that number needed to harm. I don't think they are all equal in terms of severity of in terms of ramifications. So I just--I like what you are trying to do in terms of comparing number needed to treat versus number needed to harm but I think we may be over-estimating the harms by lumping all the psychiatric and neurological together.

DR. GURAL: No; I was saying for depression only.

[Comment by sponsor off mike.]

DR. ROSEN: No, no, no. I think we are all set from the sponsor point of view. I think you made your point. Thank you very much. So let's have Dr. Kresiberg continue the discussion.

DR. KREISBERG: Well, I am not going to spend a lot of time rebutting that. You certainly are correct. We need to pick out the serious adverse effects. But the point of fact is, from other studies of intervention, it is frequently the

less serious effects that determine whether or not the patient will continue to take the medication or not.

Certainly, from statin studies, we know that the things that we can't quantify often determine the attitude of the patient about whether they will continue the medication.

The second thing is that I think the weight loss is modest and it has all of the characteristics that Dr. Hirsch described so elegantly. I, personally, believe that the sponsor's claim that the prespecified regression analysis accurately depicts what the weight-independent effects of the drug are on important metabolic parameters.

I actually like Dr. Arrone's more even-handed approach which is simply to say that the use of this drug was associated with reduction in cardiovascular risk without claiming that there was an additional mechanism beyond weight loss.

I, personally, believe that you would have to do the study to convince me that there was this

weight-independent effect. You might be interested to know that I looked up "deduced" because you use the term "deduced" in the briefing document.

In the dictionary, it says, "To reach a conclusion by reasoning, to infer from a general principle." That sort of implies that you don't need data to do it. I think you need hard data to make that claim and I don't think the data that you have is hard.

With regard to the question 2a, I am not exactly sure what that question means but I don't believe that there is sufficient safety data or sufficient data of safety of this drug to proceed.

DR. ROSEN: Thank you, Dr. Kreisberg. Dominic?

DR. CIRUALO: Dom Ciraulo. I agree with what has been said. I just want to--I will summarize. From my perspective, I think that the reports of the psychiatric adverse effects are too high and too serious, especially given the attrition. I really think that--you know, you can argue when you lose so many people from a study

that efficacy is affected. You can argue it both ways. People leave because they are not getting better or because they have gotten better.

But I think what the real implication here is, you have lost data on adverse effects and I think you have lost serious data on depression and anxiety

The other issue I would like to emphasize is that anxiety is a serious psychiatric disorder. It is not being afraid to talk to your boss. It is associated with suicide and it is not to be made light of. I think that we are somewhat underestimating that.

Then I think the other is the slide that was shown on aggression and the possibility that some of this anxiety may be more of a psychotic aggression nature. And I think that is a very, very serious problem.

I also think that the point that was made that subjects who have a baseline history of depression may be at higher risk but people who don't have a history of depression in the past are

also at risk. I am also not clear about treatment. I really don't know what happens when these people get depressed or get anxious. I understand that some of them get treated, but I worry about follow up, how good the follow up is, and what the consequences are.

So, as far as--the only thing I want to say about neurological side effects, which is not my area, I think that some of them may seem minor. Dizziness may seem minor. Balance may seem minor. But somebody falls and breaks a hip. Somebody is in a car and has a seizure. That person is affected and society is affected.

So I would not minimize the neurological consquences that have been reported. So, essentially, I vote as the others.

DR. ROSEN: So I need to query you officially. Do you believe there is sufficient safety data for rimonabant?

DR. CIRAULO: No; I don't.

DR. ROSEN: Thank you very much. Melanlie, could you introduce yourself?

MS. COFFIN: Hi. Melanie Coffin. I have to say that this is the first prescription drug advisory committee that I have sat on. The other one was for over-the-counter. So, obviously, with physicians stepping in, I assumed there would be a little bit more risk.

But I have to be very honest. As I was reading through the prep documents, my eyes got really big on quite a few issues. I think it is interesting that it has been a couple of times said that serious adverse events required hospitalization. But I would agree that a jump in anxiety is pretty serious to the individual that is actually having that.

I am concerned about the extrapolation of both the aggression in the males, or the suicides in the males, as Bob talked about and also the child-bearing. I think it is great, actually, that the sponsor did not intend to direct market for one year out of the shoot. But I will go back to what Lynn said and what I have experienced is that patients--people who are overweight and obese are

desperate, desperate, desperate, for any measure.

To see what goes on in the blogs on the websites, et cetera, word spreads like wildfire, whether there is good information to back it or not. Right now, doctors are not proactively addressing overweight and obesity with their patients and, often, it is the patient that is bringing it to them in the first place.

So I think, between those two things, you have got to watch it although I do appreciate the intent. I think that is fantastic. And I have to say, too, that the expectation of the patient--I would agree, that the patients, the dropouts, a lot of it has to do with the fact that they would like to have the weight off yesterday. And they would like all 50 pounds of it off, you know, before that.

So I think that safety data--it still makes me very uncomfortable. And so I would go with the rest of the panel on Question 2 that I would like to see a little bit more.

DR. ROSEN: So you would vote no?

MS. COFFIN: I would vote no.

DR. ROSEN: Thank you very much, Melanie. Dr. Wang?

DR. WANG: I largely agree with what has been said so I won't cover that ground again.

DR. ROSEN: Phil, could you just identify yourself again?

DR. WANG: Yes; Phil Wang. I think, although we still have some questions about the data we have seen, it appears there is an important safety signal emerging with significant associations between the agent and depression and suicidality.

So I appreciate the sponsor's efforts to go sort of in a direction of finding a subgroup that they feel might be less at risk and still benefit. So your idea of identifying those who don't have a history of depression I think is the right direction to be going in.

Unfortunately, the data you showed indicate that the doubling of risk is still present in even the subgroup that doesn't have a history of

psychiatric illness.

So I think there is a need to then continue to pursue further other subgroup analyses that maybe might indicate a subpopulation in whom the cost/benefit, risk/benefit, analysis is favorable. In the data that were raised, the reason why I was asking those questions earlier, I think there is one potential candidate group and that is the folks with higher BMIs, the extreme obesity folks. It looks like there is some preferential efficacy in them. To my back-of-the-envelope calculation, it looks like you actually have lower risks of these adverse psychiatric events in that--maybe a group, you know, with, I don't know, BMIs greater than 40 or something.

But this is all going to take more data, I think, and more subgroup analyses to sort of explore this route. So I think I would vote that more data is necessary before proceeding.

DR. ROSEN: So you would vote no in terms of the currently available dataset?

DR. WANG: Yes. Yes; I agree with what you said.

DR. ROSEN: Thank you, Dr. Wang.

DR. GOODMAN: This is Wayne Goodman speaking. This is a real quandary for me. I recognize the need for additional medications. There are very few effective treatments for obesity out there. It seems to me one option might be to consider--is to identify more stringent prescribing guidelines in a group where--I just don't want to deny this option for a subgroup of patients out there.

I think that these psychiatric side effects are prevalent. Some of them are quite significant. Some of them represent hard endpoints whereas the others are softer endpoints. There is the risk that others have mentioned that there will be some proliferation, some generalization, to other populations where the risk may be higher.

One area where I would like to see--I wish we had some additional data--is the fate of those patients who wind up being terminated from the

trial or the treatment because of development of depression. I would like to know more about their long-term fate in terms of how long they need to be on anti-depressants or whether there is actually a possibility in the future of considering the combined use of rimonabant and an anti-depressant. I understand why it was excluded from the trials.

It is hard for me, too, to try to think about my concern about a risk in the absence of the consideration of the benefit. I go back to the earlier questions I had about the quality-of-life data.

That, perhaps, troubles me more than anything else is that, when I try to reconcile--say, on one hand, well, it is clear that there is an efficacy signal. The patients are going to be enjoying some decrease in weight that has benefits, medical benefits, as well as some quality-of-life improvement.

On the other hand, it is offset by a diminished quality of life in other areas including the emotional and mental life functioning. I

understand that that may represent this disproportion of contribution of those patients who had the most adverse psychiatric events. Yet we are still left with looking at what the mean changes are. And they are pretty glaring in terms of the association between improvement and physical well being and emotional well being overall. So that probably gives me the most caution.

In terms of you want a vote? I guess I have said enough

DR. ROSEN: That's correct.

DR. GOODMAN: I would say that I would like to see additional safety data.

DR. ROSEN: So you would vote no.

DR. GOODMAN: I would vote no; yes.

DR. ROSEN: I just wanted to ask you a particular question. You seem to have focused on that quality-of-life issue that was presented in the slides by the sponsor. It seems to me that some of these were carryovers from their last visit before they dropped out. So we may be even underestimating the impairment in quality of life

because we are missing a whole group of people.

Michael?

DR. PROSCHAN: I am Michael Proschan. I think it is clear that there is a benefit of this drug. I am not sure that it is entire--well, I worry about the high dropout rate and I am not sure which way the bias goes when you use last observation carried forward. I mean, you would think, in certain ways, that that should make it look even worse for the drug because you would think that people who dropped out in the placebo arm may have been gaining weight and, if it continued, they would have gained even more weight.

On the other hand, they may have dropped out at a random high because, I am gaining weight, whereas, maybe if they had continued, they would have gotten over the hump, so to speak.

So it is hard to say which way that will go. But I think it is pretty clear that, even with that high dropout, there is some benefit of the drug on weight loss. Now, whether the effects on some of those other parameters is explained by

weight loss--I mean, I think there is certainly some evidence of that. I think they have presented some animal studies, the rat example where they tried to feed the rats the same amount as the ones that were on the drug and they still saw a difference, if I am interpreting that correctly.

And the statistical analysis that was done on these studies in people also suggests more than just the benefit you would see from the weight loss. But there is a problem with that analysis, I think, which is that, in regression analysis, you assume that the X variable is measured without error. In this case, it is measured with error and you are also interested in more sort of long-term weight loss.

And so those fluctuations in weight loss can actually cause it to look like the drug has some weight-independent effects when, in fact, there aren't any. I speak from experience on this because I am doing a very similar analysis in terms of trying to figure out how much of an effect was due to a blood-pressure reduction.

Anyway, the AEs, I have a high level of concern about all of them. I think, even if you look at the company's own tables, I think it is pretty clear that, for example, suicidal ideation is greater. I think neurological symptoms, depression, anxiety; these are biologically plausible.

I do appreciate the fact that ascertainment bias could be partially responsible. I don't think it explains it all. And no long-term data. I worry about what is going to happen when a patient is on this drug for a longer amount of time. I also worry about the fact that heavier people, although they are apparently getting more benefit in terms of weight loss, the half-life of the drug is longer and so, presumably, they might get more of the adverse consequences.

I also worry about the fact that they may take more than they are supposed to. I mean, if I lose 10 pounds with this dose, I will double it. I will lose 20 pounds.

So, for all those reasons, I have a high

level of concern and I would also vote no.

DR. ROSEN: Great. Thank you very much.

Katherine?

DR. FLEGAL: Katherine Flegal. I think this drug could be of benefit to many people but I am also concerned, as everybody else is, about the--I think the data on safety are not definitive but are very worrisome and seem to have some degree of biological plausibility. There is the high dropout rate which may minimize the number of adverse events that were actually reported.

I think that this collection is sort of a post hoc collection of events and symptoms that really have not been adequately investigated enough in detail because they weren't identified in advance.

That being said, I think we need to err on the side of caution in this case because I think one reality is that a lot of overweight and obese people are desperate, first of all not necessarily for health reasons but for cosmetic reasons and that we know particularly a lot of women are very

desperate about weight, not necessarily for health reasons.

Other research suggests that the proportion of people--there's a quarter to a third of people who are using prescription weight-loss medications are not actually overweight or obese and are not very responsive to safety considerations. So I think there is a large pool of people who may not really realize the benefits of the drug but could only realize possible adverse events and that would include a lot of people who have BMIs below 27, many of whom are probably going to be women because, down to a BMI of about 21, about half of women consider themselves overweight and would like to weigh less. These are extremely high numbers that people may not realize how high they are.

Also, lean people who smoke, a frequent reason for this failure of smoking cessation is weight gain. So you have lean people who are smoking in part to reduce their weight who may be inclined to try to use this drug to keep their

weight low. Again, they would already be people at low weight.

Obviously, people with diabetes could benefit from weight loss. But it seemed from the data presented they may experience somewhat less weight loss and also somewhat more potential harm in this case. So they may also not benefit.

So, all those things taken into account, I would say I would also vote no, we don't know enough.

DR. ROSEN: Good. Thank you, Katherine.

Jessica?

DR. HENDERSON: Hi. Jessica Henderson. I have very high concern about the safety data. When you look at the lifetime exposure in the animal studies, it is very clear that we need more long-term data in humans and especially, like has already been said, we are going to have massive use of this drug and we just have a very small group of people for a two-year study. But yet this is presented as a drug that is going to be lifetime because it is a chronic--obesity is a chronic

disease; therefore this will be long-term use.

But we don't have long-term data. I don't consider two years long-term data. I would at least want to come back to this after the CRESCENDO study comes back and at least have some five-year data.

The target population in these studies were more middle-aged and older women and that just reminds me of hormone therapy, being told that women should be on hormone therapy forever, breast-cancer survivors being told they should be on tamoxifin forever. And then we got the long-term data and it was wrong and literally millions of women were put at risk.

So that is my primary concern is the long-term data. And I agree with everything else that has been said. So I vote no.

DR. ROSEN: Thank you.

Tom?

DR. CARPENTER: Tom Carpenter. My comments are somewhat influenced by the very impressive scientific background to the system that

this drug manipulates and the highly conserved nature of the receptor through biology and the evidence that this is a very basic biological--is regulating a very basic biologic function in the CNS.

It is not a system that is directed specifically to appetite alone. Hence, I think the side-effect profile that we see reflects that. I think that there is very significant concern about particularly the depression and suicidality issues. I am a little bit less concerned but may have to do with the limited numbers in terms of--and definitions--related to the seizure data.

But I think, also, when one looks overall at the CNS data together in whichever analysis you see, there is considerable concern.

Moreover, we may be underestimating that, in part, because of the high attrition rate of the study. We tend to look at these numbers thinking in terms of percent of patients enrolled. If you convert how you are thinking about that to the actual patient exposure and you think of it in

terms of patient years, many of the patients that had adverse events and left the study because of that were exposed for brief periods of time and those numbers, then, change, I think, to a more significantly worrisome ratio.

Finally, I think there was one comment about the way future studies might be more directly presented to the committee in, say, the CRESCENDO study and others to yet be analyzed. If possible, it may be nice to have proactive plans and potentially even agreement between the company and the agency to agree upon a similar method of analysis so that some of the methodological issues that came up in the way the data was presented today could be avoided.

So, briefly, a no vote for 2a.

DR. ROSEN: Good. Thanks, Tom.

Ken?

DR. BURMAN: I am going to be succinct. I agree with most of the comments that were mentioned earlier. I do want to emphasize the dilemma of trying to balance the pros and cons of this

medication and also emphasize the divergent conclusions that are apparent to me from the sponsor and from the FDA.

I am concerned specifically about the longer-term effect over several years of this agent not only with the neurologic symptoms just noted but also with other things such as reproduction and hypertension.

I am concerned that the studies were done in mainly caucasians and may or may not apply, as was implied, to other ethnic groups. I am concerned about the ability of previous psychiatric disease as a screening method to predict whether somebody who is put on rimonabant will develop further psychiatric disease, and there obviously was a discrepancy between the two presentations.

I would like more specific information, which didn't seem to be given, on the European study, that they are ahead of us by a year and have specific information on, again, some flaws but, nonetheless, theoretical flaws, postmarketing studies. But I don't have a good feeling exactly

what are thought to be rates of the psychiatric neurological symptoms in the postmarketing studies from Europe.

All that having been said, I must come to the conclusion with the rest of the panel that the answer is no.

DR. ROSEN: For 2a.

DR. BURMAN: For 2a.

DR. ROSEN: Steve, you are a non-voting member but we would like to hear your opinion.

DR. RYDER: I just have one comment. Thank you, Dr. Rosen. My comments are not specifically directed to the NDA but just some thoughts and observations on just the general discussion that I have had the privilege of hearing today.

It is helpful to have as much specificity in the guidance as possible, and some of these comments may have some relevance there, and try to minimize any differences. Paul Woolf, I, and some of the others here on this committee sat through a couple of discussions that have taken place and

just the idea of how many patients, for example, at one year, at two year, on top dose--Eric, some of the things that you mentioned, and I know that the CDER staff have been very generous with their time in trying to help sponsors and other investigators.

I just want to encourage that so that development can be as efficient as possible and, hopefully, it can proceed to a positive outcome. But that is very helpful.

DR. ROSEN: Thanks, Steve.

So I am Chairman and I can talk as long as I want. But I am going to be very brief. I just want to emphasize two points. One is what is amazing is the biology of this system in that we don't really fully understand it. But, as Dr. Hirsch and others have pointed out, this drug works.

But it works through a different mechanism. I think that is actually exciting, that you can get weight loss through this system. But what I am really troubled by is the lack of good safety data. So if you were going to design a

study in which you knew you were going to block these receptors, it would be very clear, I would think, that you would want to look very carefully at these adverse events.

Now, in clinical research, and I have done it for a living for 20 years, AEs are not a big deal usually. They are recorded by the monitor or the nurse or whoever is in the clinic or the physician, and then they are checked off. But, in this particular case, the adverse events, not the serious adverse events, but the adverse events tell the story.

And we don't have enough information. I think that, in retrospect, when we look at the system that we are acting on with this agent, we need that information. I think Dr. Gilman appropriately asked very specific questions about these adverse events.

So they are a big deal and they are serious and, until we really know that information and we know the true prevalence of these adverse events, I think we can't make a decision.

So I think the sponsor has done a very reasonable job. They have worked with C-CASA. They have worked with the FDA. They have tried really hard. I think I would go back and ask the question, why weren't these more detailed at the beginning of these big trials when we knew that this is a central-nervous-system-acting agent that is going to have these kind of effects.

Until we have that information, I think it is very difficult for us as committee people to make those kind of judgements. So I would vote no and I already see a comment from Michael.

DR. PROSCHAN: I was going to say, in future trials, I think Dr. Posner's suggestion about measuring these things in a systematic way to eliminate this possible bias, ascertainment bias, it really important.

DR. ROSEN: Okay. I would like to move to Question 2 and I think that we have already talked somewhat about additional data. But I would like to open up the floor before the vote about what people would like the sponsor to do.

I think one thing that we have heard is the CRESCENDO study is going to be a very important study. But, again, it has to be so that the adverse events are coded and are properly interpreted and reviewed in an independent way so that we can get a good analysis.

I know the sponsors are working with C-CASA on this in a prospective manner. I would like other comments if people have any comments about what else the sponsor can do to obtain additional data.

Wayne, do you have comments?

DR. GOODMAN: Yes. I guess one of the deciding factors for me and, obviously, you could tell I was on the fence on this, was thinking about the chronicity of administration and the time course of both the changes in weight--and there is some suggestion that there is a plateauing, at least, in changes in weight.

I would like to know more about the time course, then, of the psychiatric symptoms. I think that has been described, but in a more anecdotal

way. If there was additional information that the company could provide now, I would still be interested in hearing that if that was okay with the Chair.

But my concern is that two years out, or three years out, when these patients are still taking it, that the risk/benefit ratio between the psychiatric or neurological symptoms and the benefit is going to change to a less favorable balance.

DR. ROSEN: I will take Dr. Gilman first and then Paul. I wanted to ask you, Dr. Gilman, as well, to comment on what you would want the sponsor to do as we move along in this process.

DR. GILMAN: Sid Gilman. As I indicated earlier, I would like to have more specific information about what the subject, the patient, means when he or she says "dizzy." There should be a subgroup kind of list that one can tick off and get more specific information and find out if they are all experiencing something similar or there are disparate symptoms. I think any neurologist could

help you determine what kind of list you would have.

For a second, I would like to see some better characterization of the seizures prospectively so that we get the best data we can. Now, I say that and I say prospectively. I understand that you can only get retrospective data from seizures. But it has to be obtained from the observer who was there with the patient or the patient, himself, herself, to find out exactly what happened. Was there an aura? Was there a falling-down episode? Was there shaking? Was it unilateral? And so on.

So I just think the quality of the data needs to be improved for these side effects.

DR. ROSEN: So that raises an interesting question that I just would like to ask Eric about and that is, you know, we have our classic definitions of serious adverse events. When we go through serious adverse events, it is quite detailed and the information is quite specific.

Is there any role for thinking about

seizure as a serious adverse event or, in some way, upping the documentation so that this process will be much more inclusive? I mean, seizure in an individual who has not had a seizure is a big deal.

DR. COLMAN: I think what we would do in that case is consult with our colleagues internally in neurology and see what they--of course, they deal with trials of people who have seizures. But they still might be a place to start.

MR. FRANCO: Thank you. Paul?

DR. GOODMAN: Let's face it. There is never enough safety data. You can always want more. No one will argue that more is better but then there is reality. But, in fact, we have reality; that is, we have a drug that is approved in the U.K. and in Germany and in 35 other countries.

I wonder if it is possible to piggyback on that experience something more than just a conventional postmarketing survey which we have heard about ad nauseum at these meetings which really turns out to be not much, and that is to do

a very detailed, very prospective, study of a subset of these patients from now until whenever and use that information to come back and make us all feel nice and happy without having to spend a whole lot of money going out and developing a new trial from scratch.

DR. ROSEN: So you are suggesting Phase IV for European studies.

DR. WOOLF: Well, no; not as classically defined. How about if 3c?

DR. ROSEN: Other comments?

Yes, Dominic?

DR. CIRAULO: Dom Ciraulo. I think we have to take a different approach to the adverse effects that we have seen here. I don't think we can treat it like we do in the usual clinical trial. I don't even think something like the safety GI is something that would work in this.

I think you highlighted the area--I will just stick to my area, depression and anxiety. I think you have to treat it almost like an outcome study, that you want to get together, get a group

together, get the best scales to measure anxiety, depression and other psychiatric symptoms along with the Columbia Group's suicidality methodology.

I think that is really sort of a shift from the way we think about measuring AEs because AEs seem to have become the focus of what we are talking about.

DR. ROSEN: Thank you.

Melanie?

MS. COFFIN: I would love to know more about the dropouts but you can't really do a whole lot about that. What I would like to see that might be possible is more information on the patients that are discontinued because they are put on anti-depressants, just a little bit more follow up on how long, what severity, et cetera.

DR. ROSEN: Michael.

DR. PROSCHAN: Also related to this discontinuation because of going on anti-depressants, to me that should not cause discontinuation of the study. I mean, if your drug causes people to get depressed and, therefore, they

have to go on anti-depressant and stop taking the drug and they gain a lot of weight, that is one of the consequences of the drug.

If it causes more depression, then that is a consequence of the drug. So, to me, that is not--I don't find that to be an acceptable thing to drop people when they have to go on anti-depressants.

DR. ROSEN: Right. So I think your point is very well taken. I think we have to distinguish the terms. If it is discontinuation but follow up at the end of the study, that is one thing. But dropout, or not follow a patient because they have now gone on the anti-depressant is another thing.

And I think it is really essential that that data be obtained. I absolutely agree. Tom?

DR. CARPENTER: How difficult would it be to go recover the patients that have been discontinued? There may be a wealth of data in this 50 percent that is not there. I think that would be a goldmine of completing this dataset.

DR. ROSEN: Dr. Gilman?

DR. GILMAN: I would be very cautious here. I think one would want to assess in the patients who became depressed if they stay in the trial and remain on rimonabant, you would want to be darned sure that they are being monitored carefully despite being put on anti-depressants because anti-depressants may be very weak in comparison to the depression that results from this drug.

So I would be very cautious.

DR. ROSEN: I think what Michael was referring to was just continuing to follow these patients on anti-depressants but not on active drug. In other words, just continue them in the study without active drug. Bob?

DR. KREISBERG: Well, you know, I think the sponsor has taken a big hit here and I would like to say that I think they have done a terrific job in trying to bring a unique drug to market and that--if some of you remember Woody Hayes. Woody Hayes was an Ohio State football coach and he said he needed help on Saturday afternoon, not on Monday

morning and we are giving you Monday morning advice.

It is easy to target the defects but what we really need to do is we need to work closer, I think, with you to design studies that would be satisfying and address some of these issues. And I really do think that my colleague's insightful comments about this particular system should allow us to identify areas for sort of targeted evaluation right from the very beginning.

I, personally, don't think there is much you can do with the trials that are already underway. They are what they are and they probably all suffer from this lack of specificity about definitions. So I think it is going to be hard to mine that information.

But I do think that this is a unique drug and it works through a unique system. Even though it is not as wonderful as everybody would like it to be, I can tell you, looking at the evolution of oral hypoglycemic agents and the treatment of diabetes over 40 years is that each iteration, each

generation, gets better and better. I think you have to start at this particular point and continue to evolve.

The things that I think are really important, in addition to better characterization of the adverse effects through redesigning how you are going to evaluate them is I think the diversity issue raised by Ken is absolutely crucial because not only does it minimize the utility of the drugs in African-Americans, there is no data on Hispanics who really suffer from this problem.

So I think that that becomes a crucial issue for generalization of your recommendations and claims. I do believe that head-to-head studies, looking at the metabolic changes that occur when you compare your drug with either other drugs or other forms of weight loss where you can actually get comparable degrees of weight loss, and then claim that there is something magical about this drug that goes beyond weight loss.

But I think that most of us in the field are not going to buy that right now based upon the

data. And I think that is an important issue that you have and it would be an important marketing tool if you could actually proove that.

DR. ROSEN: Thank you, Bob. Do I hear any other comments? We are going to go to a vote but, before we do, I have to admit that I forgot to announce the vote for Item 2a. The vote for 2a, to those of you in the remote situation, is 14 no and none yes.

Having gotten that out of the way, I will then ask for a vote, individual vote, on Item 3a. The question is, and I will start with Paul, based on the current data--I won't repeat the question for everybody--based on the current data, do you believe rimonabant has a favorable risk/benefit profile and should be approved for the indication of weight management in individuals with a BMI greater than 30 and 27 when accompanied by at least one comorbid condition.

DR. WOOLF: No.

DR. ROSEN: Dr. Gilman?

DR. GILMAN: No.

DR. ROSEN: Dr. Rosen says no. Dr. Kreisberg?

DR. KREISBERG: No.

DR. ROSEN: No.

DR. CIRAULO: No.

MS. COFFIN: No.

DR. ROSEN: Dr. Wang?

DR. WANG: No.

DR. ROSEN: Dr. Goodman.

DR. GOODMAN: No.

DR. ROSEN: Dr. Proschan?

DR. PROSCHAN: No.

DR. ROSEN: Dr. Flegler?

DR. FLEGLER: No.

DR. ROSEN: Dr. Henderson?

DR. HENDERSON: No.

DR. ROSEN: Dr. Carpenter?

DR. CARPENTER: No.

DR. ROSEN: Dr. Burman.

DR. BURMAN: No.

DR. ROSEN: Okay. So the vote--I'm sorry; I have one point of clarification. Dr. Hirsch also

voted no and he voted no on 2a. So there are 14 votes no, no votes yes, on Item 3a.

I think we have discussed 3b. I think there is a lot more discussion to be had. I am just looking around the committee to ask if anybody on the committee would like to add some additional comments about what additional information they need.

I would like to echo Dr. Kreisberg's comments. This is a new class of drugs and the sponsor has gone out of its way to do as much as they possibly can with the information they have. I think we all look forward to more data.

I think this is an exciting area. I think there are tremendous opportunities and I think we are looking forward to working with them, both at the FDA level and at the committee level in the future.

If there are no further comments, I would like to officially adjourn this meeing.

[Whereupon, at 4:19 p.m., the meeting was adjourned.]

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