ECS modulatory functions, leading to a number of effects that are both desirable and undesirable.

The adverse effects that are seen in animals include seizures, tremors, impaired movement, sleep disturbances, hyperesthesia, which is increased sensitivity to touch, anxiety and hyperexcitability.

They occur at the same exposures that cause the desired effect, which is to decrease appetite, to decrease food intake and to result in a decrease in body weight.

The clinical presentation that you will hear this afternoon will focus on the findings of depression and suicide, which can occur through the endocannabinoid system dysfunction, but are not readily assessed in standard animal models.

The endocannabinoid system is a complex modulatory system. It is under active investigation and we don't understand all the functions that it participates in.

The role of CB1 receptors in peripheral regulation of energy intake in adipose tissue,

skeletal muscle, and delivery in the GI tract, are indicated as tentative in the bottom part of this slide, and this is because the decrease in body weight effect can lead to these other beneficial effects in and of itself.

It may be through CB receptor interactions of rimonabant in the periphery, but it could be a direct effects of the decrease in body weight in and of itself, and the tentative nature reflects the fact that the peripheral function of CB1 receptors is under active regulation.

[Slide.]

This slide summarizes the effects of the endogenous endocannabinoids on motor effects, sensory effects and behavioral effects. This column shows the constitutive effect or the effect of endocannabinoids or endogenous endocannabinoids agonists.

This column shows you the effect in the presence of rimonabant, so if you look at regulation, modulation of motor effects, t he constitutive effect of the endocannabinoid system.

It's a decreased activity and result in an anti-convulsant effect.

In the presence of rimonabant we see the incidences of seizures, tremors, and both impaired and decreased movement. If you look at sensory modulation, the ECS system is generally thought to decrease pain. In the presence of rimonabant, we see hyperesthesia, decreased body temperature, hyperexcitability and an increase in startle response.

If you look at behavior, the constitutive effect of the ECS system is an anti-anxiety effect, also associated with somnolence and an orexigenic stimulus.

With rimonabant we see signs of anxiety, sleep disturbances and an anti-orexigenic response.

[Slide.]

CB1 receptors are conserved across animal species from rodents to primates including, for that matter, reptiles and birds. This conservation is evident by a similarity in central nervous system regional distribution and a similarity of

receptor homology, and in regard to ligand binding affinity.

Thus, the conclusions of this are that the animal models have clinical relevance, and, in fact, you heard a great deal this morning about the mechanism of action of rimonabant and its ability to decrease weight, and those effects were worked out in animal models.

Thus, if animal models are sufficient for demonstration of efficacy and the mechanism of action of the beneficial pharmacologic effect, they are also relevant, I would argue, to identify the toxicities.

[Slide.]

So, if I could summarize. The key points in CB1 rimonabant receptor pharmacology, it is that the endocannabinoid system has pleiotropic neuromodulatory functions.

The endocannabinoid system is involved in the regulation of central nervous system activity through CB1 receptors.

Both the CB1 receptor sequence and

distribution are highly conserved across species.

Rimonabant is a CB1 receptor antagonist with a complex pharmacology and similar affinity across species.

[Slide.]

This slide summarizes the nonclinical toxicology studies involves in support of rimonabant's clinical development program.

Generally a standard package of nonclinical studies was presented by the sponsor including pharmacology studies, general toxicology studies in a variety of species including mice, rats, dogs and monkeys.

Chronic toxicology studies were done in the rat and in the monkey with durations of six months in the rat and up to one year in the monkey.

Two-year rat and mouse carcinogenicity studies were performed with lifetime daily exposures of rimonabant, followed by a standard battery of genotoxicity studies, as well as the standard battery of reproductive toxicology studies in both rats and rabbits.

The results of these studies suggested that the central nervous system was a major target organ of concern. Although the nonclinical data showed signals of central nervous system toxicity, significant clinical experience existed for another more serious indication when the application was submitted and, thus, it was the more advanced clinical data which supported further clinical development for this proposed indication.

[Slide.]

This slide shows a summary of the lowest observed adverse effect level for various CNS toxicities shown across various species.

If you look at the lowest exposure resulting, for example, in mortality, you can see that rodents and rabbits, this occurs at or very close to the human therapeutic exposure following a 20 mg clinical dose. In monkeys and dogs, a slightly higher exposure would be needed to demonstrate mortality.

Likewise, convulsions occurred in mouse, rat and monkey but generally at exposures that were

less than 3 times the human clinical exposure.

The convulsions weren't observed in the dog, but tremors were. The tremors could be partial seizures that were observed at 4 times the human therapeutic exposure. If you look at the rat, and you look at the spectrum of CNS toxicities that are seen, you can see it at all the central nervous system toxicities that are observed including mortality, convulsion, tremors, motor effects and aggressiveness all occur at the human therapeutic exposure.

It is important to note that all the animal models that were used in these toxicology studies were healthy normal animals and that the central nervous system toxicities were observed as part of the twice daily clinical observations performed during the design of those toxicity studies.

If you look at motor effects or rather motor dysfunction, it occurs across species at less than or equal to 5 times the human therapeutic exposure and, although less frequently observed in

the toxicity studies, aggressiveness and anxiety were also observed at low exposure multiple relative to the human therapeutic dose or human therapeutic exposure rather.

[Slide.]

Because of time constraints I will focus the remainder of my presentation on the seizure data although clearly, this is not the only central nervous system toxicity that was observed in animals.

CB1 receptors have been shown to mediate many of the anticonvulsive effects of endocannabinoids and to play an important role in regulating synaptic transmission. The toxicology data suggests that rimonabant antagonizes these effects by disrupting the endocannabinoid system's constitutive anticonvulsant tone and subsequent regulation of neuronal excitability possibly through competition with endocannabinoids for receptor occupancy.

[Slide.]

This slide shows that there isn't an

adequate safety margin for convulsions or tremors in animals, and it occurs in various species.

This is based upon the No Observed Adverse Effect Level expressed as a dose in mg/kg in the various animal species relative to the human therapeutic exposure based on either total exposure or area under the curve, or compared to a Cmax, the highest plasma level based on a 20 mg/day clinical dose.

In animals, convulsions and tremors were seen at exposures at or below the therapeutic exposure in humans. The safety margin, as noted below, refers to the animal divided by the human exposure at which there is an absence of convulsions and tremors in the animals, so it is another way of looking at the previous table.

[Slide.]

This slide shows the progressive nature of the seizure incidence at lower doses with longer durations of treatment in the mouse, the rat and the monkey.

If you take the mouse, in the acute

studies, 2,000 mg/kg were needed to demonstrate convulsions. If you look at the subacute toxicity studies, those are studies that are less than 6 months duration. The dose, to cause a convulsion, decreases to 120 mg/kg/day.

Similarly, if you go to the chronic studies, which are lifetime exposures, convulsions are seen at 16 mg/kg/day.

Similar effects are seen in the rat if you go from the subacute studies, 16 mg/kg with demonstrated convulsions. Chronic studies, this dose gets reduced down to 6. The monkey, the effect is less dramatic but, nonetheless, it's reduced with chronic duration of dosing.

[Slide.]

This slide shows the dose dependent incidence of seizures in both male and female rats following lifetime exposure to rimonabant. Clearly, you can see low dose, mid-dose, high dose. There is an increase in the numbers of animals experiencing convulsions.

The low dose, it is important to note, is

1 to 2 times the human clinical exposure.

[Slide.]

Studies were performed that directly examine the effect of rimonabant on seizure induction. This slide from the sponsor summarizes the results of such a study.

Here, rimonabant at various doses, 10 mg/kg, 30, and 100 mg/kg potentiates the tonic convulsions and mortality in a mouse seizure model.

There is not much of an effect on clonic convulsions compared to control. But if you look at the tonic convulsions, there appears to be a trend toward potentiation. It is not statistically significant and it is clearly not just related, but it's there.

Similarly, if you look at mortality and you look at potentiation, there is also a trend towards potentiation at the higher doses. This seizure model, the seizures are induced with PTZ, which is pentylenetetrazol. It's a GABA agonist. It's a standard model.

The doses tested of rimonabant, shown in

this slide, are below the human therapeutic exposure at 20 mg/day based on the clinical dose.

[Slide.]

This slide summarizes some key points in the observed seizure findings in multiple species at or below the human therapeutic exposure following rimonabant treatment in animals.

Rimonabant blockage of CB1 receptors appears to influence the anti-convulsant tone of the endocannabinoid system. Rimonabant induced dose-dependent seizures in association with CB1 receptor antagonism in multiple species. Seizures were dependent on the dose and the duration of rimonabant treatment and, moreover, the seizures occurred at animal exposures that were equivalent to the systemic exposure in humans at the proposed clinical dose of 20 mg/day.

[Slide.]

We have experience with other CB1 receptor antagonists that are currently under development. Central nervous system toxicity is observed in some of these other applications, but it is observed

generally at a greater than 10 times therapeutic exposure.

CNS toxicities that are observed include convulsions, tremor and motor dysfunction. This suggests that rimonabant differs from the others in the class by its narrow therapeutic index. Specifically, the exposure that causes the desired pharmacologic effect, that is, weight loss, is very close, if not the same, as the exposure that causes the central nervous system toxicities.

Because of this narrow therapeutic index, the central nervous system toxicities that are seen in multiple animal species would be anticipated occur at clinical exposures in people. You will hear more about that this afternoon.

[Slide.]

This slide summarizes the clinical relevance of the central nervous system toxicities seen in the nonclinical development plan. Generally, what you see is the exposures causing weight loss in the mouse, rat, monkey, dog and rabbit. All are at or below the human therapeutic

exposure. Relative to the observed central nervous system toxicities of mortality, convulsions, tremor, motor effects and anxiety.

Again, the data is expressed as the animal exposure at the NOAEL relative to the clinical exposure at 20 mg/day. The decreased body weight and the central nervous system toxicities occur in multiple species at similar drug exposures.

[Slide.]

So, if I could summarize.

Central nervous system toxicity occurs in multiple species at therapeutic exposure levels based on a 20 mg proposed clinical dose.

Dose-dependent central nervous system toxicities occur as a result of antagonism of the CB1 receptor and disturbance of the endocannabinoid system homeostatic regulation.

The plausible mechanism of action associated with weight loss appears associated with central nervous system toxicity.

Other drugs in the class show similar toxicities but occur at much higher animal

exposures.

There are limited, if any, differences between exposures generating the desired pharmacologic effect and those associated with significant animal toxicity, that is, seizures and mortality, motor dysfunction, anxiety, aggressiveness, supporting the clinical relevance of the central nervous system toxicity.

[Slide.]

In conclusion, rimonabant is a first in class, CB1 receptor antagonist for the management of obesity.

Sufficient information exists to demonstrate a complex pharmacologic profile.

Blockade of the endocannabinoid system-mediated orexigenic stimulus may be desirable for obesity, but a similar blockade of other CNS functions under regulation by the endocannabinoid system would not be desirable.

Studies in relevant animal species show CNS toxicities at clinically relevant therapeutic exposures.

We are not alone in our conclusions and that the European Regulators in 2006 noted, and I quote, "Nonclinical studies could provide no reassurance regarding margins to the clinical exposure. Consequently, the safe use of rimonabant has to rely more on the clinical safety data and post-approval pharmacovigilance programme."

The central nervous system adverse effects are consistent with the mechanism of action and are reported in the clinic and in postmarketing reports.

Thank you.

DR. ROSEN: Thank you, Karen.

Clarifying Questions from the Committee

DR. ROSEN: The Committee now is open for questions. I will start.

It appears that the rodents are more sensitive than the larger animals; is that correct?

DR. DAVIS-BRUNO: That is an accurate assessment.

DR. ROSEN: In the seizure models with the

PTZ induction, have you tested to see if other inbred strains of mice are more sensitive or less sensitive? There are some inbred strains that are more prone to seizures where you don't have to induce them with a drug.

DR. DAVIS-BRUNO: I don't know. I am not aware of specific strains, specific studies, that have been done with rimonabant. But perhaps Sanofi wants to comment on that.

DR. ROSEN: Yes. Dr. Hirsch.

DR. HIRSCH: Two brief questions. One is the mortality that you have listed. Is that due to the things that --

DR. DAVIS-BRUNO: I think that could be implicated, sure. They seize.

DR. HIRSCH: Were there any other causes of mortality?

DR. DAVIS-BRUNO: There are no lesions, there are no histopathological lesions observed in the toxicology.

DR. HIRSCH: Question 2. Long-term studies on animals, for example, brain,

neuropathology at 1 year, 2 years.

DR. DAVIS-BRUNO: There are no observable dose-related histopathological lesions that could explain what we see.

DR. HIRSCH: So, there are no relevant long-term animal studies to indicate what might happen, the ones on rimonabant for 5 years.

DR. DAVIS-BRUNO: Let me be clear. In general, chronic studies are usually 6 months to a year duration daily dosing in rodents and in non-rodents, that is part of the toxicology package.

There were also carcinogenicity studies which were lifetime exposure, lifetime daily exposures, which were performed by the sponsor. Basically, you wouldn't expect to see histopathological lesions if the cause of death, for example, is seizure, and you don't see it.

DR. ROSEN: Other questions from the Committee?

DR. CARPENTER: Tom Carpenter, Yale.

I wondered if specific attention to

plaque-like lesions or multiple sclerosis-like findings were employed in these post-death analyses?

DR. DAVIS-BRUNO: Generally, toxicology studies do a couple of sections through brain, spinal cord, et cetera, et cetera, and there were not any lesions that were found. That is not to say that if you designed a study to specifically look at that, you might see something. But they weren't observed.

DR. ROSEN: Dr. Kreisberg.

DR. KREISBERG: Bob Kreisberg. I know you didn't touch on this, but you did allude to it. Do you have any information about the long-term cardiovascular effects?

DR. DAVIS-BRUNO: There were effects that were noted in some of the original safety pharmacology studies, in Herb[?] channels and affecting in vitro type preparations.

They also I believe did a telemeter--it was either a dog or a monkey study--and that did not show effects, so we weren't concerned about a

cardiovascular signal in the nonclinical data. It was addressed.

DR. CIRAULO: Dom Ciraulo. Again, you didn't touch on this, but while we are discussing animal models, could you talk about any animal models of depression, has that been screened?

DR. DAVIS-BRUNO: I am not aware of the sponsor performing any specific depressive animal models although they are available.

DR. ROSEN: Dr. Goodman.

DR. GOODMAN: Are you accepting questions to the sponsor or just the FDA at this point?

DR. ROSEN: I think it is to the FDA at this stage, yes.

Other comments for the FDA?

Karen, I wanted to ask you to clarify that--because I think there is a bit of confusion about the physiology of the CB1 and CB2--so it appears that both the CB1 and CB2 are found in the periphery, and CB1 is found centrally.

Do you have any sense of which--what is activated predominantly or it is a mix of CB1's

centrally and peripherally that are having the major effects?

DR. DAVIS-BRUNO: That is really hard to address, because rimonabant is distributed centrally and peripherally, so we don't have a specific antagonist that isn't excluded from the blood-brain barrier, so that we could look at some of these peripheral effects. But that is under active research investigation.

DR. WOOLF: Paul Woolf.

Is rimonabant concentration in the brain enhanced or is it simply reflective of peripheral levels? Is there active transport into the brain?

DR. DAVIS-BRUNO: Rimonabant?

DR. WOOLF: Yes.

DR. DAVIS-BRUNO: Yes, it is transported into the brain. In fact, the rat brain tissue was reported with radiolabeled rimonabant to accumulate 2-fold relative to the rat plasma, so it is clearly distributed.

DR. ROSEN: Other questions or comments from the Committee?

Karen, anything else from your end?

DR. DAVIS-BRUNO: Not from me.

DR. ROSEN: Dr. Colman?

Okay. This adjourns the morning session. We will reconvene at 1:00 p.m. for the Open Public Hearing.

[Whereupon, at 11:55 a.m., the proceedings were recessed, to reconvene at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. ROSEN: The first order of business this afternoon will be the public testimony. We have three individuals that I will introduce. Then we will go to a talk on the clinical efficacy and safety by Amy Egan from the FDA.

Right before that, we will have just a point of clarification from Karen's presentation from this morning looking at the relative toxicities of human versus the other animal models. We have had some questions about that from the committee. So Karen is going to graciously come back up and show one or two slides.

Open Public Hearing

DR. ROSEN: I just have to read this. "Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing Session of the Advisory Committee meeting, FDA believes it is important to understand the context of an individual's presentation.

"For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

"For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking."

So we have three people who have asked to talk. The first one is Dr. Sidney M. Wolfe. He will give the first presentation. Sid, could you just reintroduce yourself for the people who are in the remote room.

Sidney Wolfe, M.D.

DR. WOLFE: I am Sidney Wolfe, Health Research Group of the Public Citizen. The presentation was done collaboratively with Dr. Elizabeth Barbehenn, who used to be in the Metabolic/Endocrine Division of FDA at one time, and Ben Wolpaw who is a summer researcher with us.

I do not have any financial conflicts of interest.

The elusive idea of a magic-bullet drug that has a benefit mediated through its action on one receptor site, yet is devoid of risks at a myriad of other sites in the body, is, once again, evident with the discussion you have heard on rimonabant.

We have had recent examples including Vioxx, Rezulin and Redux where they were approved for a benefit on one site and then, in the case of Vioxx and Redux, they caused cardiovascular damage, in the case of Rezulin, liver toxicity.

But where else in the brain or other parts of the body are these CB1 cannabinoid receptors which rimonabant inhibits located?

You have heard, and I will just briefly go over, just within the brain, olfactory and cortical regions, neocortex, pyriform cortex, hippocampus, amygdala, basal ganglia, thalamic and hypothalamic nuclei, cerebellar cortex and so forth in the periphery of the autonomic nervous system, liver, muscle, GI tract, adipose tissue, pituitary gland, reproductive tissues and a lot of interesting work is going on now in terms of the effects on the cardiovascular system.

A recent review on the pharmacology of this system said, "CB system involved diverse physiologic functions that include roles in stress recovery and the maintenance of homeostatic balance. Such roles include, for example, neuroprotection." There is an interesting study just published in the last week or so in the animal model showing that you impair the neuroprotective properties of the cannabinoid system by using a blocker of it as in rimonabant.

"Modulation of nociception, regulation of motor activity, control of certain phases of

memory--"there was certainly some clinical evidence on that you have heard this morning--"modulation of immune and inflammatory responses, influence on cardiovascular and respiratory system and antiproliferation of the tumor cells."

Given the multiple sites in the brain with CB1 receptors, the extraordinarily broad kinds of psychiatric dysfunction caused by the drug, and we use this phrase "caused" carefully because these are randomized controlled trials where there is no other explanation, the myriad of psychiatric dysfunction caused by the drug in addition to which you have heard the statistically significant increased suicidality and other depressive systems are not surprising.

As seen in the table on Page 2, significant increases in anxiety, insomnia, panic attacks and almost significant increases in aggression, also seen in animal studies, and agitation in patients given 20 mg of rimonabant versus patients given a placebo.

In addition, significantly more patients

getting rimonabant required a sedative or tranquillizer or an antidepressant for adverse effects caused by the drug. This is during the course of the trial. Some of these increases are in a range, in terms of both the increase and the absolute values, they are much in excess of even the suicidality data.

For example, anxiety went up from 2.5 percent in the placebo group to 6.02 percent in the rimonabant group with the p less than 0.001. Insomnia went up also quite significantly, up 1.8-fold. Twice as many people required sedatives or tranquilizers. And the six-fold increase in aggression, not quite statistically significant but, again, concordant with the animal findings.

The evidence for increased suicidality and depression is a particular concern for a drug targeted towards the obese population that has been shown to have a significantly higher incidence of depression and eating disorders compared with non-obese individuals.

The question has been raised as to whether

or not the patients studied accurately reflected the psychiatric makeup of the obese population that we would be expected to see rimonabant treatment. The four studies, again in this table here, give information on the Hospital Anxiety and Depression Scale, HAD, data showing mean pre-treatment depression scores of approximately 3. This is in the patient population studied. The depression portion of the scale is out of an average score of a possible 21 points where a probable disorder is indicated by a score of above 8 to 11.

The average score of 3 is well below the mean value for the general population of 3.68. Given that the obese population has been found to have a 20 percent higher incidence of depression compared with the non-obese population, this number seems artificially low. Part of it may be due to the exclusion of certain groups of depressed patients. Whatever it is, it may diminish the information that we get from the study. The increases in depression and other things might be even greater if we had a more typical population

even though you have heard they are going to exclude these kinds of groups. This is easier said than done.

A related concern of significant importance is the exclusion in all RIO studies of patients on anti-depression medication. Between 2004 and 2006, 30 percent of all patients receiving phentermine, orlistat, sibutramine or diethypropion had a concurrent prescription for an anti-depressant medicine. These are drugs used for treating obesity. This strongly suggests that patients would, if this would is approved, end up taking anti-depressants and rimonabant in tandem with unknown consequences.

Another problem with the clinical studies is the fact that there was a huge dropout rate. This was not presented by the company, but the range of dropouts in the four RIO studies was between 32 and 45 percent. This limits the significance of their findings in the debate over the safety and efficacy of the drug.

The high discontinuation rate obviously

could work both on the side of safety and efficacy. You might get a better picture because of the dropouts of its effectiveness and a more benign picture of the safety profile.

Combined with other questions that have arisen during the methodologic quality of the four studies with regard to method of randomization, allocation, concealment and blinding, high attrition rates serve to throw conclusions on safety and efficacy into doubt, as I just said.

Reproductive and other preclinical animal effects. In its posted briefing document that went up on the Internet two days ago, Sanofi describes preclinical animal studies as follows: "In a comprehensive program of nonclinical studies, rimonabant was shown to have very limited potential to induce toxicity. No specific target organ pathology was identified in the completed animal studies."

This statement is, at best, misleading and more likely it is just dishonest. I will now read from a document that is up on the website of the

EMEA, the European equivalent of the FDA.

"Amongst other things, in the area of reproduction, decrease in corpora lutea and implantations, decrease in viable fetuses,"--these were at doses very close to the human dose--"increased pup mortality, decreased litter size in rabbits, and increased birth defects."

In addition to that, and these things are actually in the label on the drug in Europe--in addition there were a number of other problems including liver toxicity, genotoxicity, chromosome aberrations in lymphoma cells, mouse lymphoma cells, carcinogenicity in female rats, and hyperexcitability or aggressiveness, as I mentioned before.

The case of cannabinoid regulation of implantation and fetal development should also be taken as an example of how limited an understanding scientists have of the role of this widely dispersed neurotransmitter system. Rimonabant is the first drug in its class to be used in humans and there are many important questions that remain

unanswered.

It is interesting; the company recommended, and I have no doubt that that is what they would like to have happen, that long-term administration is required. This raises a whole issue about long-term effects both in terms of efficacy and safety. Of the studies performed to date, two had a duration of 2 years. Others were 1 year. Because rimonabant is the first drug in its class, no data evaluating the long-term effect in antagonizing this widespread cannabinoid system.

Weight loss while on rimonabant is regained after discontinuation of use which means that, if the drug is to be effective at all, it will have to be prescribed on a long-term basis as the company said this morning.

Given this fact, a complete lack of data on rimonabant use in humans over an extended period of time is cause for significant concern.

I don't have time to--how much time do I have left here? Two minutes? So I do have time. The literature on animal studies done with

rimonabant contains ominous indications of issues that might arise as people continue using the drug for longer periods of time. Zimmer, who was a fellow at the NIH for a while and is back in, I believe, Austria, now, has reported that CB1 knockout mice--these are mice that are missing this receptor which, in some ways, may be the same as knocking out the receptor with rimonabant--have significantly increased mortality due to "spontaneous deaths of unknown causes."

Zimmer, an expert in cannabinoid-system research, has also noted that the same strand of CB1-deficient mice exhibited increased loss of neurons with aging. Although this does not generalize directly to rimonabant use in humans, there is still cause for concern in the absence of studies evaluating the effects of long-term CB1 antagonism.

Other studies have shown clear effects of the CB1 receptor on the cardiovascular system in producing hypotension and bradycardia which, one would imagine, might be the reverse. It is

interesting, this morning, and other times, looking at some of these data, the expected reduction in blood pressure that you would expect in obese people when they lose weight was not found as significantly and this could conceivably be related to the fact that you are having some hypertensive effect of the drug.

A recent, very thorough, review of rimonabant published last year by the Cochrane Collaboration, which started out in Oxford but which now has branches in the United States, concluded that, one, the average weight loss is "modest" and, two, more rigorous studies about efficacy and safety are required to "fully evaluate the benefit/risk ratio of this new drug."

We strongly agree with this statement and it is a statement that clearly requires the rejection of the approval of this drug because of a lack of ability to fully evaluate the benefit/risk ratio of the drug.

I would just like to comment on what you heard from Dr. Davis-Bruno this morning, animal

models have clinical relevance, and you have seen, in a number of areas, where they do and I suspect that we would, unfortunately, see more if they had looked more carefully. Hopefully, we will not see it when the drug is not approved.

Thank you.

DR. ROSEN: Thank you, Dr. Wolfe.

The next speaker, it is my pleasure to introduce Lynn McAffee from the Medical Efficacy Council on Size and Weight Discrimination. Lynn?

Lynn McAFFEE

MS. McAFFEE: The Council does not take any funding from the diet industry, anything in the diet industry.

I wanted to just make some informal remarks to you today partly on social issues and to comment on some of the things I have heard, some of which are reassuring and some of which are just really scary.

First, I want to talk about the environment in which consumers will be making decisions to take this pill. Just in this room,

also, there is an enormous amount of weight prejudice in this room. I think we all know that. We have tremendous job discrimination pressures which are, I believe, getting worse based on the claims that we have been getting in our office.

Social discrimination, just in terms of we marry less. Educational discrimination. You can go on and on. Even rental discrimination has been found. And nothing is really being done about it. We are finding that, when we are saying, "Oh, that is not a good thing," it is not changing. It is getting worse, if anything.

So you really need to understand that people are desperate. We saw this very much with Redux and fen-fen, that the social consequences of losing weight are so significant, there is so much given you when you lose weight, so many more opportunities, that people consider it an investment in their future. They will spend any money that they can. They will take a lot of risk that you won't see people taking risk for in any other disease or condition, an enormous amount of

risk will be taken by people.

It is amazing what people will do. Some of the blogs that they have during Redux and fen-fen, anorexics were telling each other how to get fen-fen and succeeding. It is not so hard to get this stuff when it is out there. That is a part of the problem is that we have a system that really makes it easy for the unscrupulous to prey on us and to cause us harm.

I wanted to talk about some of the specific issues. First is the depression issue. I think the company has done something very good and very smart in including a little depression checklist in the physician's office. But I will tell you right now that, if this gets out to be a real big deal in the public, you can figure out how to answer those questions to get the drug. It is not laser brain surgery. And people will.

So, while that is a nice thing that you have done and, I think, very positive, it is not going to stop anybody who wants this drug. And, as I said, if it seems like there is a real weight

loss to be had, that is going to be everybody.

I have to tell you that I am very upset about it because I have a history of depression and so I can't take this drug, and I was looking forward to trying it because I have a lot of risks that I would assume based on that benefit. So that is a shame.

I think a couple of things; is this an inverse agonist drug or not? I mean, that is kind of basic and I think nothing should happen until that is really figured out because the consequences of it being one or the other is really serious.

I heard one use, or two uses, of the DPP, the Diabetes Prevention Program, Test. I want to make clear that that test didn't separate out the effects of changes in weight loss, diet composition change or exercise. They were all kind of lumped together. So I am not sure that you can really count on anything from that program.

Multiple sclerosis really sends a chill down my back and I will tell you that my partner of 21 years was just diagnosed with multiple

sclerosis. It seems to be more of an art than a science in diagnosing that. It took many months and many, many tests. I am not sure whether they have multiple sclerosis or some other strange demyelating condition specific to this. So that does not feel good. That is not good.

This whole idea of retrograde transmission is really scary. The seizures being dose and duration dependent make it really clear to me that they are related to this drug. When you get out in the public, and you increase the base of people who get this, that is really a problem. I don't like that.

The company once mentioned something about not giving this to people with uncontrolled psychiatric illnesses. I am not sure what they are going to end up doing. So does that mean that people who are on anti-depressants should take this or--I think that that has to be clarified because it seems to me that what mostly they were saying was that, if you have depression, you should not take this. So that is a very big difference there.

As was brought up before, lifetime use for this drug on a two-year trial with not that many people. It is certainly more than other trials have had but, in real life, that is not that many. That is scary. That is a lot of risk and that is a lot of money. What people are paying in England for this and all over Europe is an extraordinary amount of money.

I have heard a month's supply anywhere from $175 to $275. I don't know what it is going to be in this market, but that is a big hit. Most people who are assuming that money for themselves are thinking that you are going to have to just be able to do it for a few months. They are not going to be able to pay that through their lifetime.

I know the insurance reimbursement is something that the company would like, and I would like that too. I don't have the money to invest in it. There is a lot up in the air right now.

I want to make sure that the company makes a very clear postmarketing commitment. We had so much trouble with this with Redux. They made a

commitment verbally and then would not carry through on it. This company does seem to be a lot more responsible but I would really like to hear that they are going to do postmarketing surveillance that is really aggressive.

If you approve this drug, and, frankly, I am glad you don't have to make this decision, but if you choose to approve this drug, even though so much is up in the air, I would say that I would not want it given out to people with a BMI of 27 and comorbidities of blood pressure or cholesterol or abdominal obesity, whatever that means.

Blood pressure, as Sid mentioned, is a tricky issue in fat people. There haven't been a lot of prospective studies on this. People, frankly, have not been able to keep weight off long enough for this to really be well-studied. But, when they have something like the Swedish obesity study, which was actually a surgery study, and people kept off their weight, the blood pressure went down and stayed down for a few years and then went right back up to baseline in spite of the

weight being kept off.

So that says there are some other mechanisms possibly involved, that this is not really weight loss, the change in blood pressure is not that great anyway in this. So I think, particularly under 27, really only diabetes should be an indication.

I, frankly, would be in favor of raising the weight limit to even a BMI of 35 or something like that just to ease into it and the idea was that later on bringing in a little more people at the lower BMI. This is a very scary drug. This is a system we know almost nothing about.

What the FDA has presented so far has really scared me. I lived through Redux and fen-fen and the calls in the middle of the night and the dying people and the people who can't afford the testing they need. Nobody wants to live through that again. I would urge you to keep that in the forefront of your mind.

Finally, I want to thank you for your efforts on our behalf. We are a people who are

much discriminated against and, very often, despised by people including the medical profession. For you to take this time and energy to really try and help us means a lot.

Thank you.

DR. ROSEN: Thank you, Lynn.

Our next speaker is Caroline Apovian. She is representing the Obesity Society.

Caroline Apovian

MS. APOVIAN: Thank you. Good afternoon. I am Caroline Apovian representing the Obesity Society. We wish to make known that the Obesity Society has received unrestricted financial contributions from Sanofi-Aventis as well as from competing pharmaceutical and non-pharmaceutical companies. The Society is supportive of the development of approval of products for obesity treatment when the safety and efficacy of these products are well supported by rigorous scientific evidence.

In any decision-making about potential approval of obesity agents, this Society believes

the following statements define the context and merit consideration.

The causes of obesity are complex and multi-factorial involving genetic, behavioral and environmental factors that are only partially understood. Obesity is a chronic condition that significantly impairs the quality of life and reduces life expectancy. Obesity increases the risk of heart disease, type 2 diabetes, lipid problems, hypertension, liver disease, sleep apnea and other serious conditions.

Obesity and its related comorbidities, in particular type 2 diabetes, represent one of the major threats to the long-term health and well-being of the U.S. population.

Among obese people, weight loss achieved in the context of medically recommended programs improves quality of life, functionality and reduces the risk of developing future disease. Achievable weight losses as small as 5 to 10 percent of initial body weight appear to be sufficient to confer health benefits in patients at risk.

Currently, treatment options including pharmacotherapies for obesity are limited. With the exception of bariatric surgery, available treatments are associated with modest efficacy and all have side effects that, for some individuals, are intolerable. Additional agents targeted at new mechanisms are very much needed expansions of the treatment armamentarium.

As with people who have type 2 diabetes where lifestyle therapy and adjunctive drug treatment are current standards of care, obese people with health problems deserve similar access to healthcare delivery.

Obesity has long been associated with enormous social stigma. As scientists, we recognize that blame has no role in our discussions. As clinicians, we recognize that persons with obesity deserve our care, our compassion and our health. Obese people deserve access to safe and effective medications that can be reviewed in the same manner as are medications for other chronic conditions.

As clinician, myself, I applaud Dr. Aronne's comments earlier. We applaud the FDA for undertaking a rigorous review of the safety and efficacy data on rimonabant. The clinical and patient community expects the drug-review process to protect them against dangerous and ineffective products. Physicians are eager to have additional tools to help their patients.

We expect that the FDA will review the data on this drug by the same standards it employs for products for other similar conditions and will make its decision as expeditiously as possible.

Thank you for the opportunity to express our views.

DR. ROSEN: Thank you, Caroline.

Preclinical Evaluation of Rimonabant

[Clarification]

DR. ROSEN: We will now move to the lecture component of this. We are going to have Karen come back and just give a brief review of two slides that there was some concern on the committee's part about understanding the toxicity

data relative to the different models.

Then we will move to Dr. Egan's talk.

DR. DAVIS-BRUNO: Thank you. I understand there were a couple of slides that created some confusion and I think the confusion probably started on this one.

[Slide.]

This slide--let me try to explain in a little more detail. This slide is showing convulsions and tremor, various species. But, actually, the data is expressed as the No Observed Adverse Effect Level. What that means is this is the actual dose that the mouse got, the rat got, the monkey got, and does not show convulsions or tremors.

So it is looking at a safety margin relative to the human therapeutic exposure at a 20 mg clinical dose compared to this NOAEL dose in the animal. It is expressed here as a margin of exposure--for example, if the mouse does 20 mg/kg, that exposure compared to the human experience at a 20 mg dose. So, in this case, it is 1 times. It

is at therapeutic exposure.

The rat; the rats got 2.5 mg/kg. It doesn't show convulsions at this dose but that provides less than the clinical exposure in the rat.

Similarly, if you look at the clinical exposure based on Cmax, which is probably the most relevant for looking at convulsions and tremors, you would expect the maximal plasma level to be associated.

What I think created confusion--you can see the safety margin here is expressed as exposures in animals at this No Observed Adverse Effect Level divided by the exposure in humans at this 20 mg clinical dose. I think what created confusion was my last slide with the table.

[Slide.]

It is this one. There is a typo. I apologize for that typo. The typo here is that the therapeutic exposure here, the calculation of the animal exposure, is indicated here as No Observed Adverse Effect Level, NOAEL. That is not true.

This is the animal exposure relative to the clinical exposure so, in this case, these CNS toxicities that we are seeing there.

Does that clarify?

DR. ROSEN: I think so. I would just like to make sure everybody on the committee understands that. I think that was--I think we do understand that. Anybody have any questions or concerns?

DR. DAVIS-BRUNO: I apologize for the confusion.

DR. ROSEN: Paul?

DR. WOOLF: Paul Woolf. Is this the concentration of the drug in the animal divided by the concentration of the drug in humans?

DR. DAVIS-BRUNO: Yes.

DR. WOOLF: At the NOAEL dose.

DR. DAVIS-BRUNO: No. In this case, this is actual incidence that causes the CNS toxicity. The previous slide that I showed you was the no effect level. So we are trying to look at a safety margin in the previous slide. This is showing you the exposures in the animal that cause CNS toxicity

relative to the clinical exposure.

DR. ROSEN: Are you okay with that, Paul?

DR. WOOLF: Is it the concentrations of the drugs in the animals divided by--

DR. DAVIS-BRUNO: Yes; it is based upon exposure. It is based upon pharmacokinetics, not based on the dose in the animal versus the dose in the human. It is exposure.

DR. ROSEN: Right. That is the key, and the PK. Yes. Any other comments or questions from the committee? Thank you, Karen, for your point of clarification.

I would like to introduce Dr. Egan--oh, yes?

LCDR MILLER: Can I just make a comment to the public on Dr. Egan's slides. The handouts that were provided for the public are missing the second half of her presentation. They were not all copied. Those will be available, the full presentation will be available, on the FDA website along with all the other reading material within a week of the meeting.

Thank you.

DR. ROSEN: We, as a committee, people, have those slides, though. It is just the public would have to access them on the website until they are available.

Dr. Egan.

FDA Presentation [Continued]

Clinical Efficacy and Safety of Rimonabant

DR. EGAN: Good afternoon Chairman Rosen and members of the Committee.

[Slide.]

Today, I will be presenting the division's perspective with regard to selective safety issues from this application.

[Slide.]

First, I will briefly summarize the efficacy findings with regard to the weight-management indication. I will then focus on the specific safety concerns that are the focus of this advisory committee, specifically neurological adverse events, seizures, psychiatric adverse events and suicidality so that we may derive

feedback from you as to their meaning and significance.

[Slide.]

Rimonabant was developed under the 1996 FDA guidance for the clinical evaluation of weight-control drugs which stated that, for a weight-loss drug to be considered effective, one of the following criteria must be satisfied; the drug's effect is significantly greater than that of placebo with the mean drug-associated weight loss exceeding mean placebo weight loss by at least 5 percent or the proportion of subjects who reach and maintain a loss of at least 5 percent of their initial body weight is significantly greater in subjects on drug than in those on placebo.

I should point out that the 2007 guidance requires sponsors to meet both criteria.

[Slide.]

Rimonabant satisfied the Division's criteria for efficacy for a weight-loss product. Rimonabant 20 mg once daily along with a hypocaloric diet was shown to reduce body weight by

approximately 5 percent relative to hypocaloric diet alone during one-year trials of more than 6,000 moderately overweight and obese subjects.

As with other obesity drugs, the weight-loss efficacy of rimonabant was attenuated in subjects with type 2 diabetes and, as expected, rimonabant-associated weight loss tended to be accompanied by improvements in levels of triglycerides, HDL cholesterol and hemoglobin A1C in subjects with type 2 diabetes.

[Slide.]

Relative the placebo, rimonabant had no effect of levels of total cholesterol or LDL cholesterol and, for unclear reasons, reductions in systolic and diastolic blood pressure were less than expected given the degree of weight loss.

[Slide.]

But there area important caveats to keep in mind with regard to these efficacy data. First, one must keep in mind the high attrition rates that occurred during the RIO trials. The withdrawal rate during the first year of the four RIO studies

ranged from 32 percent to 49 percent. During the second year, 23 to 58 percent of the re-randomized subjects withdrew and there was no systematic follow up of these dropouts.

But high attrition rates are not unique to rimonabant. They tend to occur with all weight-loss drugs and with some other drugs as well.

[Slide.]

Second, it is important to note that, in the RIO studies, final weight measurements were not obtained on roughly half of the randomized participants due to the high attrition rates. Ignoring data from patients without complete follow up can introduce considerable bias into the analysis.

To account for patients who completed and those who didn't, the last observation on study was used in the statistical analyses. Measuring all participants randomized and conducting an intention-to-treat analysis, using last observation carried forward, is one approach that preserves the

rationale for randomization but it is not the only approach. Each approach has its strengths and weaknesses.

[Slide.]

Third is a concern with the generalizability of the population. The study enrolled predominantly middle-aged caucasian females. Again, this is not unique to rimonabant but was also seen with sibutramine and orlistat. However, statistical analyses showed a significant treatment by age group interaction in both RIO North America and Rio Lipid, the treatment effect being greater in subjects under the age of 65 than in those 65 and older.

Similarly, the treatment by race interaction was significant for RIO North America, Rio Europe and Rio Diabetes. The mean rate change was consistently greater in Caucasians than in blacks and it should be noted that subjects with a history of significant depression were excluded from the trials despite the belief that the prevalence of depression may be greater in the

overweight and obese population.

I will now turn to the safety data.

[Slide.]

This slide depicts the database that was employed in the safety assessment of rimonabant. As you can see, it includes data from a variety of patient populations; schizophrenics, alcoholics, cigarette smokers, in addition to the obese and diabetic subjects consider in the efficacy assessment.

The trial designs were varied as well including different durations, sizes, randomization schemes, drug exposure and drug dosages. For this reason, our analyses often focused on the RIO studies and the studies in diabetics.

[Slide.]

This slide provides a summary of the overall exposure to rimonabant, 20 mg. As you can see, despite the overall large number of participants reported in the database. Approximately 1600 to date have taken the drug for one year and 441 subjects have taken it for two

years.

I point this out because many of you have expressed a concern about this being a chronic medication, a life-long medication. We are looking at data from 441 patients who have had two years of exposure to date.

[Slide.]

Because of the varied nature of the data and the complexity of the datasets where adverse events were not all located within a single dataset but spread across three datasets, the analyses were difficult especially for safety signals where there were low event rates.

For the purposes of today's analysis, we have focused on the largest of the three datasets, the adverse-event dataset, and for studies where subjects were re-randomized to a different treatment arm, such as 20 mg to placebo. or 5 mg to placebo, we focused only on those subjects who received the same treatment during the entire study.

This was done because of the long

half-life of the drug, about 16 days on average, and the difficulty in assigning the adverse event to a particular treatment arm if it occurred after re-randomization, especially if it occurred during the first 90 days after re-randomization.

I point this out because we know we are losing events by doing this. So you should view or analyses as conservative and an underestimate of the true risks associated with the use of rimonabant.

I will spend a few minutes explaining how the data were analyzed for the specific areas of safety concern, neurological, adverse events including seizure and psychiatric adverse events including suicidality.

But one further comment by way of explanation. Our numbers will differ from the sponsor's as we could only reasonable evaluate completed studies for which clinical-study reports, complete datasets, case-report forms and patient narratives for events of interest had been provided to us. Thus, our cutoff date was December, 2006

and the sponsor's was, in some cases, March of 2007.

[Slide.]

The purpose of the statistical analysis was to estimate the effect of rimonabant versus placebo on safety outcomes. Meta-analyses were performed stratified by study. The studies included were 14 randomized, Phase II and III trials. Per-study sample sizes ranged from 20 to 3,000 per group. The duration of the studies ranged from 4 weeks to 104 weeks.

The primary treatment-group comparison was rimonabant 20 mg versus placebo.

[Slide.]

The primary statistical measures of risk between the two groups were the relative risk, the odds ratio and the risk difference. A few studies had unbalanced randomizations, notably RIO North America and Rio Europe. The meta-analyses were stratified by the individual trials in order to maintain the individual study randomizations and individual study results.

For safety outcomes, with relatively rare events such as seizures and suicidality, an exact meta-analysis and a fixed-effects meta-analysis were performed. For safety outcomes with more common events such as neurological adverse events and psychiatric adverse events, fixed- and random-effects meta-analyses were used.

Data from only the first randomization were included in the primary analysis and sensitivity analyses were conducted that included the additional events from second randomizations.

[Slide.]

One of the deficiencies highlighted in the original review pertain to neurological adverse events. Neurological symptoms including sensory changes, motor impairment and cognitive difficulties appear to have been common in the clinical trials but were not fully characterized. Specific measures were set up to retrospectively obtain and capture neurological symptoms from the 12 completed Phase III studies.

[Slide.]

As a quick reminder, CB1-receptor density is particularly high in the cerebellum, cortex, hippocampus, hypothalamus and basal ganglia, areas of the brain that affect memory, motor function and reward behaviors. They are also present on the peripheral nerves. They play a neuroprotective role in both the central and peripheral nervous systems.

[Slide.]

While the overall rates of neurological adverse events were not terribly different between rimonabant and placebo occurring in 27.4 percent of rimonabant-treated subjects versus 24. 4 percent of placebo-treated subjects.

The vast array of these events gave us a considerable sense of uneasiness. The neurological adverse events were not insignificant. They were responsible for 3.5 percent of the discontinuations due to adverse events from the RIO trials among rimonabant subjects versus 1.4 percent of placebo subjects.

These next slides are meant to highlight

this array of different neurological adverse events reported during Georgetown RIO trials. They are grouped according to the areas of concerns; sensory changes, motor impairment and cognitive disorders.

[Slide.]

This first slide summarizes the various preferred terms that were specified by Sanofi in their statistical analysis plan as illustrative of sensory changes. Overall, sensory changes occurred more frequently in rimonabant than in placebo. 14.1 percent versus 9.4 percent.

As you can see, this category was driven predominantly by the adverse event of dizziness which occurred in 8.5 percent of rimonabant subjects versus 5.6 on placebo.

But let me just highlight a few and, by no means, is this a comprehensive list. But you can see paresthesia, hypesthesia, dysesthesia. You have impairments in taste, dysgeusia and, down here, ageusia. You have loss of smell, anosmia, parosmia, and then a whole host of various visual disturbances.

[Slide.]

This slide illustrates the preferred terms for motor impairment. First is specified by Sanofi in their statistical analysis plan and then with additional terms which the division considered to be of significance.

Looking at the sponsor's specified data alone, motor impairment occurred more frequently in rimonabant subjects than in placebo subjects, 1.7 percent versus 0.5. When the other events of interest are added in, those numbers become 3.1 percent versus 1.2 percent.

As you can see, this category was driven predominantly by tremor which occurred in 1 percent of rimonabant and in no placebo subjects. But, again, I point out, dysphonia, aphonia and dysarthria and balance disorder, restless leg, motor dysfunction, clumsiness. Again, this is not a comprehensive list but this gives you a flavor for the array of different neurological events we were seeing.

[Slide.]

This slide highlights the preferred terms of cognitive disorders. Overall, cognitive disorders occurred more frequently in rimonabant than in placebo, 5.4 percent versus 3.3 percent.

As you can see, this category was driven predominantly by amnesia and memory impairment. But, again, the array of symptoms is worrisome; disturbance in attention, lethargy, disorientation, confusional state, cognitive disorder and memory loss.

[Slide.]

This slide provides a forest plot summary of the relative risk of a neurological adverse event which is a composite of all the nervous-system disorders using the updated RIO database. This represents the random effects meta-analysis. As you can see, the combined estimate is 1.7. This was of nominal statistical significance.

What should be noted in this slide as well is the relative risk in RIO Diabetes which was a concern to us because of the neurological

complications of the disease, itself. And, despite improvements in subjects' underlying diabetic condition, they appear to have a slightly higher risk of a neurological adverse event on rimonabant.

[Slide.]

So we looked at the two large studies in diabetic subjects, RIO-Diabetes and SERENADE. SERENADE was a Phase III-B study conducted in treatment-naive type 2 diabetics. This forest plot depicts the relative risk in these two studies.

As you can see, the combined estimate is 3.1. And you can see by the size of this box, which correlates with the precision, really, of the point estimates, that SERENADE added very little to the analysis. But, nonetheless, the risk appears higher in this subpopulation.

So you can see, individually, the numbers of events are small. But, in aggregate, they are worrisome especially given the fact that we don't have follow up or imaging studies on many of these patients.

I am just going to review one of the

patient narratives here as it highlights a concern of ours over the accurate characterization of neurological adverse events. This is a case of a 59-year-old female with no relevant medical history who was enrolled in SERENADE.

The patient was discontinued from the trial due to depressed mood with suicidal ideation on about Day 139. The subject was reported as being recovered from these symptoms seven days later at which time she reported moderate aphasia and moderate vision blurred. These symptoms were reported as not recovered at the end of study which was two months later.

Despite this, no neurological consultation or imaging study was performed. The case-report form indicated that a complementary investigation was performed for this subject which revealed, "no pathological finding." However, no report was in the case-report form. The complementary investigation was apparently an eye exam, although it is unknown if it was performed by an ophthalmologist or a family doctor.

[Slide.]

There is evidence from clinical trials with multiple-sclerosis patients that cannabinoids can reduce the spasms, spasticity or tremor of MS. Furthermore, results from studies in mouse models of MS suggest that CB1 or CD2 receptor activation by either exogenously administered or endogenously released agonists may oppose the progression of MS by slowing the neurodegenerative process, reducing inflammation and promoting remyelation.

[Slide.]

The number of cases of MS seen in rimonabant trials and postmarketing to date have been small. Two cases of confirmed--and I should mention this is data that we received, this is information that we received, from the company--two cases of confirmed MS occurring in subjects receiving 5 mg of rimonabant in the RIO studies and one case of unconfirmed MS in a subject receiving placebo in the RIO studies.

There were two subjects from the smoking-cessation trials both on 20 mg who had

suspected cases of MS and postmarketing reports received to date include one case of optic neuritis in a subject who had been taking rimonabant for approximately one month and her MRI report suggested MS. One additional case was reported in a woman with a history of MS who had an exacerbation of her MS within five days of starting rimonabant necessiting discontinuation of the drug and hospitalization.

Given the delay in diagnosis that is often seen with MS, and the often non-specific nature of the neurological symptoms and signs with which patients present such as depression, dizziness, vertigo, fatigue, numbness, tingling, visual impairment, weakness, tremor, impaired coordination and balance, coupled with the myriad vague neurological adverse events seen in the rimonabant trials, the lack of investigation of many of these adverse events and the lack of systematic follow up of subjects who discontinued from the trials, the unmasking or exacerbation of MS remains a theoretic possibility albeit one that is biologically

plausible.

[Slide.]

Because of the pre-clinical safety signal for seizure, Sanofi was asked to further evaluate the potential risk of seizures in the rimonabant clinical-trial database by performing string searches on the narratives of all rimonabant studies to identify potential cases of seizure.

[Slide.]

Cannabinoids possess anti-convulsant properties and the endocannabinoid system has been implicated in the regulating seizure threshold, duration and frequency. It is speculated that epileptiform seizure activity elicits an increase in the on-demand synthesis of endocannabinoids resulting in increased activation or pre-synaptic CB1 receptors with subsequent regulation of neuronal hyperexcitability and seizure termination.

[Slide.]

You have heard about the preclinical toxicology data from Dr. Davis-Bruno. But, to summarize, 6 percent of rats and mice and 20

percent of monkeys developed seizures while exposed to doses of rimonabant, 0.5 to 2 times the 20 mg dose versus 1.5 percent of control mice and no control rats or monkeys.

That, in conjunction with the fact that rimonabant accumulates two-fold in the brain with multiple dosing, so AUC:Cmax ratios probably overestimate safety margins in humans, formed the basis for our concerns regarding the seizure potential in humans.

[Slide.]

It should be noted that subjects were excluded from rimonabant trials for the presence of any clinically significant neurological disease, the presence of treated epilepsy or the prolonged administration of neuroleptics within three months prior to screening visits and subjects were discontinued from the trials for the use of neuroleptics.

[Slide.]

In the original submission to the NDA, a total of 7 cases of seizure were reported in the

four RIO trials, 4 on rimonabant 20, 2 on rimonabant 5 and 1 one on placebo. In the updated NDA, 19 cases of seizure have been reported in completed rimonabant clinical trials, 16 of which occurred during the treatment window.

All of these cases were considered in our analyses regardless of the adjudication process. We felt it was important to analyze all of the suspected cases of seizure as the adjudicators were attempting to ascertain retrospectively whether a seizure had occurred but, in many of these cases, no relevant investigations had been performed at the time.

So we weren't convinced that the adjudication process provided any meaningful clarification. Of the 16 cases, 9 occurred on rimonabant 20, 2 on rimonabant 5 and 5 on placebo.

As you can see, the majority of these occurred in the obesity trials.

[Slide.]

This slide presents the person-year analysis of all 16 cases of seizure and then the

person-year analysis of the cases occurring in the obesity studies. As you can see, the incidence rate for seizure in the obesity studies is 2.7 per 1,000 patient years for rimonabant 20 and 0.44 per 1,000 patient years for placebo, a relative risk of 6.1, albeit with a confidence interval of 0.94 to 137.

[Slide.]

In ongoing studies, where randomization is 1 to 1, there have been 8 cases of seizure reported. These include 6 cases on rimonabant 20 and 2 on placebo. The numbers remain small. However, the imbalance between rimonabant and placebo persists.

[Slide.]

Given the known anticonvulsant properties of endocannabinoids and the preclinical finding with rimonabant, and given the 16 cases of seizure which occurred during the trial despite efforts to exclude high-risk patients, as well as the continued imbalance in the occurrence of seizure in ongoing trials, we remain concerned about

rimonabant's potential to increase seizure risk.

Additional clinical experience will clarify this potential risk.

[Slide.]

Psychiatric symptoms, including depression, anxiety and insomnia, occurred frequently during the trials. Many of these symptoms required ongoing treatment with anxiolytics and/or hypnotics. Anti-depressants were also frequently prescribed although their use was grounds for discontinuation from the trial.

[Slide.]

Endocannabinoids are important modulators in pathological conditions such as anxiety, phobias, depression and post-traumatic-stress disorders. CB1 receptors are abundant in the prefrontal cortex of the brain, an area of the brain that is thought to be involved in the regulation of mood, aggression, impulsivity and decision making.

Additionally, CSF levels of the endogenous cannabinoid anandamide correlate inversely with

psychotic symptoms in schizophrenic patients and it sidewalk believed that anandamide has a protective role in schizophrenia.

[Slide.]

Therefore, the emergence of psychiatric symptoms not only depression, anxiety and mood disorders but also aggression, anger and psychosis with the use of a cannabinoid receptor antagonist or inverse agonist is biologically plausible.

There is also reason to believe that overweight and obese patients may have a predisposition toward depression. In the rimonabant studies, subjects were excluded from the trials for the following: the presence of any clinically significant psychiatric disease, a history of severe depression defined as depression necessitating hospitalization, or a history of two or more recurrent episodes of depression, or a history of suicide attempts or the prolonged administration--I'm sorry; that should be bulleted over. That was actually a different exclusion criterion--but the prolonged administration of

anti-depressants within 3 months prior to screening.

Furthermore, they were discontinued from the study if they were started on an anti-depressant. A total of 11,225 patients were screened in the RIO studies. A total of 113, or just 1 percent, failed screening due to these exclusion criteria.

[Slide.]

Despite these exclusion criteria, the medical histories of subjects who were enrolled in the RIO studies revealed that a significant number of them had an underlying medical history of depressed mood disorders and disturbances. This slide depicts the breakdown by study. The pooled analysis revealed that the baseline history of depression was slightly higher in the rimonabant 20 group at 7 percent versus placebo at 6 percent.

However, I would point out that only l.4 percent on rimonabant 20 versus 1.1 percent on placebo reported their depressive symptoms as ongoing and trial entry.

[Slide.]

This slide indicates the terms that were used to evaluate the psychiatric profile of rimonabant. This is the standard approach to recording adverse-event data from clinical trials and it is based on the Medical Dictionary for Regulatory Activities, or MedDRA.

Terms under the Primary System)rgan class, or SOC, psychiatric disorders, under the high-level group terms and then under preferred terms. The high-level group terms that we focused on were anxiety disorders and symptoms which include such preferred terms as anxiety, nervousness, stress and tension, depressed mood disorders and disturbances which included depression, depressed mood, anhedonia and dysthymic disorder, sleep disorders and disturbances which include insomnia, parasomnia, and somnolence--again, this is just a brief listing--and mood disorders and disturbances which include affect alteration, crying and mood altered.

[Slide.]

Overall, subjects in the rimonabant 20 mg group were more likely to experience a psychiatric adverse event than those on placebo. In the pooled RIO studies, in subjects receiving the same treatment during the entire study, 26 percent of rimonabant's treated subjects versus 14 percent on placebo experienced a psychiatric symptom reported as an adverse event.

Again, because we don't include events occurring in subjects who were re-randomized during a second randomization to a different treatment arm and because we have confined our analyses to the one adverse-event dataset, this should be viewed as an underestimate.

The incidences of psychiatric adverse events in all of the high-level group terms were higher for rimonabant than for placebo; anxiety disorders at 11 percent versus 5 percent, depressed mood at 9 percent versus 5 percent, sleep disorders, 8 percent versus 4 percent and mood disorders and disturbances 3 percent versus 0.8.

An overriding theme is the almost 2 to 1

imbalance that seems to occur repeatedly.

[Slide.]

Here we are looking the relative risk of experiencing a psychiatric adverse event in the RIO studies. Again, this is a composite of all of the preferred terms. The relative risk, using the random effects model, was 1.9. This was of nominal statistical significance.

[Slide.]

We then performed some additional analyses looking at the relative risk of a psychiatric adverse event by age, gender, geographical location and degree of weight loss. It appears that the risk may be higher in the 65 and older age group relative to the under 65 with relative risk of 3.1 and 1.7 respectively.

There was no difference in relative risk between U.S. and non-U.S. participants, 1.7 and 1.8.

[Slide.]

With respect to gender, the relative risk trended slightly higher for males than females, 2.1

versus 1.7. Because of a possible association between weight loss, itself, and symptoms of anxiety and depression, we looked at the relative risk in 5 percent weight-loss responders versus non-responders. As you can see, the relative risk was really no different regardless of the weight-loss response, at least when defined by a 5 percent cutoff.

[Slide.]

Because there was a relatively large number of subjects who were enrolled in the RIO trials with a baseline medical history of depressed mood disorders and disturbances, we decided to look at those individuals relative to the larger group to see how many of that went on to have a psychiatric adverse event during the trial expecting, of course, that having a baseline history of depression would increase their risk of experiencing such an event.

And, indeed it did. The incidence of a psychiatric adverse event in subjects who had a baseline history of depression was 32.2 versus 17.6

among patients who did not have a baseline history of depression. But keep in mind that subjects with more severe forms of depressed mood disorders were excluded from the trials and also bear in mind that this also indicates that roughly 88 percent of subjects who experienced a psychiatric adverse event did not have a baseline history of depressed mood disorder and disturbances.

This is in contrast to what the company has told you that having a baseline history of depressed mood is predictive for who will have difficulties with rimonabant.

[Slide.]

These psychiatric adverse events, in general, more often necessitated discontinuation of study drug. Psychiatric adverse events accounted for 8.5 percent of the discontinuation from the study among subjects on rimonabant versus 3 percent of placebo subjects. Most subjects were reported as recovered or recovering from their psychiatric adverse events at study end. However, subjects were reported as recovered even if their symptoms

resolved because of treatment with an anxiolytic or hypnotic or anti-depressant.

Here you see that 8.5 percent of rimonabant subjects who were enrolled--and this is the whole group--8.5 percent of people who were enrolled in the RIO studies on rimonabant 20 mg required the institution of an anxiolytic or hypnotic during the trial versus 4.1 percent of those on placebo.

Another 4.8 percent of subjects required institution of an anti-depressant versus 2.9 percent of those on placebo. These numbers are felt to be an underestimate because some subjects were placed on a beta-blocker for their anxiety symptoms. Our review of the patient narratives and case-report forms reveals still others whose treatments were simply not recorded in the datasets.

[Slide.]

Our conclusion was that rimonabant 20 mg was associated with an approximate doubling of the risk of a psychiatric adverse event and a roughly

three-fold increase in discontinuation from the trials due to these events. These events included predominantly anxiety disorders and symptoms, depressed mood disorders and disturbances and sleep disorders and disturbances.

This was from trial data in subjects in whom major psychiatric disorders had been excluded. What remains unknown is what the experience with rimonabant will be in a less highly screened and potentially more depressed patient population.

[Slide.]

In the original NDA submission, one case of suicidal ideation in a subject on placebo was reported. Initially review of the patient narrative and case-report forms by the medical reviewer revealed several other cases which had not been reported. It was at that time that Sanofi was initially asked to reassess the database to investigate for other cases of suicidality.

Then, subsequently, the division also requested that Sanofi obtain a formal assessment of suicidality from Dr. Kelly Posner's group at

Columbia University. You were introduced to Dr. Posner's methodology earlier today.

[Slide.]

This slide again reviews the various categories of interest within the Columbia classification system. These categories break down into definitely suicidal, categories 1, 2, 3 and 4, or possible suicidal, Columbia categories 5, 6 and 9.

[Slide.]

A total of 1201 patient narratives were prepared by Sanofi and submitted to Dr. Posner's group for a blinded analysis. The analysis identified 91 cases of either definitely or possibly suicidal. This included five cases which occurred on haloperidol active treatment.

The majority of cases were assigned to Columbia category 4 which is suicidal ideation. Of the 91 cases, 64 were considered to be suicidal ideation. This included 14 cases occurring on placebo, 10 on rimonabant 5 and 40 on rimonabant 20.

Now I would like to take a couple of minutes to explain the methodology employed by our statisticians in the selection of studies to be used in the analysis of suicidality.

[Slide.]

A total of 13 studies were used in our analyses, RIO North America and EFC 4796, which was a large smoking-cessation trial, re-randomized patients during a maintenance phase after the randomized treatment. Only data from the first randomization was used in the primary analysis.

The control group employed for study EFC 4796 was rimonabant 5 mg as there was no placebo group in the first randomization. Sensitivity analyses were performed both including all suicidality events and ignoring the second randomization as well as excluding studies with a second randomization.

[Slide.]

Thus, the total number of suicidality cases contributing to the analyses is 74, 46 on rimonabant 20 which included: four suicide

attempts, 39 suicidal ideations and 3 not enough information, non fatal; 8 cases of suicidality on rimonabant 5 mg, 1 preparatory act toward imminent suicide, 6 suicidal ideations and 1 not enough information, fatal; and 20 cases on placebo, 7 suicide attempts which, I should point out, 3 occurred in the schizophrenic trials and 3 in the alcoholic trials and 1 in the smoking-cessation trial and 13 cases of suicidal ideation.

[Slide.]

This slide illustrates the results of the fixed effects meta-analysis. Again, I remind you that, in the smoking-cessation trial. EFC 4796, that we have used the 5 mg group as the control group because there was no placebo group in the first randomization.

As you can see, by this very small point estimate, it really adds little to the composite analysis but, nonetheless, I point that out.

The odds ratio for the incidence of suicidality, rimonabant 20 versus placebo for all of the studies contributing to the analysis is 1.9

which is of nominal statistical significance.

[Slide.]

Here we are looking just at the 7 obesity studies so you can forget about that smoking-cessation and whether or not we should have used 5 mg as our control arm. You can see our point estimate has changed very little, still 1.8.

I should point out that sensitivity analysis, adding the second randomization events to the first randomization, resulted in an exact text odds ratio of 1.93.

[Slide.]

To date, four completed suicides have been reported, 3 in the entire rimonabant clinical-trial database and one postmarketing. All of the cases of suicide occurring during rimonabant clinical trials have occurred in subjects on active treatment, none on placebo.

To briefly summarize these cases: in RIO North America, a 63-year-old gentleman taking rimonabant 5 mg; in STRADIVARIUS, which is an ongoing study; a 36-year-old male on rimonabant 20

mg; and, in CRESCENDO, a 77-year-old male on rimonabant 20 mg. I know that the sponsor highlighted this as a case where the gentleman had stopped rimonabant a week before he committed suicide. Just to clarify that, that is absolutely true and the reason he stopped it is that the IRB at that investigation site insisted that a letter be circulated warning of the risk between rimonabant and suicidality; postmarketing, a 33-year-old male on rimonabant 20. Again, the details on this case are sketchy but we do know that this gentleman had a BMI of less than 20.

[Slide.]

But even if you believe that there is an association between rimonabant and suicidality, what is the nature of that association? Was ascertainment bias a factor? Ascertainment bias is generally a concern when doing epidemiological studies but this concept has been suggested in the association between anti-depressant use and suicidality in adolescents and young adults.

Depressed individuals who are placed on an

anti-depressant become activated and are more apt to vocalize their suicidal thoughts or subjects whose social anxiety is effectively treated with an anti-depressant may exhibit increased verbalization and communication with others.

But depressed patients were specifically screened out of the rimonabant trials--and for a reason, I might add. And rimonabant is not an anti-depressant.

[Slide.]

Is it that patients who report common drug-related adverse events may be questioned more about other adverse events compared with placebo patients?

For example, as was recently suggested in an editorial in the New England Journal of Medicine, the increased reporting of sexual dysfunction in depressed patients taking an anti-depressant might lead to further questions about other adverse events and possibly increase the odds of reporting suicidal symptoms.

But the most common adverse event in

rimonabant-treated patients is nausea. Would increased reporting of nausea in a population of non-depressed patients on rimonabant lead to increased reporting of suicidal symptoms? And, besides, depressive and anxiety events were reported, on average, two months later than nausea events.

[Slide.]

Were rimonabant-treated subjects more apt to make more unscheduled visits, again, due to other side effects of the drug such as nausea, and voice other side effects at those visits? But the mean and median number of study visits were the same for both the placebo and the rimonabant groups and the dataset which contained unscheduled visits such as the clinical laboratory datasets were all reviewed and did not reveal any disproportionality between treatment groups and the number of unscheduled visits.

[Slide.]

Ascertainment bias was an interesting hypothesis. If you believe that this explains the

increased rate of suicidality in rimonabant subjects, you must assume that it is operative in 9 of 13 studies and it explains odds ratios varying in magnitude from 1.4 to 16.7. You must also assume that there is an equal background rate of depression in placebo and rimonabant subjects as suicidality is a symptom of depression.

But, as you recall, the rates for depressed mood-disorder adverse events were 9 percent in rimonabant subjects and 5 percent in placebo subjects.

For those who would say that, perhaps, ascertainment bias explains the higher reporting rates for depressed mood disorders, I point out that a larger percentage of patients treated with rimonabant discontinued early from the trials due to depressive disorders and a larger percentage of rimonabant subjects required anti-depressant therapy.

These outcomes, perhaps more indicative of more severe forms of depression would, I believe, be less susceptible to ascertainment bias.

[Slide.]

Or is it the weight loss, itself, and not the drug that is prompting the suicidal ideation, the so-called semi-starvation neurosis? Subjects who experience significant weight loss may exhibit psychiatric disorders such as depression, anxiety and suicidal ideation.

[Slide.]

We explored that possibility here. This slide looks at the weight change from baseline in suicidality subjects, indicated by the blue circles, relative to the mean weight change in subjects who did not experience suicidality, indicated by the yellow lines. The red lines indicate 1 standard deviation above and below the mean.

If, indeed, the weight loss was the cause of the suicidality signal, we would have expected to see more of these circles concentrated down in this area. But, if anything, they are concentrated around the mean and above the mean. So we don't believe that these data support that hypothesis.

[Slide.]

Is the association due to chance? You can never rule out chance but, again, is it chance in 9 of 13 studies?

[Slide.]

Or is the association causal? And we strongly believe that it is causal. We know that it is biologically plausible given the role of the endocannabinoid system specifically the CB1 receptor function in the central nervous system. After all, that is why the sponsor excluded depressed patients.

We find a similar increase in the risk of depression in the clinical trials and suicidality is a symptom of depression. So it is not really surprising. In fact, it would have been more surprising if we didn't see it.

[Slide.]

So, in summary, our meta-analysis indicates an increased risk for suicidality, specifically suicidal ideation, in subjects taking rimonabant 20 mg versus placebo. There is an

increase in relative risk of 80 to 100 percent and an increase in absolute risk of 0.3 percent.

This correlates with one additional case of suicidality per year for every 300 patients treated. And these estimates may be low, given the higher percentage of rimonabant-treated patients who drop out of the study due to psychiatric adverse events.

[Slide.]

Rimonabant is currently approved in 30, I guess now 37, countries. As of March 1st, 2007, an estimated 100,000 people, mostly from the United Kingdom and Germany, have been prescribed rimonabant. The top ten preferred terms reported to the European regulatory authorities to date are; depression, nausea, depressed mood, anxiety, fatigue, dizziness, sleep disorder, suicidal ideation, agitation and asthenia, not surprising given what was observed in the clinical trials.

I am just going to ask Dr. Eric Colman to come up for a minute. He is going to explain some of the data that we have received from the EMEA.

[Slide.]

DR. COLMAN: These are data that we just obtained within the last week and, in some cases, actually yesterday. But I think it is important to show the folks these data. This is one advantage of not approving a drug too soon because the Europeans approved it first. So we can go to them now and ask for their experience after they approved it and get a better sense what is going on.

But, what we wanted to do was look and see what rimonabant looked like compared to the two other weight-loss drugs that had been around for 7 or 8 years So, we focused on that. But what this shows you, and I will just remind you that rimonabant, the approval began around this time last year. Sibutramine was approved in Europe in 1990, and orlistat was approved in 1998 in Europe.

So, this is from the same database, the numbers you are looking at, and these are cumulative since the dates of approval. What you see here are the total adverse events for any

event, anybody's system. These are the total number of cases that were spontaneously sent to the system.

So, for rimonabant, you have 384 cases. Sibutramine, you have 567, and orlistat, you have 2,734. Orlistat clearly is used more than sibutramine in Europe, and I believe that is true in this country, as well.

So, those are the total number of all adverse events in this data system.

Now, this column shows you the number of psych-related adverse events for these various drugs. And. again rimonabant over the course of about a year, there are 208 psych adverse event cases, sibutramine 117 and orlistat 208.

So, you can see a function of the total number of AEs, the psych Aes for rimonabant make up 54 percent of the total adverse events in this system. That compares with 21 percent with sibutramine, and it is not surprising. As we discussed earlier, sibutramine is an antidepressant-like in terms of its pharmacodynamic

action. It is centrally active agent.

Orlistat, which is really not absorbed into the system, you wouldn't expect any real psychiatric effect, at least direct psychiatric effect, and that only makes up 8 percent.

So, clearly, within one year, over half of all the adverse events are being contributed to by psych-related adverse events.

[Slide.]

Again, these are data from the EMEA, postmarketing data spontaneously reported. We wanted to know how many cases of suicidal ideation the EMEA had for these compounds. Again, orlistat has been on the market over there since 1998. They have 14 cases of suicidal ideation.

Sibutramine has been on the market in Europe since 1999. They have 15 cases of suicidal ideation. Rimonabant has not even been on the market for one year, almost one year, and they have 27 cases of suicidal ideation.

[Slide.]

DR. EGAN: It is interesting to look at

this number because this is about what we would have predicted based on our absolute risk.

To our way of thinking, the risk-benefit analysis sorts out this way. Rimonabant is effective at reducing body weight and rimonabant associated weight loss does improve triglycerides, HDL cholesterol, and hemoglobin A1C and fasting insulin levels, and there are probably benefits that are yet to be identified.

The risks associated with the use of rimonabant include an approximate doubling in the risk of psychiatric adverse events specifically depression, anxiety, insomnia, and mood disturbances, an approximate doubling in the risk of suicidality, specifically, suicidal ideation, an increase in a constellation of neurological adverse events of unclear significance, a possible increase in seizure risk, an increase in nausea and vomiting--which we haven't really discussed today although it is the most commonly reported adverse events, and many of these risks appear more pronounced in diabetics--and as yet to be

identified risks, and there will be further risks.

Our knowledge of the endocannabinoid system is still evolving and there is a lot more to be learned, but keep in mind the signals we are seeing are in a relatively small and highly select population, carefully screened and receiving drug in a controlled setting.

The potential market for this drug and our continued uncertainty about its risks, both known and unknown, lead to our concern about the use of this drug in the general population.

Weight loss may have benefits in and of itself. However, the effect of drug-associated weight loss on cardiovascular morbidity and mortality remains unproven. The results of studies, such as the Women's Health Initiative, highlight a concern with continued reliance on surrogate endpoints that ultimately do not achieve the desired goal of reducing cardiovascular morbidity and mortality.

In that regard, rimonabant's lack of effect on LDL cholesterol or blood pressure is

certainly notable.

[Slide.]

I would just like to briefly mention an ongoing clinical outcome trial that Sanofi is conducting. It is called CRESCENDO for Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes. 17,000 abdominally obese patients at risk for cardiovascular disease are to be enrolled. The study is 50 months in duration. The primary outcome is myocardial infarction, stroke, or cardiovascular death. The study is scheduled to be completed in January of 2010. This may answer the question of whether the improvements observed in these surrogate endpoints are clinically relevant.

[Slide.]

I just wanted to take a moment to acknowledge all the members of our review team for their tireless efforts in this review process.

[Slide.]

We have prepared the following three questions for your discussion and input. I can