treatment-naive diabetics with no background therapy, there were two cases of mild symptomatic hypoglycemia, one with rimonabant, one with placebo.

[Slide.]

So, in the obesity program, adverse events were mostly of GI, neurologic and psychiatric origin. They were of a similar nature in the diabetes population with additional events, such as hypoglycemia, muscle spasms and paresthesias.

[Slide.]

In the obesity and diabetes programs, deaths were few and balanced across the doses - 3, 3, and 4, as you can see.

The same was the case with diabetes. Ongoing clinical trials have recruited more than 14,000 patients at risk for cardiovascular outcomes and are being monitored by an independent data and monitoring committee.

[Slide.]

We will move on to an in-depth review of the adverse events of interest.

[Slide.]

Rimonabant acts both centrally and peripherally. Adverse events of interest were psychiatric and neurologic events, as shown.

Because of their medical importance, we examined suicidality and depressive disorders. In addition, we will also discuss anxiety, which was reported in the clinical studies.

Finally, we will review the neurologic adverse events with special attention to multiple sclerosis and seizures.

[Slide.]

With the advice of FDA and the Swedish health authorities, the specific methodology was implemented prospectively during the course of the RIO studies to specifically monitor depressive events.

Any symptom possibly attributed to the depression by the investigator triggered a psychiatric consultation to better assess the diagnosis using DSM-IV criteria

But to increase the sensitivity in

addition to the spontaneous open questioning from investigators, a patient self-assessed scale, the Hospital Anxiety and Depression Scale was completed regularly during the 7 obesity studies to help the investigator to identify undetected cases when the depression subscore of that scale reached 11 or greater and, it is important to note that, on that scale, there was no question for suicidality.

In a retrospective assessment we went back with cooperation from the sites and on recommendation of the FDA, we went back to all cases of neuropsychiatric events to the site and to all patients who received antidepressant therapy, or who had severe anxiety or other psychiatric disorders.

All these cases were fully documented to a specific questionnaire, focusing at the site level on outcome and associated symptoms including suicide attempt and ideation in this retrospective assessment and through collection of source documentation including medical reports and investigator notes.

Finally, and this is important, if a patient during the course of the studies required antidepressant therapy in the RIO program, he or she was automatically discontinued from the study treatment to avoid the confounding effects of the therapy on body weight loss.

[Slide.]

Under the MedRA safety classification, the high level group term depressed mood disorders and disturbances is shown here, 4.5, 8.4 percent, approximately a 4 percent difference.

This breaks down into two subclassifications which may look very similar in terms of the wording, and there is approximately a 2 percent difference there. But they do have different clinical earmarks.

[Slide.]

The medical history part of the case report form sometimes had written in a past history of depressive disorders from the site.

On the left, you can see that the rimonabant and placebo treated patients with mood

alterations were very similar more or less, with a past history of depressive disorders recorded in the case report form of about 15 percent, a quarter needed to stop the treatment whether it was placebo or rimonabant.

The corrective therapy was about a third of patients--two-thirds did not require it--and the median time to recovery was very similar between the groups when there was therapy or not, and there were no hospitalizations.

So, there is really no distinguishing earmarks on the rimonabant and placebo site there.

Similarly, for patients who had depressive disorders, these were very similar, 40 percent past medical history of depressive disorders, about 60 percent discontinued. Corrective therapy, usually antidepressant therapy in over 70 percent.

Given the small numbers it is hard to really say because we have the small numbers on this side. There were hospitalizations, somewhat more observed here, but it was 1 out of 43, 4 out of 106 compared to the mood alterations.

So, this group is similar to itself, this group is similar to itself. The difference is when you go across the line. Patients with depressive disorders more often had a history of past depressive disorders. They more often had discontinuation, need for corrective therapy, and there were occasional hospitalizations.

So, mood alterations with depressive symptoms are not the same at all as depressive disorders.

[Slide.]

Now, I am going to look at it the other way around. In the previous slide, we saw that given mood alterations of depressive disorders, a past history of depressive disorders was more frequent in the latter group.

A feature that was the case with both placebo, as well as rimonabant-treated patients, each side was similar to itself in terms of rimonabant and placebo.

In this slide, we look at the situation the other way around. Given a past history, was

there a greater likelihood to develop these disorders in the study.

On the left, in patients with no past history of depressive disorders, which of course is the majority of the database, the numbers look very similar to the overall safety profile I showed a few slides back.

In spite of 2 percent difference here, 1 percent, 2 percent here, I am highlighting this line because I want to keep your eye on it.

In the patients with a past history, which are here, fewer, what you can see is that mood alterations with depressive disorder is doubled if you had a past history and so did the rimonabant.

Skip the yellow line. Anxiety doubled. Everything doubled when you were on the side with a past history. The yellow line is different. You went up 8- to 9-fold. On the placebo side, if you had a past history, you were more likely to have a depressive disorder on the placebo side.

On the rimonabant side, same thing, about 9-fold. So, whereas a past history tended to raise

all boats about 2-fold for these, with depressive disorders, there was an amplification of about 9-fold for both placebo and rimonabant equally.

So, a past history predicted a future event more often, in general.

[Slide.]

So, in summary, depressive-related events were reported by investigators more often with rimonabant and, among these adverse events, we can identify two different types. The mood disorders that generally recovered without the need for corrective therapy or discontinuation, and another category of depressive disorders which required more frequently corrective treatment and hospitalizations and there was a consistent but modest difference between the placebo and the rimonabant groups.

Now, as seen in other studies, patients with a past history of depressive disorders are at a risk of another event, a fact that was as true for placebo in these studies as for rimonabant.

Therefore, in considering who is the right

patient for rimonabant from a safety point of view, we will recommend not treating patients with a history of depression or suicidality, not treating patients with an active diagnosis of depressive disorders or current antidepressant therapy.

This is the overall difference in the original table of adverse events. If we were to exclude past history of depression, you see you go from 3.9 and 1.7. You can see the 2.2 percent difference, and you can see it is much more now, it is about 1.3 if you exclude the past history alone.

[Slide.]

In patients with depression as we heard this morning from Dr. Posner, the most serious concern is the possibility of suicide. The following slides are related to suicidality, which refers to any suicidal thinking or behavior. You have heard a lot of this already, so I will go through it a little faster.

[Slide.]

Working with FDA, as I said, the sponsor went back to the sites, requested source level

information on more than 4,000 patients who had neuropsychiatric events in the RIO and the STRATUS smoking program. We summarized this information in blinded anonymized narratives of the events, prepared from over 22 studies, completed clinical studies for evaluation by C-CASE.

These included the Phase II studies, as well as the methodology calling for all completed studies, that were double-blind, randomized, clinical studies with more than 20 patients per group.

The results of this retrospective data collection was developed with an analysis and methodology by Dr. Posner and her colleagues as she discussed this morning, and it is now a standardized approach recommended by FDA based on the previous experience with the antidepressants.

[Slide.]

I won't go through the scale, which is shown here, other than to say there were groupings as part of the subsequent analysis, which was definite suicidality, which was 1, 2, 3, or 4. So

that was grouped as a definitely suicidal behavior or activity. And then we had 5, 6, and 9, as Dr. Posner indicated as possible. 7 and 8 were considered neither definitely nor possibly suicidal.

Because of the rarity of these events, all Phase II and all Phase III studies were included, including alcoholism, schizophrenia, and, based on a classification across these studies, whether it was smoking, diabetes, or obesity.

And 88 cases under placebo or rimonabant were identified. Twenty were in the Phase II schizophrenia and alcoholism studies, certainly a more vulnerable population, and suicidality cases were identified retrospectively from source documentation. Sometimes there was no exact time of occurrence recorded.

So, all cases were attributed to the first randomized treatment, whatever the randomization was at that moment. So, if a patient had been re-randomized downward to a placebo or a lower dose, we attributed the event to the original

higher dose.

[Slide.]

The results are shown here. These are the numbers here for placebo, rimonabant, rimonabant, for categories 1 through 4, definitely suicidal, possibly suicidal, 21 cases, 11, 48.

This is the tabulation of the data as we collected it using the method I just spoke of. This way of considering all the studies differs from the FDA where meta-analytic techniques were used to adjust for the structure of individual studies.

Using that approach, FDA used 5 mg as a placebo for studies without a placebo arm. It was a stand-in for placebo. Using that approach, STRATUS-worldwide, which was a large study of 5,000 patients in smoking, the 5 mg arm was used in their analysis as a placebo when compared to the 20 mg arm in that study.

As Dr. Rosenzweig has shown, the 5 mg dose is active with statistically significant weight loss. For that reason it is an active dose, not a

placebo dose. If FDA is to consider for some safety analysis that 5 mg is a placebo or inactive, then, for clarity and consistency, it should consider all events on 5 mg as the equivalent of placebo events.

Clinical data and pharmacology show us that 5 mg is active and therefore, the sponsor has considered 5 mg as an active case and classified the events accordingly.

Although this can be explained further in the discussion period, we will consider the suicidal ideation data for the obesity and diabetes shown on the next slide.

[Slide.]

In the completed Phase II and Phase III studies for obesity, for the completed studies there was 1 case of suicide attempt. By the C-CASA analysis, there was no classification 1 of completed suicide.

What we wanted to look at here is the suicidal ideation 0.36, 0.62, approximately a 2-fold imbalance that we see for suicidal ideation

in the obesity and diabetes studies. Under the possible suicidal events, they are much less frequent and there does not appear to be a signal there.

The important point to make is that among the cases of suicidal ideation reported in the obesity studies, as shown here, 100 percent, all of these cases were associated with a concomitant depressive disorder or adjustment disorder as Dr. Posner has indicated today.

These did not occur as isolated events. Moreover, in addition to the concurrent illness, half of them, 50 percent, had a past history of depressive disorders. And that was true for placebo. It was true for rimonabant. And most had significant life stressors at the time.

These patients recovered with corrective treatment of the associated depressive events, 3 patients were hospitalized, 1 on placebo, 2 on rimonabant 20 mg for depression and major depressive disorder.

[Slide.]

Now, in addition to the previous analysis we just showed, we performed a supplemental meta-analysis which contrasts with the FDA's analysis. We used a meta-analysis technique using the so-called Peto method. The Peto method, looking at the overall database, yielded an odds ratio of 1.3, which crossed below 1, and went up to 2.3. This is in contrast to the overall assessment of 1.9 with the lower limit of 1.1 and up to 3.

Why the difference from the FDA analysis, why 1.9, why 1.3? The estimates of the two special population studies, schizophrenia and alcohol, in obese patients, here 1.8, 1.6, and the special populations 1.4 and 1.1, are largely consistent with this analysis between the two approaches.

Where the analysis differs is in this smoking cessation line. Again, this is due to the handling of 1 placebo-controlled study, the STRATUS worldwide study.

This was a study in patients motivated to quit smoking. Patients were randomized either to 5 mg or 20 mg for a period of 10 weeks and a quit

phase during the first two weeks. Those who were abstinent at the end of 10-week period were re-randomized in a similar fashion to RIO-North America. Any event that occurred afterwards was always attributed to the previous higher dose.

In order to adjust for that study structure where there was no placebo control, FDA used the 5 mg as the placebo control, which we do not feel is appropriate for several reasons.

First, as there were other rare events which occurred in the 5 mg group, either less frequently or not at all in the 20 mg group, this introduces inconsistent handling of the 5 mg group data as we move from one analysis to the other. When is the 5 mg a placebo and when is it an active dose?

The sponsor took an approach of using placebo-controlled studies only where a placebo is always a placebo.

Secondly, the incidence rate of suicidality for the 20 mg group in the uncontrolled STRATUS-worldwide study for the 20 mg was about

0.40 percent, very similar to other studies in the STRATUS program, so that treatment arm did not influence much the overall estimate for the 20 mg group whether including or excluding the 20 mg.

However, because of the unusual zero event rate in over 2,000 patients in the 5 mg group, deeming it as a placebo controlled as the FDA did, significantly dilutes the estimate of the placebo rate, substantially.

Therefore, the sponsor conducted the meta-analysis without this study using only placebo-controlled studies, using the Peto method, and yielding the overall estimate of 1.3 with a confidence interval which shows that the overall odds ratio for suicidality is not significantly different from 1.

[Slide.]

This table shows our current experience with rimonabant. In the completed clinical trials, it was the one case on the C-CASA table where it was felt not to be sufficient data for classification as a confirmed suicide, the

investigator reported it as a suicide, we are counting that as an investigator reported suicide.

This is the most current exposure in patient years and, in the completed trials, the event rate per 100,000 patient years is 14. And, for patients with a BMI over 30, in the U.S., the base rate is expected to be about 13. So, we have 14 in the completed clinical trials.

As of May 2007, two reported cases of suicide in the ongoing clinical trials and 1 postmarket case of suicide was reported. This one is via secondhand information and the patient allegedly receiving rimonabant. The data are very, very unclear at this point.

[Slide.]

I want to review briefly the narratives of these patients. This 36-year-old man was in the STRADIVARIUS study looking at atherosclerosis progression, had been exposed for 10 months, had a myocardial infarction one week prior to inclusion.

After 8 months, the patient who had no psychiatric history presented with a depressed

mood, irritability and fatigue. There were serious financial stressors at the time, depression worsened within 3 months with no corrective treatment and no psychiatrist or specialist was consulted.

CRESCENDO is the ongoing cardiovascular outcome trial, 77-year-old man. Again, this was received on May 22nd, very recently. Forty-five weeks into the exposure on rimonabant. He had a prior history, past history, of depression at age 40, and additional further episodes.

About 10 months after the study start, patient became depressed and he discontinued rimonabant on his own. He visited a psychiatrist who prescribed an SSRi but committed suicide one week later. The psychiatrist evaluation revealed depression, loss of energy and interest, marital difficulties, and the progressive worsening of neuropathy.

[Slide.]

In the third case, RIO-North America, 63-year-old man on 5 mg. Please remember that was

not the dose, 5 mg is the case here. Gunshot wound. Apparent suicide according to the investigator. Depressive symptoms and anxiety. At the last visit, however, there was no sign of despondency, hopelessness or outward signs that the patient was suicidal.

But from the nurse, it was found patient couldn't eat and had slept 30 hours, was found dead in front of his house. There was a past involvement in the Federal Witness Protection Program and he was pending a very important court decision according to the medical notes.

[Slide.]

For the ongoing studies, the Phase IIIb studies, C-CASA has evaluated the data from our ongoing studies as of May 29, 2007. Similar blinded review of clinical information was performed on 35 cases of potentially suicidal behavior or ideation.

There was an imbalance seen in the definitely suicidal classification of 1 through 4, of 0.30 versus 0.14 percent. Based on the

estimated--this is the estimated exposure because these trials are ongoing and double-blind.

As I said, the postmarketing case for which we have very little information, and the recent case in CRESCENDO are included here. But it is important to note that suicide attempt, the overt act with the intent to die, No. 2 here, there were two cases of suicide attempts in placebo with the intent to die, 2 suicides here in the rimonabant group, suicidal ideation, as with the obesity and diabetes study. The imbalance is about 2, 2.5 fold, 0.11, 0.28.

So, at the current time, based on the C-CASA analyses, the blinded analyses, there has been one suicide in the completed trials and in the ongoing trials it is 2 with 2 suicide attempts also noted on placebo.

We continue to closely monitor suicidality in the ongoing studies with a scripted psychiatric questionnaire including a search for suicidal ideation.

What I would like to inform the Advisory

Committee about today is that in the ongoing and future clinical trials of rimonabant, in order to better establish the extent and significance of suicidality, Sanofi-Aventis will be implementing the questionnaire discussed today by Dr. Posner and her colleagues.

We will be using that going forward. Basically, if you want to get the answer, you have to ask the question, and that is the lesson of the questionnaire. We will be using that.

[Slide.]

We have reviewed suicidality-related events and they are completed in the ongoing studies, as well as the postmarketing experience to date. It was an imbalance and definitely suicidal behavior and ideation in the obesity and diabetes studies, 0.65 versus 0.36 percent, driven largely by the differences in suicidal idea.

There was one suicide reported in the completed trials in a patient randomized to 5 mg at a rate consistent with the epidemiologic studies in that population, and the ongoing studies, a similar

picture emerges.

When there was an imbalance in suicidal ideation, but not behavior, with two completed suicides in rimonabant 20 mg, and two suicide attempts on placebo. It is important again to repeat suicidal ideation did not occur in isolation, on the contrary, it was always associated with other psychiatric disease, most often depressive disorders that were medically manageable.

Overall, the rates of suicidal ideation and behavior are low. You saw the epidemiologic figures this morning from Dr. Posner. Consequently, a causal relationship has not been established between suicidality and the use of rimonabant.

[Slide.]

Anxiety-related and panic disorders were also reported with anxiety 5.9 percent on rimonabant being more frequently reported than with placebo 2.1 percent, an incidence over placebo of about 3.8 percent.

Again, anxiety and panic disorders are not formal psychiatric diagnoses. These are based on verbatim statements of the investigators with classification and evaluation by the MedRA hierarchy.

[Slide.]

The main characteristics of the anxiety disorders and symptoms were comparable, past history of depressive disorders much less frequent. Treatment discontinuations on the order of 15 to 20 percent, compared to the depressive disorders, which was about 70 percent.

Corrective therapy, usually anxiolytics in about 40 to 50 percent, very comparable times to recovery whether or not there was corrective therapy, and really no significant medically important cases. The one hospitalization was in a patient with a panic disorder, tachycardia, and diaphoresis and chest pain. It was a 3-day hospitalization.

[Slide.]

We performed an extensive review of the

neurologic symptoms, such as sensory changes, motor impairment and cognitive difficulties according to the categories agreed with FDA. This review includes reports of complementary consultations and investigations as part of that retrospective assessment.

Shown here for the obesity studies and also similarly for the diabetes studies, sensory changes were the most frequent, the higher frequency in rimonabant 20 mg as compared to placebo. Again, dizziness of approximately a 3, 3.5 percent difference.

A paresthesia on the order of half a percent difference. Again, the latter occurred more frequently in the diabetic patients. Two cases of paresthesias were actually transient ischemic attacks.

In the motor impairment category, there was really no event that met the 1 percent criteria difference, but tremor was close, so we put that up here. It is about 0.9 versus less than 0.1 percent.

In the rimonabant group, there was no serious case of tremor. It was not Parkinson's disease. It was not felt to be medically important or require hospitalization, and patients maintained rimonabant or placebo in about 80 percent of cases, or rimonabant for 80 percent of cases.

Cognitive difficulties are shown here, 4.1 versus 2.1, a 2 percent difference. It was most often reported as a short-term memory loss, memory impairment, or amnesia. No case was felt by the investigator to be medically important or require hospitalization.

Fifteen percent of patients discontinued rimonabant, most did not, and 12 percent discontinued with the placebo, so the discontinuation rates between rimonabant and placebo for memory loss were very similar.

[Slide.]

What about the neurologic adverse events that led to actual discontinuation of the therapy?

Discontinuations for neurologic events was infrequent, but there was an imbalance. Overall,

2.2 percent of patients discontinued rimonabant due to neurologic AEs compared to 0.6 percent on placebo group with the most common reason being dizziness. But it should be noted that dizziness was often reported in concurrence with GI symptoms, such as nausea.

[Slide.]

This table addresses the issue raised by FDA on the cases of multiple sclerosis. This table shows the incidence of new cases of multiple sclerosis occurring during the clinical trials. It is a little busy, but there was one placebo case, 2 at 5 mg, and none at 20 mg with a patient year exposure estimated there for the placebo, the event rate was 29. It was a very wide range, of course, given one event.

When you look at 5 mg and 20 mg, we consider those active doses. We had two cases at 5 mg, none at the proposed therapeutic dose. The event rate, again given a scant number of cases, is 29 with a very wide interval.

So, when you consider the one and the two,

there is no increase there. The FDA has questioned the multiple sclerosis diagnosis in the placebo case.

The sponsor consulted Dr. Dan Michael, a neurologist, to review this case. He has confirmed the diagnosis. Dr. Michael is here today and available to discuss his evaluation.

There was one case here. At the end of April postmarketing, it was not confirmed. There have been no cases of reconfirmed multiple sclerosis in postmarketing. But there was one case of bilateral papillitis, optic neuritis one month after starting rimonabant reported as a potential multiple sclerosis. But the MRI results are not available to the sponsor, and it was rated as suspected MS, multiple sclerosis by the reporter.

[Slide.]

In addition, there has been a case of a patient with existing multiple sclerosis who experienced vomiting and a gait disturbance 5 days after starting treatment. It is not a new case, it's a patient with multiple sclerosis who had a

gait disorder with vomiting a few days after starting rimonabant.

An MRI was obtained. There was no change from the previous MRI four years before, and the gait disturbance resolved within 3 days.

[Slide.]

In addition, the FDA has listed two potential cases of multiple sclerosis and I would like to briefly discuss them here.

In addition to the three confirmed cases that were discussed in the prior slide, there was one case of a patient evaluated for MS but who did not meet the diagnostic criteria. A 49-year-old woman evaluated for a balance disorder. The MRI scan was not consistent with MS. Updated information. We got information on this patient. It is 3 1/2 years later now. The patient has had no new events and has had normal annual examinations. This is not a case of MS.

In the second case, the patient had pre-existing MS diagnosed 5 years prior to entering the study. During the treatment period, the

relapses have been similar to those before the study and also after the study. This not a new case of MS.

[Slide.]

I will now move to the evaluation of seizures. In Phase II and Phase III, patients with treated epilepsy with anti-epileptic therapy were excluded. However, patients with a medical history of epilepsy or seizures, not currently treated, were allowed in.

Forty-eight patients of such a history were randomized in the trials. Because the cases of seizures were again rare, we analyzed all the databases for Phase I, Phase II, Phase III including vulnerable populations for seizures, such as schizophrenia and alcoholic patients in Phase II.

We took this approach in order to be comprehensive and not to miss any trials or any patients. For completed studies, we searched for all potential cases, not only those reported by the investigators as seizures and coded accordingly by

MedRA, but also cases evocative of seizures using a string search, which is very hard to read probably, convulse, petit mal, grand mal epilepsy tonic/clonic, and so forth.

So, this was a big search for seizures, ostensible and perhaps occult. All the identified cases were reviewed blindly by two neurologic experts who had access to all of the available source information and, in some questions, where they raised questions, we went back to the sites to get the information if it was available.

[Slide.]

FDA and the sponsor analyzed the seizures differently, and this is based on Table 31. FDA included only studies with a report of a seizure, of which there were 8. Cases that were excluded were those in the placebo run-in on the lead-in, and three months after the study end, the lead-out, if you will.

They included cases in non-placebo-controlled phases or studies, a similar theme to what I have said before with 2 cases and

20 mg, and the overall comparison was 20 mg versus placebo. The sponsor analysis is on the right, included all the completed studies without events.

It included all the reported seizures whatever the phase. I compared rimonabant all doses versus placebo. Two analyses were performed; all seizures, possible, likely or unlikely, and those that were felt likely or possible seizures as assessed by the external experts.

[Slide.]

This is the sponsor analysis. Nineteen cases were reviewed by the experts. Fourteen were assessed as likely or possible and the five were felt to be unlikely.

The number of events per patient year--this is an incidence rate now. These are the patient years right here, 3200 to 3600, all 19 cases, and you can see that the incidence rate is 0.23 for placebo, 0.2 for rimonabant 20, and 0.06, all doses culminating in 0.16. And when you take the confidence interval of all doses versus placebo, the relative risk is 0.68 straddling 1.

That is all cases.

Now, when you take the cases that were reviewed and felt likely or possible by the experts, we have 0.17. Two cases didn't make it in placebo. And we had 3 cases didn't make it in placebo in 20, it is 0.17, and the answer is the same. The risk ratio straddles 1. There was no increased risk in this very large database of the completed clinical studies.

[Slide.]

I would like to compare the FDA analysis on top with part of the table. I simplified the table but it is the same numbers as you saw before, excluding the two placebo run-in cases and the one late event and including 2 mg cases where we have no placebo, you see. We kept the active dose, no placebo. These are the numbers here, and then you have the 20 mg versus placebo at 1.69. But even with that analysis, you see the relative risk straddles 1.

[Slide.]

This is just a summary, just so you don't

have to go back, is the sponsor analysis, all studies, all cases, unlikely, possible likely, includes all reported cases. We showed them here. This is the number you just saw. If we do the 20 mg versus placebo comparison instead of all doses, you get 1.08, again straddles 1.

So, no matter how you do it, you get a relative risk that is on both sides of 1.

[Slide.]

Ongoing studies. There have been 8 cases of possible seizures reported. All were blindly adjudicated by the same experts, the same system, and then unblinded. This is what it turned out.

Eight cases. There were four on 20 mg, two on placebo felt to be possible or likely, two were felt to be unlikely. That is the split. If you count them all, all the 20s is seizures, then, you get 0.15 percent. If you use the adjudication, the possible or likely, you get 0.1 percent, numbers that are very similar, similar to that observed in the completed studies.

This information is very, very important,

because we were alerted by toxicological preclinical data, which suggested early that we might have a problem.

During the Phase I studies, a little later, and a repeated dose study for 21 days, three weeks, up to 60 mg, three times the therapeutic dose, there were no seizures.

You supplement that clinical experience with the many analyses that have been done, the large clinical database, which we have in obese patients, is very reassuring. There is no increased risk of seizures that we have shown.

[Slide.]

Now, I would like to conclude with our assessment of overall safety and make some points with another agent, with a favorable benefit-risk profile.

The rimonabant development program has been, continues to be an extensive program. in addition to the more than 6900 patient years of exposure, the trials have shown a consistent safety profile with no new signals in the postmarketing

worldwide experience with more than 100,000 patients treated since the approval in Europe one year ago.

Rimonabant is well tolerated in obese and diabetic patients. We will focus, not on the GI, we will focus on the adverse events of special interest in patients, something that is of interest to them, of course, and their treating physicians.

I would like to frame this in a way to address the questions submitted by FDA on the sufficiency of the demonstrated safety profile.

First, depression. This was reported more often with rimonabant with a consistent but modest imbalance compared to placebo. Compared with a placebo, the need for corrective therapy, the time to recovery are very similar.

Second. Although there was an imbalance in suicidal ideation, this was always associated with a treatable depression or adjustment disorder, very consistent with a much larger experience that Dr. Posner and her colleagues had with this issue over all.

The report suicides, very rare in the completed clinical trials. Comparable to the expected background rates, because of the many reasons listed on the way we obtained this information, no causal link has been shown with the use of rimonabant.

Moreover, I will repeat now we will be using the questionnaire to prospectively assess suicidality in the ongoing and future clinical trials, the one proposed by Dr. Posner today.

The most frequent neurologic events were dizziness, paresthesias, hyposeizures, tremor and memory loss with no imbalance in the really important ones, which would be serious cases, or reasons for discontinuation.

Finally, with multiple analyses, there was no signal, no signal for an increased risk of seizures.

Treated patients with epilepsy were excluded from the Phase III studies. They are now allowed in these on-scoring studies because these studies are being monitored by an independent

external DMC, and we do have experience now on the risk of seizure. There is no risk of seizure that we have shown.

For the general population, however, we do not recommend patients who are currently being treated for epilepsy to be included.

[Slide.]

I would like to put into perspective the reported safety profile of rimonabant by briefly considering another agent. You heard briefly today about sibutramine. It's an approved agent for weight loss. This is relevant text from the package insert. It is very appropriate given our discussion today. This is the fragment I have taken out.

Cases of depression, suicidal ideation and suicide have been reported rarely in patients treated with sibutramine. However, the relationship has not been established between the occurrence of depression and/or suicidal ideation and the use of sibutramine.

If depression occurs during treatment

with sibutramine, further evaluation may be necessary.

Now, this fragment of the label may appear of concern, of course, especially without knowledge of the clinical utility. My point is that the safety of this drug or any drug can only be evaluated in light of the demonstrated benefits and the medical need that it attacks.

So, as I finish my presentation, I hope the Advisory Committee will agree with me that the sponsor, through a series of integrated and consistent trials in obesity, overweight and diabetes patients has identified the safety profile of rimonabant and the issues that will need monitoring and appropriate labeling.

To this point, that the safety profile can only be interpreted in light of the demonstrated benefits discussed by Dr. Rosenzweig for reducing weight, reducing cardiovascular risk in patients who are overweight and obese patients, as well as the highest risk patients, the highest risk patients with type 2 diabetes having diabetes is

the same as having had a heart attack in terms of future cardiovascular risk and that continues to be a growing and still challenging medical need.

[Slide.]

Finally, Mr. Chairman, members of the Committee, after one year of use in Europe and other countries worldwide, the postmarketing experience of rimonabant confirms the overall safety profile that has been defined in the submitted dossier.

Based on the data presented today, the sponsor has defined a safety profile that identifies the right patient, and more importantly, the wrong patient for rimonabant.

As Dr. Gural said moments ago, patients with a history of depression of suicidality, current depression, are receiving antidepressant therapy are not the right patients, and neither are patients at this time with treated epilepsy.

We have not had the time to discuss all the safety data and we will be available to the committee if there are further questions.

Thank you, Mr. Chairman.

DR. GURAL: Thank you, Dr. Chew.

I would now like to review with the Committee the risk management plan that Sanofi-Aventis is proposing.

[Slide.]

The risk map will take three main elements. First, it will focus on the identified risk. As we have heard this morning, there are three risks associated with the use of rimonabant - that of increased risk in patients with depression, potential risk in patients receiving antiepileptic therapy and, lastly, the short-term use.

[Slide.]

We will also discuss today some intervention tools for the reduction of these risks and the minimization, and, lastly, we will discuss how we will assess the effectiveness of those tools.

[Slide.]

First, as we identified this morning and throughout the course of the discussion, three

primary risks have been associated or identified with rimonabant as indicated in this slide.

[Slide.]

We are recommending a number of approaches or interventions directed not only at the health care provider, but also at the patient and the family.

These are not only in terms of the routine measures, which will include for the health care professionals, continuing medical education, product focus education and an awareness campaign.

There will also be enhanced measures. A tool which we are going to call the physician's check list, which I will describe to you in just a few moments, a medication guide according to the CFR and agreement with the FDA.

An early patient access program, which we will describe and, lastly, something that we are calling now a physician-patient treatment plan, again bringing the patient and the physician together on the treatment of the disease.

For the patient and the family, there will

also be the routine measures; that is, we will provide education. Education will be the cornerstone for this RMP, not only for the disease, but an awareness of how to treat and how to diagnose some of the events that are seen with this. Obviously, the medication guide will be a key part to this, to be given every time a prescription is given to the patient.

The early access program will be the same as the one that is for the health care providers and, lastly, the patient/physician treatment plan will also be part of that.

[Slide.]

I will give you details on all of these in just a few moments.

[Slide.]

Let's start first, though, with what is the patient's access program? It will use -- what assessments rather will be used during this time? It will start with the patient access program. So, as soon as the product is launched, we will start this.

We will have enhanced pharmacovigilance program with detailed and very specific forms for 1A depression or a seizure is reported spontaneously through postmarketing surveillance, so that we can capture as much data as we can.

Being mindful that postmarketing is exactly what it says, it is voluntary. The physicians will be requested to fill out the form, but we cannot compel them to complete it

[Slide.]

Also, for those patients and physicians who are actively participating, we will do a survey of them to see how they are satisfied with the tools that we have.

Once we have a full commercial launch, we will have a prescription survey. Again, something that is currently being used in Europe, which we will fly here in the United States. I will show you some of the assessment tools that we have used so far with this.

We will also be looking from an epidemiology point of view, at both the health care

insurance claims data bases, both automatic and manual and, lastly, we have just reached an agreement with the American College of Cardiology, to institute a disease registry in collaboration with them.

Let me just show you a little bit about our experience in Europe to date. Specifically, with the UK prescription survey. As I told you before, rimonabant was approved in June of 06 in the European Union and launched in June of 06 in the UK.

Shortly after that, we did a prescription survey, one in which we consulted with physicians who are prescribing rimonabant, asked them to give us information on their last three patients to whom they prescribed rimonabant and provide us some specific details on that.

As we could see, in September of 06, approximately 1.4 percent of the patients who had been prescribed rimonabant had severe depression or a history of severe depression.

We reacted very swiftly to this,

reinformed our health care representatives or sales persons, as they are called, to reeducate the physicians that the inappropriate patient for the use of rimonabant is one with a history of severe depression.

The effectiveness of this was noted and the next time we did the evaluation, which is in November of 06, and you could see there was a reduction from 1.4 percent down to 0.4 percent of the patients having severe depression at baseline.

In the most recently completed analysis, this now has dropped to even less than 0.1 percent, demonstrating that we do have an effective way, through our risk management plan, to observe what the risks are and to try to minimize them through an educational process.

Clearly, what we see, though, is a risk minimization plan is not a static plan. It is one that is a dynamic plan needing and requiring constant revision. So, the implementation tools that we are putting together now are for the initial phase of the RMP.

We will use them. We will measure and assess their utility. We will review that information with our key stakeholders, which are physicians, patients, various societies, health care's authorities including the United States and others.

We will have a report which will be reviewed by those stakeholders, reviewed by the FDA, possible modifications, and re-implementation of those new tools, and then the process will start again.

[Slide.]

So, what are the key messages--and I said education was the key to what we were dealing with--what are the key messages that we want to get across?

First, we want to talk about the disease. We want to talk as obesity is a chronic disease requiring long-term therapy, comprehensive treatment, always including diet and exercise, lifestyle changes, that the treatment of obesity itself is associated both with positive and

negative mood alterations; that obesity is associated with several comorbidities including not only hypertension, dyslipidemia and diabetes, but also the potential for depressive disorders and, lastly, depressive disorders should be recognized and their consequences readily diagnosed and treated appropriately.

[Slide.]

What are the key messages that we are going to provide on rimonabant? Again, at the time of the prescription, patients are to be screened for who is appropriate and who is not, and who is not are those patients with a past history of depressive disorders and/or suicidality, those patients who have a diagnosis of depressive disorders, whether treated or not, and those on current antidepressant or anti-epileptic therapy.

Obviously, other elements of the prescribing information, once agreed upon with the FDA, will be included as part of those tools. Clearly, one of the keys, as mentioned by Dr. Rosenzweig, is the disappointment of patients in

what they perceive to be the overall benefit, so prior to the initiation of therapy, there will be a treatment plan between the patient and the physician to set realistic expectations for what the weight loss could be.

We will be stressing the need to have a reassessment on an ongoing basis of those patients, at 1, 3, 6, 9, and 12 months following the first year of therapy. Obviously, as we are going on, these dates and times will be modified.

[Slide.]

As we said, depression was noted during the rimonabant treatment, so this is one of the things that we will clearly be identifying to the patient and their physicians, as well as the family members, to look for and any suspected treatment of depressive disorders should institute an appropriate therapeutic action, which would include the discontinuation of rimonabant.

[Slide.]

Now, what does this physician checklist look like? We have not yet fully agreed on what

this will look like. We will institute a dialogue with physicians and survey to gather the right information. But currently, conceptually, what we have is a form.

There is a two-sided form, and I will show you the other side in just a minute, where the physicians would be queried and making sure that they ask their patients the right question about the treatment for depression, previous history, and the treatment for the epilepsy.

Being mindful that many physicians often treat the patient, not only the primary health care provider. But it could also be the cardiologist. It could be a neurologist, et cetera. So all the information then would be gathered in one spot.

[Slide.]

What is it exactly that we are going to ask the physician to do? Again, on the back side, we are going to make it very simple, a very simplified form to be used, just to ask a very simple two-point question that has been validated, that during the past month, have you or have you

been bothered by feeling down, depressed or hopeless.

Obviously, this questionnaire has been validated and the reference is here. And have you been bothered a little, no interest or pleasure in doing things?

If either one of those are answered yes, then, further evaluation of the patient is recommended prior to the initiation of therapy with rimonabant.

As I said, there are two parts to this. One is the physician, the other is the patient. So, to that end, we are recommending a medication guide. In this medication guide, which will be prepared in accordance with the CFR, obviously agreed upon with the FDA, we will also be providing information to the patient and to their family, again stressing the need to be mindful of depression.

This wording will look very familiar to those of you who have participated in the previous evaluations of the antidepressants. It is

patterned very closely to that. So, we will use tools that are already in place to help us monitor for depression.

[Slide.]

Let's come back to the disease awareness program. Sanofi-Aventis is firmly committed that we will not institute any direct to consumer advertising for rimonabant for at least one year following the launch. We want to make sure that patients and physicians are well educated on the use of the product.

We will be providing, though, however, a web site which will educate patients about disease awareness--that is, the disease awareness of obesity--stressing again that diet and exercise and lifestyle changes are the most effective way for dealing with this condition.

[Slide.]

As I mentioned before, there is a unique opportunity here to involve both the patient and the physician in their treatment plan. It will consist of four elements. Obviously the physician,

health care professionals, patients and their families, and pharmacists. Material would be produced in a language that is appropriate for its intended audience, so the physician, the patient, whether it's in English or in Spanish, these will all be worked out.

There will be a suggested dialogue that the patient and the physician have at each one of their visits. The tools, which I will briefly identify now, are both the physician tool kit and a patient family tool kit, something tangible for them to have in their hands, as well as we will be looking at the feedback to monitor the effectiveness of this through monthly physician surveys and monthly patient surveys.

[Slide.]

So, what is this? What is this tool kit?

Well, the tool kit is a disease awareness, the U.S. package insert, the physician checklist, which I just tried to identify with you, an identification of what are those most frequently prescribed antidepressants and anti-epileptics, not

that physicians don't know what they are. But sometimes the list may be so long, we want to remind them of them.

We also wanted to give them and provide them tools for assessment of depression, as well as suicidality, and a reminder of what those other adverse events are, that are part of the approved package insert.

[Slide.]

It will be again for disease awareness and the medication guide, which is dispensed each time a prescription is given. They may or may not know all of the antidepressants or antiepileptics, so commonly used ones, including the generic, as well as the trade name will be provided.

There will be a self-assessment tool developed for the detection of depression and an agreement on the return visit schedule. And they will keep a treatment diary, something that they will have to monitor their progress as they go along.

[Slide.]

This is just a schematic diagram trying to indicate here, at the time prior to prescription were the two elements, and then at one month, 3, 6, and 9 and 12, the progress that the patients will make.

[Slide.]

Just as an example. What is a potential physician/patient dialog to look like? First, to talk about the benefit of rimonabant, have they had any benefit to measure the weight, to measure the height, weight, to adjust the diet and exercise program, prescription of any code therapies if necessary to treat other co-morbidities and, obviously, to be mindful of the adverse events especially those with depression.

On the other side, the dialogue should take place between the patient and again the caregiver or the family, looking again for the benefit, so charting their progress towards an agreed-upon goal realistically, as well as changes in their mood, dizziness, sleeping, feeling anxious, et cetera.

I talked about also a patient access program. What is that? This is a tool again to evaluate the appropriateness of the RMP. It will be a controlled launch; that is, we will introduce the product gradually into the marketplace.

Physicians again will be provided with educational material and the Lessons Learned from this will enable us to understand better, how to launch the product fully. What is it? This program will include 20,000 appropriately-trained and educated physicians. Each of these 20,000 physicians will enroll 10 appropriate patients to be treated with rimonabant, appropriate and not appropriate as we have identified.

[Slide.]

There is going to be an assessment based on monthly message recalls to make sure that the patient and t he physician are using the product properly, the benefit-risk profile is being maintained and, again, just like we did in the UK, to have some follow-up, again tracking in the patient diary.

[Slide.]

As we did in the UK, we will also institute a series of prescription surveys. The one that I am going to display to you here now is one involving approximately 2,400 patients. It is a number that we have chosen based on the fact that we want to have 800 patients per sample. We want to take the three most recently prescribed patients from the physicians. And we want to collect this data in four month intervals, so that we have a good estimation of what is happening in these patients during the first year of launch.

Again, to make the modifications back to the RMP as we did for the UK.

[Slide.]

So, in summary, we have identified the three key elements of the RMP, those being the identified risks, those tools that we will use for the intervention, and an assessment.

Also, here should be included the re-evaluation of the RMP in a very iterative way, so that it will be a living document.

[Slide.]

Again, I come back to what I put on the very first introductory slides. Who is the appropriate patient to be treated with rimonabant? Again, the emphasis is it is not everyone, so the physicians and the patients should take together the decision as to who is right for the treatment, not only in terms of the potential benefit, but also those in which we have identified some potential risks.

[Slide.]

Clearly, the sponsor is committed to working very closely with the FDA and other groups, both patients and physicians, to implement as quickly as possible following the approval of the product and RMP. That will address the growing and serious problem of obesity in the United States.

Thank you very much.

DR. GURAL: It would now be my pleasure to introduce Dr. Louis Aronne, who is Clinical Professor of Medicine at the Well Cornell Medical College and is Director of the Comprehensive Weight

Control Program at the New York Presbyterian Hospital.

Over the past 20 years, Dr. Aronne has been active in the research and treatment of obesity. Dr. Aronne was the editor of the NIH Practical Guide to the Treatment of Obesity, which we heard earlier this morning.

Dr. Aronne is also the past president of the American Obesity Society.

Dr. Aronne.

Benefit/Risk of Rimonabant

DR. ARONNE: Mr. Chairman and members of the Committee, I would like to conclude this morning's presentation with an evaluation of the benefit and risk of rimonabant. I would like to make four main points.

First, that obesity is a chronic disease which requires many different treatments, treatments we don't currently have. The pathophysiology of obesity involves overactivity of the endocannabinoid system. CB1 blockade thus addresses an underlying mechanism of weight gain

and fat accumulation, which translates into clinical benefits for the patient.

Second, that the patients I see, the high risk, obese patients with sleep apnea, diabetes, cardiovascular disease also seen by cardiologists, endocrinologists in clinical practice could benefit from rimonabant.

Third, that the risks associated with its use are manageable through health care provider and patient awareness of these adverse events, together with a clearly defined strategy to identify susceptible patients, and finally, an expeditious management plan for patients with adverse events.

Let me begin with the pressing medical need addressed by rimonabant.

[Slide.]

Obesity is the leading cause of both diabetes and heart disease. Current treatments for diabetes and heart disease don't address the underlying obesity and its many other complications.

Here we see the positive relationship

between weight and the risk of developing diabetes, hypertension, coronary heart disease and gallbladder disease.

Even within the normal range of weight, the relationship is positive. The relationship between obesity and diabetes is so steep it goes off this chart. See here, even within the normal range, it goes off this chart.

Accordingly, current guidelines for managing patients with diabetes and other obesity-related diseases specify that assessments of risk factors should include obesity and that risk factor reduction should include weight loss in obese or overweight patients.

[Slide.]

Here, we see the continuum of treatment options. First, we can do nothing to manage weight and, in my opinion, this is not an acceptable option. The real need is to treatment patients with multiple complications of obesity with a treatment for obesity rather than the 4 to 6 or more drugs often taken by patients with diabetes,

hypertension and hyperlipidemia. Several million Americans fit into this category.

When weight loss is achieved in this patient, the benefit is clear, because obesity treatment not only improves these diseases, but it also improves their joint problems, inflammatory markers, their sleep apnea and quality of life in a way that those other treatments just can't.

It can reduce the number of medications used and therefore, the side effects associated with the use of multiple drugs.

Now, in the non-pharmacologic domain, we have non-prescription herbal preparations and dietary supplements which make up the majority of the market. People use them because they have no options.

In this case, there is little evidence of benefit and safety. Diet, exercise and behavior is the treatment of choice, but it doesn't work as well as we would like.

Currently, two medications are available for use. They are underutilized, orlistat, because

of the possibility of gastrointestinal side effects, sibutramine, the possibility of increased blood pressure.

Compare that to the 11 classes plus combinations available for the treatment of hypertension.

At the extreme end of the spectrum, we have surgery. In evaluating the benefit and risk of rimonabant, one comparison could be with lap band surgery, which is now being evaluated as a treatment for those with a BMI as low as 30 with complications.

I think this comparison is an important one for it underscores how difficult it is to get our patients to lose and maintain weight loss. While lap band surgery produces about 17 percent weight loss in patients with a BMI less than 35, it is associated with a surgical risk of 8 percent and a mortality of 0.4 percent.

It is of interest that in the lap band registration trials, in which an operation is performed and a plastic device inserted, that must

be manipulated, only 77 percent of patients completed one year and 64 percent completed two years of the trial.

Twenty-three percent of patients required re-operation for complications including gastric dilation, band slippage, and erosion. At 36 months, 23 percent were lost to follow-up or had no information available, and 15 percent had the device explanted. Mortality was 0.5 percent.

The maximum weight loss was 18 percent over the trial. Based on the same type of analysis, weight loss with rimonabant would be 11 percent. I believe this comparison puts in perspective the weight loss, the possible complications associated with weight loss, and the difficulty we face in performing these types of trials.

[Slide.]

It is important to recognize that the weight regulating systems are redundant, biased towards weight gain and prevent weight loss. The endocannabinoid system is now known to be a

modulator of some of these pathways and it plays a role in the overall regulation of energy balance.

As you have heard, every animal model and several human studies have demonstrated an association between overactivation of the ECS and obesity. Given the relationship between stimulation of CB1 receptors and the pathophysiology of obesity, CB1 blockade is a logical and rational target for weight management.

Thus, in much the same way that an angiotensin receptor blocker reduces blood pressure, we can now block the receptor which plays a role in the pathophysiology of obesity. The result is an improvement in multiple comorbidities.

The use of CB1 blockers makes physiological sense.

[Slide.]

What are the actual benefits? In my opinion, the improvement in glucose, HbA1C, triglycerides, HDL cholesterol, blood pressure and inflammatory markers represents the best current estimate of efficacy, for we know that there are

surrogate markers of improvements in health outcomes, but there are other health benefits, as well.

So, while weight loss is indeed a critical outcome, the impact of the weight loss on comorbidities including an improvement in quality of life tells the real story of benefit, and they all go in the same direction towards improvement.

[Slide.]

Finally, and most importantly, is the issue of safety, a major concern of patients, clinicians and regulators. While we would like to have medications without side effects, that is just not possible.

The question then is how to minimize risk when you have a drug with the potential health benefits of rimonabant. The safety profiles of rimonabant has been characterized in clinical studies of over 7,000 patients and postmarketing data on more than 100,000 patients.

Treatment with rimonabant has been associated with a higher incidence of depression

and anxiety, especially in patients who have a past history of these disorders. Depression and anxiety are more common in the overweight and obese and these patients should be excluded from treatment with rimonabant.

I would liken this clinical decision to that of the decision to forego a bisphosphanate in an osteoporotic patient with an esophageal stricture, or a beta blocker in an asthmatic with coronary artery disease.

This is what we do in practice every single day. The health care provider makes a decision about treatment after reviewing the indications and contraindications of the treatments available, weighing the risks and benefits of the treatment.

[Slide.]

Here, you see a comparison of the same side effects compared within the class of obesity drugs. Nausea, depression and anxiety have been reported to some extent with other medications within the class and, indeed, medications in other

classes including those used to treat migraine headaches and skin disorders.

In my experience as an investigator, i have seen depression emerge in patients treated with drugs in this category. The onset of the depression was a few days to weeks after starting treatment. The patients we saw had a past psychiatric history. They felt fine within a few days of discontinuing the medication and, thus, in my experience, the adverse events have been manageable.

[Slide.]

In order to screen susceptible individuals and detect those who develop symptoms of depression and anxiety as soon as possible, a clearly defined strategy of education, screening and monitoring should be implemented.

Here, we see questions referred to earlier. We use questions like this, right now, as part of our initial evaluation because depression is a contraindication to treatment. So, this is an appropriate part of the initial evaluation of the

patient who is being treated for their obesity.

Appropriate labeling combined with a comprehensive educational and monitoring program where the patient and health care providers is an appropriate measure for minimizing risk.

[Slide.]

So, in conclusion, I see rimonabant as an addition to the very limited armamentarium of tools for managing overweight and obese patients with multiple risk factors.

It addresses the pathophysiology of obesity and its metabolic consequences. It addresses body weight and it improves multiple risk factors. It improves the quality of life. It may reduce the risk of developing type 2 diabetes. The safety profile has been defined, but we know that, as with any drug, the evaluation of safety is an ongoing process.

There is a plan for minimizing risk, which includes education of patients, health care providers, screening for depression and suicidality, strategies for monitoring and

management.

[Slide.]

Finally, let's apply insights gained from the Diabetes Prevention Program to the weight loss seen with rimonabant.

Based on data from the DPP, the weight loss achieved with one year of treatment with rimonabant, diet and exercise would reduce the risk of developing type 2 diabetes by 80 to 90 percent in those at risk.

Looking at this another way, it would more than double the number of people who did not develop diabetes compared to those on diet and exercise alone.

Rimonabant could thereby prevent or delay the associated microvascular and macrovascular complications we see with type 2 diabetes. Rimonabant has the positive attributes of a treatment option to address the medical needs of many of the patients that I see every day.

Given an effective method for screening out patients susceptible to side effects and a

clinically viable strategy for managing adverse events when they occur, I believe that rimonabant can offer a positive balance between the likely benefits and potential risks for a group of patients who need better options.

Thank you.

DR. GURAL: Mr. Chairman, that concludes our presentation.

DR. ROSEN: Thank you, Dr. Gural, and if you could stay up there, so that you or somebody of your sponsor will be able to address questions from the committee.

I would like to start with Dr. Gilman.

Clarifying Questions from the Committee

DR. GILMAN: I have two questions actually.

The first one relates to the slide showing quality of life in the RIO pooled ITT analysis. In our handout material, it is on page 42. It shows beneficial effects with respect to quality of life. This is a pooled ITT, so they intend to treat the entire population. And yet that same set of

studies showed a 34 to 47 percent dropout rate plus a number of adverse events.

So, how do those two phenomenon jibe? These seem like very positive results and yet we have a huge dropout rate.

DR. GURAL: Dr. Rosenzweig, could you address that?

DR. ROSENZWEIG: So, your question is addressing the quality of life data and whether we take into account the dropout rates during this assessment? Is that the correct understanding?

DR. GILMAN: No, my question relates to the discrepancy that I see between a very positive set of data here in the bar graphs on my page 42, and yet there is a very high dropout rate and a very high prevalence in the study of people with untoward effects including depression, et cetera, et cetera. How do these two phenomena jibe?

DR. ROSENZWEIG: My understanding is that the patient expectations about their body weight loss is tremendously more than what can be delivered by a drug. They expert to lose a lot of

weight and then when they don't lose that body weight loss that they expect, they drop out from the trial.

So, we cannot capture that patient, and they drop out, and the one having an improvement. These data of the patients which are dropping out are still captured using the LOCF, so probably this is minimizing the effect, the beneficial effect of the quality of life.

DR. GILMAN: I don't think I made my question clear.

DR. ROSENZWEIG: Maybe I can ask Dr. Durrleman to come to the microphone and give his perspective on this.

DR. DURRLEMAN: Dr. Durrleman from Sanofi-Aventis.

The LOCF analysis that is being done to analyze the quality of life considers the last observation carried forward. Therefore, those few patients who discontinue for those adverse events are considered in this analysis with the last values they have under treatments. Obviously, what

happens to them following treatment discontinuation is not included in the quality of life assessment.

So, in a way, the data indicate that in the large majority of patients who do not experience psychiatric adverse events or other adverse events, possible negative quality of life in a few patients with adverse events.

So, here you have the full set of data.

DR. ROSEN: So, I guess the question is you don't track those patients after they fall out of a study to ask them their quality of life indices once they have dropped out of the study, correct:

DR. DURRLEMAN: This is correct, after the patients discontinue treatment, so the last observation is carried forward.

DR. GILMAN: Then, it is not true that this is the ITT data, this is incorrect, is that right?

DR. DURRLEMAN: What happens and it is a common problem in quality of life analysis is that when you have attrition, it is very hard to

indicate because the patients have discontinued.

DR. GILMAN: One minor question. What is it like to patients who are on drug and eat? Do they lose the appreciation for food? Do they just lose hunger? Can they enjoy their food? Can they taste their food?

DR. ROSENZWEIG: Yes, we have measured that during our clinical trial. The hunger is decreasing, but the enjoyment with food is maintained.

DR. GILMAN: Something I haven't really talked about is the dropout rate, and there is a 40 to 50 percent dropout rate in the four RIO trials.

Sort of a couple of related questions. Is the weight proportional to the original body weights, getting back to the expectations of people wanting to lose 150 pounds, if you started at 400 pounds, and you lose on the average of 5 kilos, that is not going to meet your expectations.

Number two, what is the pattern of the dropout rate, why did they drop out compared to the placebo and when? That hasn't been discussed at

all by you guys.

DR. GURAL: Some very interesting questions and comments. Dr. Rosenzweig, if you could address this and relative to our experience with reported literature for other products.

DR. ROSENZWEIG: So, your question is about dropout rates and when and why? Is weight proportional to the original weight loss:

Let me first cover the continuation and discontinuation rates at one year, if I can have the slide on. These are the completion rates across the four studies and, as you can see here, rimonabant 20 mg and placebo had about the same completion rate, in fact, a little bit more on rimonabant.

These were the dropout reasons for subject requests here. Adverse events, lack of efficacy for compliance and loss to follow-up.

When did the dropout rates occur was your question also. The dropout rates, and I don't have slides for this, but the dropout rates were more frequent during the initial part of the treatment.

During the first three months, the dropout rates was more permanent and especially due to subject request, both arms, yes.

Your third question is about the weight loss in terms of percent of body weight; is that correct? I think I have in the backup data, data about body weight loss in expressing percent from the initial body weight.

Would that answer your question?

DR. GILMAN: Yes.

DR. ROSENZWEIG: The body weight loss in terms of percent was about the same than the one expressed in kilogram, because the patients were, on average, 100 kg on average. So, a patient lost 4.7 percent of their initial body weight loss on rimonabant 20 mg as compared to placebo. The patients who were the heavier lost a little bit more than the patients of the lower BMI. There was 1 percent more body weight loss compared to the initial body weight in the patients with BMI over 40 as compared to the one with BMI less than 40. But the response in terms of body weight loss of 4

percent, you know--maybe I can go back also to the patients who met the criteria of 5 percent body weight loss, which is another way to look at this data, which I didn't present. It was in the briefing package.

Can I have the slide on, please.

These are the patients meeting the 5 percent decrease in their body weight loss as compared to the initial body weight that was in your point.

These are the figures of rimonabant 20 mg, 5 mg, and placebo in four RIO trials. As you can see here, on each of the trials, the proportion of patients matching this decreasing 5 percent of their initial body weight loss on rimonabant 20 mg was clearly very highly significantly different from placebo.

DR. ROSEN: Thank you.

Dr. Goodman, please.

DR. GOODMAN: I want to return for a moment to the quality of life measures, this time, though, the slide No. 82, which is on page 41, the

SF-36. I want to make sure I understand this figure correctly.

It appears that on the physical functioning there is an advantage in quality of life for rimonabant but, if you look at social functioning and role of emotional functioning, the role of emotional functioning and mental health functioning, you see actually deterioration in both groups but statistically greater in the study group.

Could you comment on that, if I interpreted that correctly, one, and, two, how do you explain that association, could patients at the same time, or would the same patients, be experiencing improvement in physical well being, but emotionally, they feel worse? Could you just clarify it, please.

DR. ROSENZWEIG: Your observation is correct. With this generic instrument of SF-36, there was a kind of changes in all directions, changes in physical function. There was also comparison to placebo, well, less of a decrease in

bodily pain as relative improvement.

There was also relative improvement with general health, deteriorating on placebo. But that is statistically significantly different on rimonabant. But you are right.

On the emotional role and the mental health, there was more decrease on the rimonabant 20 mg, and we looked at these data. And this is driven by the patients which experience the mood disorders described by my colleague, Dr. Paul Chew.

However, these differences that you ask, that are statistically significant, taking into account the number of patients that we have, the number of observations are at two points on this SF-36 scale and, really, when we looked at that patients with the mood disorders, you have a decrease of 20 in these patients, so the difference in these subsets of patients, they are really driving this difference that you see in the general population due to this difference, so whatever the mood disorders occurred on placebo or on rimonabant, there was a decrease of 20 in these

patients driving this difference.

Your second question was about how I reconciliate these effects, is that correct?

DR. GOODMAN: Yes. I think you may have already partially answered that to say there was a contribution by the ones that mainly were experiencing depression.

DR. ROSEN: We have time for one ore question before the break. Dr. Proschan.

DR. PROSCHAN: I was wondering. You mentioned that people who go on antidepressants are discontinued. I wondered, is such a person counted? I assume they would be counted as having an AE by virtue of having to go on the antidepressant. But would that necessarily be a serious, you know, an SAE?

DR. GURAL: Dr. Chew. As Dr. Chew approaches the podium, clearly, according to the protocol of the completed Phase III protocols in the obesity, the RIO studies, any patient who experienced a depression and required antidepressant therapy was required by the protocol

to discontinue the study involvement.

DR. CHEW: Dr. Proschan, patients who develop depression regardless of whether they needed antidepressants was considered an adverse event, and the physicians were urged to do that.

The seriousness classification would be if it was medically important, required hospitalization, a prolonged hospitalization, was imminently life-threatening, so it would depend on the aspect of that.

Bud I did want to get back to one point, if I could, Mr. Chairman.

DR. ROSEN: We are running late, so I think we should wrap this up if you were satisfied with the response to that question.

DR. PORSCHAN: Yes. The only thing I just wanted to say is that you may be undercounting SAEs because that patient could have had an SAE later as a result of that depression, and you won't count that.

DR. CHEW: We did go back on all patients who had antidepressant therapy or neuropsychiatric

events, over 4,000 queries, 4,000 patients to specifically assess that point.

DR. ROSEN: Dr. Colman.

DR. COLMAN: Could the sponsor put up Slide 130.

I just wanted to clarify and put some of this into perspective. I don't know if this was mentioned, but this language from the sibutramine or Meridia label, it's another weight loss drug, this comes from the postmarketing report section of the labeling. If you read the first paragraph of that section, it says, "Voluntary reports of adverse events temporarily associated with the use of sibutramine was listed below. It is important to emphasize that although these events occurred during treatment with sibutramine, they may have no causal relationship with the drug."

In fact, we will be showing you some data later--it still is postmarketing data, but it is data from the same database, so that we can show you comparative data for orlistat, sibutramine and rimonabant, which I think is important.

I would also point out that in this same section of the sibutramine labeling, you will find event terms, such as heart arrest, increased salivation, hypothyroidism, hypoglycemia, nasal congestion and alopecia.

Another point I would like to make is sibutramine was originally developed as an antidepressant back in the early mid-to-late 1980s. Apparently, it didn't pan out too well, but it is chemically, its mechanism of action is very similar to Effexor. It's a norepinephrine and serotonin reuptake inhibitor.

Now, during the original obesity trials for sibutramine, which involved about 3,000 patients up to a year, there were zero suicides, no complete suicides. Furthermore, the agency, as most people know, in the past year or two has been looking at antidepressants and suicidality in extensive detail and, as you know, the current labeling for antidepressants for adults for major depressive disorders, there is no warning about suicidality. It has been limited to pediatric

patients where they have seen perhaps a signal, and even that is debatable. But there is a labeling warning about suicidality in children taking antidepressants if they have major depressive disorder, and we did put some of that language in the Pediatric Section of the Meridia labeling.

So, I think those are important facts that were not brought out that need to be kept in mind.

DR. ROSEN: Thank you, Dr. Colman. We will reconvene at 20 minutes past the hour.

[Break.]

DR. ROSEN: We could reconvene if everybody would take their seats.

There has been a request to have the questioners from the committee identify themselves. We have a remote viewing area for reporters and media, and they would like very much to have the committee members identify themselves prior to asking the question.

So, if all of us on the committee could remember to say who we are before we preface the question.

Let me just give you a brief update while people are getting to their seats about our schedule. What we are going to do now at 11:15 time, which is really 11:20, Dr. Karen Davis-Bruno is going to talk to you about the preclinical evaluation of rimonabant and then we will have time for questions, the lunch break will be at 12 o'clock, and at 1 o'clock we will hold the public hearing, the open public hearing at which three people will be testifying, followed by an FDA presentation by Dr. Egan.

I think without further ado, if everybody can take their seats, we will get started with the second part of the morning session, the preclinical evaluation by Dr. Karen Davis-Bruno from the FDA, Division of Metabolic and Endocrine Drug Products.

FDA Presentations

Preclinical Evaluation of Rimonabant

DR. DAVIS-BRUNO: Thank you. I have been asked to present today a nonclinical overview which will focus on the central nervous system toxicities associated with rimonabant.

[Slide.]

My presentation will include, first, a discussion of the role of the endogenous endocannabinoid system or ECS, followed by a brief discussion of rimonabant's pharmacology, focus on it mechanism of action, and then turn to an overview of the nonclinical toxicology studies focused on the central nervous system findings in various species, and then briefly conclude with a discussion of the clinical relevance of those central nervous system toxicities in the multiple species.

[Slide.]

The endocannabinoid system or ECS is a complex endogenous intercellular signaling system, which plays a modulatory role in a variety of functions in both the central and the peripheral nervous system.

The regulation of the endocannabinoid system in a variety of functions including energy balance, stress recovery, food intake and metabolic homeostasis are among the most extensively studied

functions of the endocannabinoid system. Indeed, you have heard a great deal about all of these earlier this morning as they function in the control of appetite and energy metabolism.

They have been implicated in the pharmacologic activity of rimonabant.

The endocannabinoid system is also involved in a number of other regulatory functions including cardiovascular effects and depressive effects, as well as modulation of the endocrine axis, the hypothalamic pituitary adrenal axis, and immune modulation.

I will focus my presentation on the neuroprotective effects of the endocannabinoid system, which are involved in the regulation of motor behavior, cognitive and memory functions.

[Slide.]

As you have heard earlier, the endocannabinoid system is comprised of a number of components including the endogenous ligands or the endocannabinoids. The structure of two of these endocannabinoids is indicated on this slide,

including anandamide and 2-arachidonoylglycerol.

Most of the endocannabinoids are lipophilic molecules and are derivatives of arachidonic acid, which is an important membrane constituent.

The endocannabinoids are synthesized on demand and they are not stored in vesicles like traditional neurotransmitters or traditional hormones. They act locally in an autocrine or paracrine fashion and are rapidly degraded following cellular reuptake in subsequent hydrolysis.

Endocannabinoids are versatile signaling mediators involved in a broad spectrum of physiological processes. The proteins involved in the synthesis, the membrane transport and the metabolism of endocannabinoids are also components of the endocannabinoid system but they are not listed in the slide.

The endocannabinoids bind to G-protein-coupled cannabinoid receptors indicated as CB1 and CB2. There are other non-CB1 and

non-CB2 cannabinoid receptors which have been recently identified but their roles are under current research investigation.

CB2 receptors are implicated in immune function and they have also been identified most recently in the central nervous system having originally been thought to be located only in the periphery.

The functions of CB2 receptors are less well understood than those of the CB1 receptors, which is our focus today. CB1 receptors are located in the central nervous system in the brain and in the spine, and also in the periphery in a variety of tissues including adipose tissues, skeletal muscle, liver and GI tract.

These peripheral receptors are also under active research investigation. CB1 receptors function in the regulation of food intake and energy metabolism, which is among the most extensively studied roles of the ECS, and you have heard a great deal about this.

Stimulation of CB1 receptors by cannabis

and its derivatives is associated with increased intake of palatable foods and has made the endocannabinoid system a therapeutic target for the treatment of obesity and for the generation of weight loss.

Rimonabant, which is our focus today, is the first in class, CB1 receptor antagonist in this system.

[Slide.]

This slide depicts the regional distribution of CB1 receptors in the central nervous system. There is a correlation between CB1 receptor presence in these important brain regions and the established regulatory roles of the endocannabinoid system which we have already discussed.

For example, basal ganglia and cerebellum are both involved in movement control and these regions have enriched concentrations of CB1 receptors.

[Slide.]

The hippocampus, involved in learning,

memory and stress, as well as the cerebral cortex involved in higher cognitive functions, are also enriched in CB1 receptors.

The hypothalamus and the medulla are both implicated in appetite control but, interestingly, the density of CB1 receptors in the hypothalamus is relatively low compared to the other brain regions. This suggests that factors other than receptor density, such as receptor effector coupling efficiency, which we will discuss shortly, may be involved.

Lastly, the spine is involved in peripheral sensations including pain responses and also contains CB1 receptors. CB1 receptors are widely expressed in the brain and are present at different levels in different neuronal subpopulations and brain regions. There is apparently no strict correlation between the levels of receptor expression and function.

[Slide.]

We have discussed some of the modulatory roles of the endocannabinoid system and now we need

to understanding how it performs these roles. Briefly, depolarization of neurons leads to induction of endocannabinoid synthesis, which modulates the synaptic transmission via CB1 and other receptors.

The endocannabinoids act as retrograde signaling agents which selectively and restrictively decrease synaptic input onto a stimulated neuron and modulate the constitutive tone of the endocannabinoid system.

This retrograde neurotransmission is a process that challenges the traditional concept of one-way neural transmission.

On this slide you can see that CB1 receptors are present in both presynaptically and postsynaptically. They are also present on interneurons but this function is less well understood.

Essentially, postsynaptic depolarization opens voltage-gated calcium channels leading to an increase in intercellular calcium and this calcium then activates enzymes, which synthesize the

endocannabinoid.

Depicted in this slide is postsynaptic glutamate receptors which are linked to a specific endocannabinoid 2-arachidonoylglycerol, and this endocannabinoid then is released from the cell and binds to the presynaptic CB1 receptors.

CB1 receptors are generally considered inhibitory to neurotransmitter release. The inhibition of neurotransmitter release is mediated through a complex interaction with G-proteins, which modulate inhibition of the presynaptic cells' calcium channel, thus, decreasing the probability of neurotransmitter release.

This retrograde neurotransmission can occur at both excitatory synapsis, such as glutamatergic synapses, as well as inhibitory synapsis, such as GABAergic.

Endocannabinoids can serve as inter- and intra-cellular signaling molecules. The literature supports endocannabinoids as versatile signaling mediators that act in a paracrine/autocrine manner independent of synaptic transmission in various

cells including adipocytes, hepatocytes and in glial cells.

[Slide.]

The pharmacology of the endocannabinoid system is very complex and it can produce effects on several levels including those at the tissue level, at the cellular level, and at the molecular level. We have already discussed those functions at the tissue level including the effects on motor behavior, cognition, memory and sensory effects.

At the cellular level, endocannabinoids can affect neurotransmission specifically through this somewhat unique mechanism of retrograde neurotransmission. This can lead to modulation of neurotransmitter activity of various neurotransmitters including GABA, dopamine, serotonin, glutamate, effects on the vanilloid receptor, the NMDA receptor, the acetylcholine, norepinephrine, anorexin 1. These are all based on literature.

Moreover, you have seen in the previous slide that endocannabinoids can affect ion channel

function. There are a variety of calcium channels that are affected, as well as potassium channels, and the literature indicates that even sodium channels may be affected through this system.

What I haven't discussed is the complex interactions of CB1 receptors with other central nervous system receptors, such as specifically forming multimeric interactions of CB1 receptors with other CNA receptors either with other CB receptors forming homomeric complexes or forming hetromeric complexes with dopamine receptors, opioid receptors and adenosine receptors.

This can significantly increase the complexity and the pleiotropic effects that can be generated by the endocannabinoid system. On the molecular level, pleiotropic effects can occur as far as signal transduction effects go in that endogenous endocannabinoids inhibit the activity of adenylate cyclase and the phosphorylation pathway of protein kinase A, as well as cause stimulation of a variety of map kinases. These two functions together lead to effects on gene expression.

Moreover, there are multiple G-proteins that are coupled to CB1 receptors, and this effect really depends upon the ligand that you look at, the tissue that is involved, as well as the dose used as many of the endogenous endocannabinoids, especially anandamide and THC are reported to have U-shaped dose response curves.

The multiple G-proteins link to particular CB receptors and those G-proteins can have multiple effects in among themselves.

[Slide.]

Our understanding of the endocannabinoid system, or ECS, has been limited by the lack of selective pharmacologic tools until the advent of rimonabant as a selective CB1 antagonist.

Rimonabant has been described in the literature as having partial agonist and inverse agonist activities. Its role as an inverse agonist as you have heard earlier refers to its ability to module the constitutive ECS tonicity.

It is thought to shift the CB1 receptor from a more active to an inactive state, resulting

in an overall decrease in ECS tonicity. This slide graphically depicts a typical dose-response curve demonstrating what a full agonist and antagonist and an inverse agonist would do.

Rimonabant binds at the agonist receptor binding site and it thought to result in opposite effects, that is, to generate negative intrinsic effects as you heard in Dr. Mackie's presentation.

Generally, inverse agonists are effective in receptors that have an intrinsic activity, such as the cannabinoid receptors. It is has also been originally described for GABA, benzodiazepine receptors. Again, the effect that you see depends upon the ligand you look at, the tissue you look at, and the dose.

Rimonabant can also elicit effects that are independent of the CB1 receptor, for example, rimonabant can displace ketamine at the PCP binding site of the NMDA receptor with similar micromolar affinities.

[Slide.]

So, there are three mechanisms that have

been proposed to explain rimonabant activities. The first mechanism is that rimonabant can compete with the endogenous endocannabinoids for CB1 receptor binding.

The second mechanism involves inverse agonism resulting from the negative modulation, the CB1 receptor constitutive activity, and this is thought to occur predominantly through allosteric effects, moving the receptor from a more active or on state to a more inactive or off state.

The third mechanism that has been proposed is that CB1 receptor independent mechanisms, as you have heard earlier, the antagonism of endogenous adenosine at A1 receptors can also occur.

It is important to keep in mind that based on Dr. Mackie's comment this morning, that the animal studies have shown that there is clearly distribution of rimonabant into the central nervous system of particularly rodents, and that the concentration based upon radioligand studies have shown there is approximately a 2-fold accumulation in rat brain tissue relative to plasma.

So, if you look at the IC50s for these particular receptors, it is potentially possible that you could achieve concentrations or rimonabant that are near the IC50s for these other non-CB receptors.

[Slide.]

There is sufficient evidence to demonstrate a complex pharmacologic profile of rimonabant and its interactions with the endocannabinoid system. Blockade of the ECS orexigenic stimulus either in the central nervous system or in the periphery may be desirable with obesity, but pleiotropic central nervous system functions under ECS regulation would also be antagonized by rimonabant, resulting in dysregulation of important nervous system functions.

This is consistent with the central nervous system toxicities that are seen in animals at clinically relevant exposures following rimonabant treatment. Rimonabant, acting as an antagonist at the CB1 receptor interacts with the