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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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Sanofi-Aventis

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C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order

DR. ROSEN: Good morning and welcome to the Endocrinologic and Metabolic Drugs Advisory Committee Meeting. I am Dr. Clifford Rosen and I am the Acting Chair of this Committee.

We have a full agenda and a full room, so we are going to try to stick to our schedules. I am going to start first by providing an introduction for each of the members who will go around the room.

Before that, I need to read something. Today's meeting will have a lot of discussion, which will result in recommendations at the end of the day for the FDA. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing details of this meeting with the media until its conclusion.

I would like to start by brief introductions around the room, so everybody is familiar with the people on the Committee. I would

like to start with Dr. Parks on the righthand side and we will move counterclockwise.

Introductions

DR. ROSEBRAUGH: Dr. Parks has instructed me to start, so I always do what she says. I am Curt Rosebraugh. I am the Deputy Director of the Office of Drug Evaluation II.

DR. PARKS: I am Dr. Mary Parks, Director, Division of Metabolism and Endocrinology.

DR. COLMAN: I am Eric Colman, Deputy Director, Metabolism and Endocrinology.

DR. EGAN: I am Amy Egan, medical reviewer.

DR. DAVIS-BRUNO: I am Karen Davis-Bruno, Supervisory Pharmacologist, Division of Endocrine and Metabolism.

DR. WOOLF: I am Paul Woolf, Chairman of Medicine, Crozr-Chester Medical Center in suburban Philadelphia.

DR. HIRSCH: Jules Hirsch, Professor Emeritus at Rockefeller University.

DR. GILMAN: Sid Gilman, Professor of

Neurology, University of Michigan Medical Center.

LCDR MILLER: Cathy Miller, FDA Advisors and Consultants Staff.

DR. ROSEN: Clifford Rosen, Senior Scientist at the Jackson Laboratory.

DR. KREISBERG: Bob Kreisberg, Birmingham, Alabama.

DR. CIRAULO: Domenic Ciraulo, Chairman of Psychiatry at Boston University School of Medicine.

MS. COFFIN: Melanie Coffin, Patient Representative.

DR. WANG: I am Philip Wang. I am the Director of the Division of Services and Intervention Research at the National Institute of Mental Health.

DR. GOODMAN: Wayne Goodman, Chairman of Psychiatry at the University of Florida.

DR. PROSCHAN: Mike Proschan. I am a statistician at NIAID.

DR. FLEGAL: Katherine Flegal from the Centers for Disease Control and Prevention.

DR. HENDERSON: Jessica Henderson. I am

the Consumer Reviewer.

DR. CARPENTER: Tom Carpenter, Pediatric Endocrinology, Yale University.

DR. BURMAN: Ken Burman, head of Endocrine at the Washington Hospital Center.

DR. RYDER: Steve Ryder, Pfizer R&D, Non-Voting Industry Rep.

DR. ROSEN: Thank you, Steve.

The agenda will be as previously published. We will have three people speaking at the open public hearing starting at 1:00 p.m.

Cathy has a Conflict of Interest Statement.

Conflict of Interest Statement

LCDR MILLER: The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the agenda for today's meeting and all financial interests reported by the members and consultants, no conflict of interest waivers have been issued in connection with this meeting.

We would like to note that Dr. Steven Ryder is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry.

Dr. Ryder's role on this committee is to represent industry interests in general and not any one particular company.

Dr. Ryder is employed by Pfizer. Pfizer makes a competing product to Zimulti.

We would also like to note that Dr. Kelly Posner has been asked by the FDA to participate in this meeting as a guest speaker. Dr. Posner is employed by the New York State Psychiatric Institute's Department of Child Psychiatry.

Dr. Posner reports that she has had research support from Sanofi-Aventis, the sponsor of Zimulti, and three of its competitors, Abbott Laboratories, GlaxoSmithKline and Novartis.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to

exclude themselves from the discussion and their exclusion will be noted for the record.

With respect to all other participants, we ask that in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. ROSEN: Okay. We are going to have Dr. Eric Colman give a brief introduction and overview, and also a presentation.

Introduction/Background

DR. COLMAN: Thank you, Cliff.

We have a fairly full agenda today, so I will try to keep these comments to a minimum. First, I would like to thank Dr. Rosen for agreeing to serve as Chair on this meeting. I would also like to thank the standing and temporary committee members for making a commitment and being here today. It is very important to us.

As you know, we are going to be talking about rimonabant today. This is a first in class

cannabinoid I receptor antagonist/inverse agonist. The focus today is on rimonabant's use as a weight management product, specifically, its efficacy and safety when used as a weight management product.

The target population is individuals who are obese and moderately overweight. Dr. Kelly Posner will begin this morning's presentations with a summary and overview of the Columbia Classification algorithm of suicide assessment. Her talk will orient us for later discussions about the relationship between rimonabant, depression and suicide, suicidality obviously a big concern for us.

Following that, Sanofi has a series of presentations ranging from mechanism of action to a proposed risk management plan, and then we will complete the morning session with a presentation by Dr. Karen Davis-Bruno, a pharmacologist from the FDA, who will give us thoughts on the preclinical evaluation of rimonabant.

Following the lunch break, we will have the open public hearing and then we will have the

final presentation of the day by Dr. Amy Egan, FDA Medical Officer, who will be discussing for the most part some key safety issues and concerns with rimonabant.

If we keep to the schedule, we should have about two and a half hours for discussion. Let me remind you of the issues, the point of discussion, and the questions that we will be asking the Committee to address towards the end of the meeting.

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

A question that we will be asking you, do you believe that the currently available data sufficiently characterize rimonabant's safety profile and, if no, please discuss what additional data should be obtained.

The third question reads as follows:

Based on the currently available data, do you believe that rimonabant has a favorable risk-benefit profile and should be approved for the indication of weight management in individuals with a body mass index of greater or equal to 30 and greater than 27 when accompanied by at least one comorbid condition.

Again, if the answer is no, please explain why and discuss what additional information the sponsor could obtain that might improve rimonabant's risk-benefit profile.

Again, on behalf of the Division and the Agency, I would like to thank all of the Committee members and our guest speaker for taking the time and energy to be here today for this meeting, which I think we all agree is a very important meeting.

DR. ROSEN: Eric, are you going to present the plaques to the people who are departing, or Kelly? Okay.

DR. PARKS: This year, as some of you may know, four of our members on the Endocrine and Metabolic Drugs Advisory Committee will be

retiring.

Present with us today are two of them, Drs. Thomas Carpenter, pediatric endocrinologist who has been with the Committee since July of 2003, and Dr. Steven Ryder, Industry Representative, who has been with the Committee since February of 2004.

We would like to express our great appreciation for their contributions over the years to many, many advisory committees and their expertise. We look forward to further communication and collaboration with them over the years.

Thank you very much.

[Applause.]

DR. ROSEN: My thanks as well for coming to the last meeting, last and very important meeting.

Thank you, Dr. Parks.

I think we will start with Dr. Posner, who will present the guest speaker presentation on suicidal issues. She is from the Department of Child Psychiatry at the New York State Psychiatric

Institute in New York.

Welcome, Dr. Posner.

Guest Speaker Presentation

Suicidality Issues in Clinical Trials

Columbia Suicidal Adverse Event

Identification in FDA Safety Analysis

DR. POSNER: Thank you. Good morning, everybody.

[Slide.]

As mentioned, I am here to give you some perspective and clarification on what we mean by suicidality in this context.

[Slide.]

I just wanted to take a moment to clarify my disclosures. All the original work that I am going to be describing was commissioned and funded by FDA only. Subsequently, we had research support from numerous pharmaceutical companies through Columbia and RFMH only to help execute FDA's suicidality classification mandates and have never taken any personal compensation or support.

[Slide.]

My classification co-investigators, Dr. Oquendo, Dr. Gould and Dr. Stanley, I would like to thank for all their work, and I will be talking about a prospective scale that I am going to go into more detail, as well as the contributors to that.

[Slide.]

Where does this suicidality issue, where did it all begin? Well, the problem is in the field of medicine and even in psychiatry, we are challenged by a lack of clarity about how to define even the most basic suicidal behaviors and corresponding to that, we have no well-defined terminology. This cuts across clinical and research settings.

What happens is this lack of systematic or standardized language really shows itself very much across all clinical trials and what we see is the same behavior or the same event is called 10 different things - attempt, non-attempt, threat, gesture. They are often pejorative and they are based on incorrect notions about the relationship

between seriousness and lethality.

[Slide.]

So, what that leads to is difficulty in interpreting the meaning of reported adverse events that occurred in any of the controlled trials. What happens is that adverse events that should have been called suicidal may have been missed, and adverse events that may have been inappropriately classified as suicidal.

[Slide.]

Now, these are real examples. This whole story began, as many of you know, with the pediatric antidepressant story and these are real examples of the difficulties that I am talking about in adverse event labeling.

These came from the pediatric clinical trials. So, the first one, 10-year-old male exhibited symptoms of personality disorder. One day later patient attempted to hang himself with a rope after a dispute with his father, yet the preferred term was "personality disorder," nowhere is suicidality indicated.

The overdose of 6 capsules was in fact intentional, yet called accidental overdose and neurosis.

Patient took 11 tablets, called medication error. One of my favorites, before his mother is called to the site, he wrapped a cord from the mini-blinds around his neck, called hostility.

[Slide.]

If you have been following this, we call this the "slap heard around the world," because it has been written about a lot when these issues are discussed. Somebody somewhere called a slap in the face a suicide attempt and the update said, my God, how can we have such an important safety analysis with data that is not interpretable.

What is really interesting to note is that the severity goes both ways. It is not just pharmaceutical companies calling things less severe than they should be. They are calling a lot of things more severe than they should be because there is no training and there is no systematization, and nobody knows how to do this

the right way.

So, after we did the pediatric trials, the system was mandated across, you know, antidepressants, anticonvulsants, et cetera, so we have seen thousands and thousands of adult examples, and I can tell you the problems are very much as apparent.

So, this is an example of an adult case. Patient made attempt to stab himself in the abdomen, which resulted in minor injury only. This was not considered a true suicide attempt and no action was taken, not significantly significant, called trauma.

[Slide.]

So, what do we need to do to address this problem? Well, Columbia was commissioned by FDA, and we knew we had to apply a common set of guidelines. We needed to speak the same language across all these trials and, of course, we needed to look consistently. And we wanted to have a meaningful language, of course. So we developed what was the most research-supported approach and

that is called the Columbia Classification Algorithm for Suicide Assessment which, as you know, is the system that was used with the data today.

[Slide.]

Now, what were we actually classifying in these trials or any of the others? What happened is the FDA asked the companies to do electronic text string searches of their databases, so you can see the terms there "suicide" or "overdose" attempt, cut, hang, gas, et cetera. And anytime an adverse event term with one of those terms came up, they were supposed to flag it and write a narrative about it.

They were permitted exclusions for events that represented obvious false positives like "gas" and "gastrointestinal." But, you know, when we saw all the variability of the labeling, the first time around we said, you know, we really should broaden the search to make sure no suicidal events were missed, and then ask for all accidental injuries, all serious adverse events, and all deaths, which

is what was done here, as well.

So, then, the companies constructed narratives of those events and sent them blinded to us for classification.

[Slide.]

Now, when I say "blinded," of course, we wanted to have the most conservative, unbiased approach possible, so any company, any study, all these things are blinded, drug name, company name, patient ID numbers, obviously, active or placebo arm, but even any and all medication names and types, because it may be that some meds are associated with a particular side effect profile and thus could potentially bias something.

Of course, we blinded those labels that had been given originally by the investigators. Okay. So, that is what we did.

[Slide.]

What is this scheme? The primary thing that we needed to do for FDA and for these studies was separate suicidal events from non-suicidal events.

So, those blue boxes are what went into every primary analysis, suicidality analysis, whether it was this or the antidepressant, and what we mean by what we think are suicidal is completed suicide, suicide attempt, suicidal ideation, and preparation behaviors.

But as you know, these studies weren't set up to assess for suicidality, so we had to have some other classifications to put the events in that could have been suicidal. But we just didn't have enough information.

You can see self-injurious behavior with unknown intent. There may have been narratives that said patient cut wrist, and they may have been cutting their wrist because they were trying to kill themself or they may have been cutting their wrist because they were self-mutilating and trying to feel better, we just didn't know.

So, that is what we call the worst case sensitivity analysis, you know, where there was not enough information. But they may have been

suicidal.

[Slide.]

These are the codes that were used here and everywhere else. And you can see the 1 through 4 are all the primary suicidality codes and then they go down in order of severity in terms of not enough information and then all the others that have nothing to do with suicidality.

[Slide.]

I am not going to go into every definition. But the whole scale, the whole system was really very much driven by the definition of suicide attempt, and this comes from Dr. Mann's scale, the Columbia Suicide History form. At Columbia, 20 years of research support doing it this way. As I said, we went for the most research-supported thing that we could get.

What we mean by suicide attempt is a self-injurious act committed with at least some intent to die, as a result of the act.

The first thing to note, it is a self-injurious act, there does not have to be any

injury or harm, just the potential for it. So, the guy puts a gun in his mouth, pulls the trigger and, fortuitously, the gun fails to fire. It is still a suicide attempt even though there is no injury.

These are the common misperceptions that lead people to call things by the wrong names.

Non-zero intent, often people have mixed motives when they are dealing with suicidality, so only a piece of them should have wanted to kill themselves when they were engaging in this behavior and that is enough to call it suicidal. Intent can be inferred from circumstances or it can be explicit obviously.

[Slide.]

Suicidal ideation definition. This is thoughts of wanting to be dead, wanting to die or ending one's life. Very clearly, it has no behavior associated with it. It is just a thought. For example, following a fight with her boyfriend, patient thought about taking an overdose to end her life.

Patient was feeling depressed and thought

his bad luck would never change and wished he were dead.

[Slide.]

So, what were our findings? The C-CASA findings, which are about to come out in the American Journal of Psychiatry, were very interesting.

What we found is remember we broadened the search to make sure nothing was missed. We found more suicidal events overall, so it was well worth going through, looking through the accidental injuries and things. But fewer events were labeled suicide attempt.

In the antidepressant analysis, 50 percent of the cases were not called suicide attempts. The pharmaceutical companies called 45 cases suicide attempts that we thought shouldn't be called suicide attempts, really decreasing the harm ratio dramatically.

We had excellent reliability. FDA did an independent audit. They called C-CASA robust and reproducible, demonstrating excellent

transportability for situations like we are in today.

What is really interesting is that there was an analysis in the pediatric antidepressant trials that relied just on the pharmaceutical company labels before we applied this system and, when you compare the two findings, they were made up of one-third different cases, so people said, well, there were similar results. But they were actually made up of different patients, really confirming the reason for having done this.

[Slide.]

Furthermore, the safety analysis using this system had more precise estimates of risk and tighter confidence intervals compared to the prior analysis that relied on the sponsor ratings, also reduced estimates of risk.

This is consistent with previous findings that misclassification leads to overestimation of true risk.

[Slide.]

So, we did the best we could with limited

data and I want to spend a moment talking about what the limitations of this data actually are, because I think it is very critical to the discussion today.

As I said, these studies were not designed to assess for suicidality. These studies, the antidepressant studies even were not. Association does not mean causality. Just because we see this association, it does not mean that the drug is necessarily causing the association.

There has been a lot of discussion through the years and in other settings that what is a very plausible alternative explanation to this causal link, well, it is something called ascertainment bias.

When people are on active medication, they have more side effects - headache, stomachache, et cetera. They may just have had more contact with their provider to hear about a suicidal occurrence as opposed to it being a true difference in risk. And the only way you can end up knowing that that is the case is by having prospective future

systematic monitoring, so that is one alternative explanation that may account for the differential among drug and placebo in all of these safety analyses.

[Slide.]

Now, just to support that theory, first, in the pediatric analyses, they did have some systematic data, so depression scales were collected in most of those pediatric trials, Hamilton Depression Rating Scale, et cetera, and FDA did an analysis of the suicide item data, systematic suicide item data, and it did not confirm the risk.

So, when you looked systematically, it did not show a signal. But, when you looked at the spontaneous adverse events, it did show a signal. And there are many analyses since then that have shown this kind of confusing and compelling discrepancy, meaning that it is possible that these adverse-event data are somewhat misleading or false. We just don't know; right? We have reason to question.

[Slide.]

How do we think we fix the problem? Systematic administration of a tool designed to track suicidal events across a treatment trial. This Columbia Suicide Severity Rating Scale is the prospective version of the C-CASA system that we developed for FDA, and this is the way to get better safety monitoring and avoid inconclusive results.

I just wanted to say also that on the first slide, this is a collaboration between a lot of leading experts and Columbia and Pittsburgh and Penn. Dr. Mann is here, one of my lead authors.

[Slide.]

This is the reason why FDA is often recommending it in ongoing and future studies in other areas, as I said, developed by leading experts, very, very evidence based. It is feasible and low burden, typical administration time is not more than five minutes, usually less.

It assesses both behavior and ideation--other scales just look at one or the

other--and it really appropriately assesses and tracks all suicidal events, so we don't call a slap in the face a suicide attempt. We just call the right thing suicidal, and we can control for all those other alternative explanations like ascertainment bias. So, this is better systematic monitoring to give us better answers.

[Slide.]

You can see it gives a study or a person everything we needed to fix the problem - the definition, the probes, the questions, things to allow people to put things in the right boxes, so we can get better safety answers.

[Slide.]

That was behavior.

[Slide.]

This is ideation, operational as the way we have always thought about it from a wish to die through active or planning intent.

[Slide.]

We got together, the authors got together and said what is the minimum amount of information

that one would need in any setting to ask about.

Well, one of those things is lethality, so only when there is an actual attempt does somebody ask about lethality, because it is critical data in a study or any other setting to collect. And then we have other features of ideation, frequency, duration, controllability, et cetera. All these items are significantly predictive of completed suicide. We said what is the minimum amount of information any setting would want to ask about for tracking and severity.

[Slide.]

Various uses. Within a study are multifold treatment benefit outcomes, safety outcomes, clinical safety monitoring. It is coordinated efficiently with other measures. It is easily coupled with inclusion/exclusion. As many of you may know, historically, in studies, in the past, exclusion criteria have been totally arbitrary, serious risk. Nobody knows what that means exactly, so this can help move things in a number of directions.

[Slide.]

Its current use, we have four years of use in clinical trials, large multi-site industry nationally and internationally, a range of therapeutic areas, as you can see, over 20 languages, NIMH trials, surveillance efforts, community clinics.

[Slide.]

In conclusion, intervention trials using prospective and systematic measurement of suicidality would certainly more clearly delineate the relationship between suicidal adverse events and medication treatment.

Consistent assessment can give us more meaningful data, not only within a study, but across studies, improving these pooled analyses for a better understanding about both benefits and safety.

Again, this improved assessment is also critically necessary to better inform risk-benefit analyses, which is why we are all here today.

[Slide.]

Just finally, some perspective on suicidal ideation which will get a lot of attention today. It is very important to remember that suicidal ideation is a symptom of depression. It is a symptom of depression.

Lifetime prevalence of depressive disorders is 29 percent.

A key thing to remember, CDC data, an estimated 10.5 million people will experience suicidal ideation in a year, while 30,000 people will commit suicide. A lot of people will have these thoughts, they are part of depression. It doesn't mean that. It is always very important to keep these numbers in mind.

Thank you.

DR. ROSEN: Dr. Posner, if you would stay around, I would like to ask the committee if they have any questions for Dr. Posner.

DR. PROSCHAN: I was wondering how often you would recommend giving that assessment.

DR. POSNER: Actually, we spend a good bit of time talking to other groups at FDA about

this, and the way we see it and they see it is you give it, every visit, the same way you would give any other rating scale, depression, side effect, or anything.

Otherwise, if you don't, you are just getting back into the same question, the same challenge, not getting optimal data.

DR. ROSEN: I would like to ask is there any specific training necessary for people who are conducting the trials to log onto this or to know exactly what they are asking?

DR. POSNER: The training is very similar to the training of all the other scales that you are familiar with, whether it is ADHD or depression. We go to an investigator, start-up meeting, give the training. We have given, you know, half-hour teleconferences nationally and internationally, usually about 25, 30 minutes.

There are manuals, training tapes.

DR. ROSEN: Is there any hesitancy on the part of the clinical nurse coordinator or the research nurse to provoke or to ask these

questions, or to get that kind of information?

DR. POSNER: My anecdotal experience has been a bit of the opposite. People say uh, finally, something that helps us make sense of this in a better way.

DR. CIRAULO: As you presented that last slide in statistics, that was very helpful. Could you clarify for me what are the data of fleeting suicidal ideation in a general population?

DR. POSNER: Well, you know, I don't think we have very good data about the nuances of ideation like that, frequency, types, et cetera. We do know generally that whether it's a passive wish to die or an active thought, this is the prevalence rate.

So, these kind of measures and things are going to help us get better answers to those questions.

DR. CIRAULO: And this scale would help discriminate the sort of fleeting suicidal ideation which is common in the population?

DR. POSNER: Yes, exactly, so as I said,

it articulates a passive wish to die, you know, a wish to die all the way down to plan and intent, so you can distinguish those things and then get frequency, duration, et cetera, all those features about each one of those things.

It is a good question and I appreciate it.

DR. ROSEN: Other questions or comments from the review panel?

Okay. Thank you, Dr. Posner.

I think we are going to start. We are a little ahead of schedule actually, but we are going to start our sponsor presentation.

The first presentation, the introduction will be Dr. Gural from Sanofi-Aventis. Welcome.

Sponsor Presentation

Sanofi-Aventis

Introduction

DR. GURAL: Good morning, Mr. Chairman.

Members of the Advisory Committee, Food and Drug Administration, consultants and interested parties: I am Richard Gural. I am the Vice President for Drug Development within Scientific

and Medical Affairs within Sanofi, and I will be the moderator today for the company.

We are here to present the results of the clinical studies of rimonabant in the treatment of obesity and type 2 diabetes.

The agency has asked the committee to consider the three questions outlined to you this morning by Dr. Colman and hopefully, we will be providing you information which will allow you to fully deliberate on these questions.

[Slide.]

Our presentation today will include brief introductory remarks made by myself followed by a review of the mechanism of action by Dr. Ken Mackie from the University of Indiana.

The medical need, clinical benefit and efficacy data will be presented by Dr. Rosenzweig of Sanofi-Aventis, followed by a review of the safety by Dr. Paul Chew.

I will then present again a management of the risk of rimonabant followed by the overall clinical benefit by Dr. Lou Aronne.

[Slide.]

Rimonabant has been developed in accordance with both the 1996 and the 2007 guidance documents for the development of drugs for the control of obesity.

These included not only the duration and the size of the study, but also the efficacy criteria. Indeed, we will see that the size of the studies conducted exceeded the number of patients and the duration to be included.

[Slide.]

Also, in these guidance documents, the patient population was clearly identified and we have studied both patients with a BMI greater than 30 kg/m^2 without comorbidities or 27 kg/m^2 with comorbidities as identified here.

Also, the 1998 and 2000 guidance documents on the development of drugs for the treatment of obesity has also been followed.

[Slide.]

Now, exactly, what are the studies that we will be reviewing with you today? RIO-North

America, which stands for rimonabant in obesity, was conducted in North America and it had a duration of 1 year on drug followed by re-randomization, the design of which Dr. Rosenzweig will present to you this morning.

Studies were also conducted RIO-Europe, Lipids, and Diabetes. All four of these studies were conducted on a global basis and represent a Phase III development program and were conducted in accordance with the guidance documents.

We also have conducted studies in the treatment of diabetes in patients who have failed or had inadequate control, metformin or sulfonylurea, or in a recently completed study at SERENADE in treatment-naive, type 2 diabetic patients.

[Slide.]

Safety will be one of the key topics that we will discuss today. As you can see from this slide, nearly 7,500 patients were treated with rimonabant at a dose of 20 mg, which is the recommended dose, for a duration between 1 day and

2 years.

The overall patient safety database in the controlled studies during the development is represented here at a number of 15,000. They came from 1,000 or more patients in clinical pharmacology, 1,000 patients in our Phase II program, 5,400 patients from the obesity diabetes program, which will be discussed in greater detail today, and about 7,500 patients from a smoking cessation development program. Dr. Chew will be reviewing all of this data with you today.

[Slide.]

We did not stop there. As you will hear later, rimonabant is currently approved in 37 countries, marketed in 18. So, we have benefit from information that is from our postmarketing surveillance of almost 110,000 patients. We have approximately 14,000 patients from ongoing studies, as well as 15,000 patients from our completed Phase I and Phase III.

This gives a total exposure of database of approximately 140,000 patients.

[Slide.]

We haven't stopped, though. We did not stop at just the development of the drug in the treatment of obesity, we also evaluated, as you can see here, rimonabant in a number of therapeutic indications specifically addressing the potential for prevention of cardiovascular risk.

A currently ongoing study called CRESCENDO, which the FDA referenced in the briefing document, is currently enrolling approximately 8,000 patients out of an anticipated 17,000.

The rest of the studies that are identified here, including RAPSODI in the prevention of type 2 diabetes, have been fully enrolled, and the numbers are represented here. We are continuing to collect the data and that will also be discussed from the safety point of view today.

It gives us the number, as I previously mentioned to you before, of approximately 14,000 patients in our ongoing studies.

[Slide.]

Now, what is Zimulti or rimonabant? Rimonabant, as you have seen, has been extensively published. It is a selective and neutral antagonist of the CB1 receptor and we will hear later this morning from Dr. Mackie on the characterization of this activity.

Zimulti, in its proposed market image, is a 20 mg tablet intended for once daily administration along with breakfast.

[Slide.]

Just briefly, I would like to summarize some of the hallmarks of the pharmacokinetics of rimonabant. This also has been extensively studied, as you saw in the patients represented during the Phase I trial of approximately 1,000.

The hallmarks of rimonabant pharmacokinetics is that it has good absorption. It is extensively protein bound, approximately 99 percent. It has a modest accumulation on once-a-day administration and a long terminal half-life of 16 days in patients who are obese.

As rimonabant is metabolized, both the

CYP3A4 and amidohydrolases, the effects of the potent inhibitors of the 34A is modest, resulting in approximately a 2.7-fold increase in rimonabant exposure.

Finally, as rimonabant does not inhibit the CYP3A enzymes, drug-drug interactions through these mechanisms are not anticipated.

[Slide.]

Let me just review briefly with you the current regulatory status of rimonabant. As I mentioned before, it is currently approved in 37 countries and marketed in 18. In Europe, the marketing application or the MAA was submitted in April 2005 via the centralized procedure. It was approved in June 2006.

The indication in Europe is as you see here, as an adjunct to diet and exercise in the treatment of obese patients with comorbidities especially that of type 2 diabetes or dyslipidemia.

As you may know, in Europe, when a product is approve via the centralized procedure, it is approved in 25 countries simultaneously, all with

the same label and the same indication, through a patient information leaflet and a package insert known as an SMPC.

Immediately following the approval in June 2006, the product was launched in the UK, and I will be showing you later today some of our experience with that, and we will be discussing that, as well, during the safety presentation.

[Slide.]

Currently, within the EU, a type 2 variation is pending for the treatment of diabetes based on the information that you have also in your dossier today--that is, the RIO-diabetes, as well as the SERENADE studies.

Later today, I will be discussing a Risk Minimization Plan that we will be employing in the United States. I would just like to emphasize that this is not just for the United States. Currently, a Risk Minimization Plan is part of the core risk-benefit that we have for rimonabant, it is being applied in the UK, as well as the rest of Europe, and again I will be showing you some of

that data later today.

[Slide.]

Where are we in the United States? An NDA for rimonabant was submitted in April 2005 using the same data that was submitted in the European Union.

In February of 2006, an approvable letter was obtained from the Division following a number of interactions with the Division where we thoroughly reviewed the approach and the type of data necessary to address the elements of the approvable letter, a complete response was submitted in October 2006.

This response included an updated safety from both the completed and the ongoing studies, as well as most recently information from our experience based on the postmarketing information coming from Europe through a procedure called a PSUR, or a Periodic Safety Update Report.

We reviewed all neurological and psychiatric events and, as you heard from Dr. Posner, we employed the C-CASA as part of the

analysis for suicidality, as well as, you will hear today we are proposing a risk management plan.

During the review of the application, the agency asked for, and we agreed to, a 3-month extension for the review of the file based on the size of the information that is contained within it.

At that time, we took the opportunity to submit the SERENADE data, which had been recently completed during and following the complete response in October, and, of course, today, we are having the Advisory Committee with you here today to review this information.

[Slide.]

Our NDA submission in October contained two indications. It contained an indication in the treatment of obesity, as identified here, as well as use in patients in combination with metformin or sulfonylurea who have not had adequate control.

[Slide.]

We will hear a lot today about the safety of rimonabant. We will hear a lot about the

efficacy of rimonabant. But who is the right patient to receive rimonabant? Not everybody.

Rimonabant is intended to be used in patients with a BMI greater than 27 kg/m^2 with at least one cardiovascular metabolic risk factor and/or a BMI greater than 30 without any of the comorbidities.

Since obesity is indeed a chronic disease, long-term administration is recommended for rimonabant. We will hear a lot about the safety, so it is important to note now who is not the right patient to be administered rimonabant.

Who is not appropriate is a patient with the past history of depressive disorders and/or suicidality, or patients with a diagnosis of depressive disorders, or patients currently under antidepressant therapy.

We will also have a discussion today about seizures. You will see that we are also recommending that the appropriate patient not to receive rimonabant will be one who is on current anti-epileptic therapy.

So, the right patients are those for which the indication is sought. The inappropriate patients are those who have depressive episodes in the past, or currently on it, or those who are currently receiving anti-epileptic therapy.

[Slide.]

With us today, we have a number of consultants and experts. These experts and consultants have participated with us both in the development of rimonabant and in preparation for the Advisory Committee today.

They include experts in the area of mechanism of action, endocrinology. Many of these names are familiar to many of us. Internal Medicine.

[Slide.]

And because of the unique nature of rimonabant in Psychiatry.

[Slide.]

And Neurology. Also, the risk management plan has been thoroughly reviewed with the Epidemiology and statistical support.

[Slide.]

Now, it will be my pleasure to introduce Dr. Ken Mackie, who is Professor and the Chairman of Neuroscience at Indiana University and the Linda and Jack Gill Chair.

Dr. Mackie has published extensively in the field of endocannabinoid receptors and is dealing with the mechanism of action for rimonabant.

Dr. Mackie.

Mechanism of Action

DR. MACKIE: Thank you, Dr. Gural.

[Slide.]

Good morning, Mr. Chairman, members of the Committee, ladies and gentlemen, I would like to give you an overview of the mechanism of action of rimonabant today with an eye towards its clinical efficacy and potential safety concerns.

[Slide.]

My talk will cover four points. First, I will briefly introduce endocannabinoid system, then, I will talk about the pharmacological

properties of rimonabant relevant to its mechanism of action, present evidence for the hyperactivity of the endocannabinoid system in obesity and type 2 diabetes and then, finally, I will present preclinical data providing the rationale for the therapeutic use of rimonabant in treatment of obesity and type 2 diabetes.

[Slide.]

The modern era of cannabinoid research and the discovery of the endocannabinoid system really dates back to 1964 with the discovery of delta-9 THC as the primary psychoactive constituent of cannabis by Raphael Mechoulam and his group.

This was followed by a period of productive research, culminating in the cloning of CB1 and CB2 receptors, as well as the discovery of their endogenous ligands, endocannabinoids, and anandamide, and 2-arachidonoylglycerol

An important distinction between endocannabinoids and the more classical neurotransmitters like glutamate and acetocholine is that they are not synthesized ahead of time and

stored in vesicles; rather, they exist in new membrane as preformed lipid precursors and are made on demand by specific enzymes following specific stimuli.

Together, it is the endocannabinoids, the cannabinoid receptors, and their synthesizing and degrading enzymes that comprise the endocannabinoid system.

A variety of evidence suggests that the endocannabinoid system exists to fine-tune various physiological processes, sort of running in the background you might think of it. However, it can be detrimental when it is overstimulated in certain diseases, such as obesity.

Key to today's discussion is that rimonabant, the first CB1 receptor selective antagonist was developed in 1994.

[Slide.]

CB1 receptors are widespread throughout the brain including cortex, amygdala, basal ganglia and hypothalamus, which isn't shown in this section, in the brain is present on subpopulations

of both excitatory and inhibitory neurons thus predicting a priori defective cannabinoid receptor activation of blockade is rather problematic.

It is also found in peripheral nerves including those that innervate the gut and help to control the sensations of satiety.

Surprisingly, to those of us who came to the cannabinoid field from neuroscience was demonstration of cannabinoid receptors on a variety of peripheral tissues including adipocytes, liver, and skeletal muscle.

In many of these tissues, CB1 receptor levels are regulated during pathological conditions such as cirrhosis and obesity.

[Slide.]

Rimonabant was discovered to be a high-affinity CB1 receptor antagonist blocking the effects of THC and other cannabinoids both in vivo and in vitro.

An important consideration for any antagonist is its selectivity. As can be seen in this binding experiment shown on the left here,

rimonabant has a high affinity for CB1 receptors and a relatively low or very low affinity for CB2 receptors, the most closely related other GPR coupler receptor.

Endocannabinoids interact with a number of other proteins and ion channels. As listed in the table to the right are some of the more prominent receptors and ion channels that endocannabinoids interact with, and you can see that rimonabant has a very, very low affinity for any of these compared to the CB1 receptor.

Not shown here on the chart, but mentioned in FDA's presentation is A1 adenosine receptors, I would like to comment that rimonabant has an affinity of greater than 10 micromolar for A1 receptors.

[Slide.]

Rimonabant is an inverse agonist, a term that may be unfamiliar to some of you. On the next two slides we will consider what an inverse agonist is and its implications for rimonabant's pharmacology.

[Slide.]

Shown on the left here in yellow is the behavior of a classic neutral antagonist, which merely prevents agonists from binding to the receptor. If applied to a system that is maximally stimulated here, you can see increasing concentrations of neutral antagonists eventually reverse the response, bringing it down to the baseline level.

However, the pharmacology of many antagonists n clinical use, for example, metoprolol and losartan, cannot be explained by simple neutral antagonism, thus, the concept of inverse agonism has been developed.

It is important to emphasize that inverse agonists are not an exotic species. It has been estimated that 85 percent of G-protein coupler receptor antagonists are actually inverse agonists.

Typically, for an inverse agonism to be detectable, a receptor must have a level of constitutive activity. That is shown here on these two lower curves, so this is the baseline activity

in the resting state.

Increasing concentrations of inverse agonists will drive that level to less than zero. It is very important to realize, though, that just like with agonists, inverse agonists can have differing potencies, as well as efficacies, so inverse agonism is not a black and white property. It is very graded response.

Particularly key is the concentration over which you see neutral antagonism for an inverse agonist versus true inverse agonist effect, which we will revisit later.

One way of thinking of inverse agonists is the binding of inverse agonists can be thought to lock the receptor in an inactive state.

The take-home message for this slide is the important distinction between antagonist and inverse agonist effects is that in the absence of agonist, a neutral antagonist will have no effects, while inverse agonists may have unintended or unexpected effects.

[Slide.]

Does rimonabant behave as inverse agonists? One way to see if an antagonist shows inverse agonist is an artificial system where you have expressed receptors at a very high level in a cell line. But a moralistic situation is to use natively expressed receptors.

This is one such experiment using CB1 receptors expressed in natively expressed cerebellar membranes. The orange curve shows that in the absence of an agonist, increasing concentrations of rimonabant do not inactivate the CB1 receptors shown by no change in GBMS binding, which is a measure of global G-protein activity.

Only when you get up in very high concentrations of rimonabant, greater than a micromolar, do you see inverse agonism.

You will see throughout my slides SR141716, which was the developmental name for rimonabant. However, if you stimulate CB1 receptors with anandamide and then treat them with increasing concentrations of rimonabant here, you can see the classic neutral antagonism that appears

well before inverse agonism.

Just to provide a frame of reference, the steady state trough concentrations of rimonabant in the human studies is about 200 nanomolar, which would put it in this range here, clearly below the range that you see inverse agonism.

Therefore, rimonabant acts as a neutral antagonist at CB1 receptors in clinically encountered concentrations. Thus, as it will be used clinically, it will likely have an effect only in the presence of endogenous cannabinoid tone.

In more complex systems, it is difficult to determine if a change in response seen when giving an inverse agonism is due to true inverse agonism or merely antagonism of endogenous tone.

The only way to determine this unequivocally for CB1 receptors is to prevent endocannabinoid synthesis and we just don't have the tools to do that currently. Nonetheless, in many in vitro and in vivo models, the efficacion rimonabant is neutral.

An example of relevant for potential

adverse effects is shown in this slide looking at excitatory corticosteroidal transmission. A common action of cannabinoids including the endocannabinoids is to inhibit neurotransmission.

Here, the amount of neurotransmitter release is indicated by the dots. You can see the application of a synthetic cannabinoid in this experiment decreases the amount of glutamate release, so decreases glutamate neurotransmission.

Now, if rimonabant was acting as an inverse agonist in this system, you would expect to see an increase in neurotransmission when it is applied, however, you do not see that. Instead, what you see is just neutral antagonism of the synthetic cannabinoid applied here.

Again, in this system, which is a little bit more complex, it behaves as a neutral antagonist. This is still only slice experiments. What about animals? There is limited sort of global animal data but a very interesting paper that was recently presented looked at the effects of rimonabant on cerebral blood flow in awake

animals using fMRI and, in those studies, while rimonabant blocked the increase in cerebral blood flow seen with cannabinoids, by itself, it has no effect.

[Slide.]

So the endocannabinoid system is here, and those of us who work and enjoy, is involved in many processes. Some of these effects are mediated by CB1 receptors, but it is very important to appreciate that many of them are mediated by non-CB1 mechanisms.

A few of those non-CB1 mechanisms are shown here including CB2 receptors, GPR55, the abnormal cannabidiol receptor, TRPV1 channels and serotonin 5HC3 channels.

So, some of the endocannabinoid mediator processes that have a prominent non-CB1 component, that are relevant to today's discussions are analgesia, amelioration of neural inflammation, such as MS, bone remodeling and control of vascular tone.

The multiplicity of endocannabinoid

actions is complex. Perhaps a useful analogy for thinking of it is epinephrine and beta blockers. While beta blockers will attenuate the chronotropic effects of epinephrine mediated by beta1 receptors, they will have no effect on the vasoconstriction mediated by alpha receptors.

Similarly, blocking CB1 receptors does not antagonize all endocannabinoid signaling. Thus, it is important to appreciate that if activating the endocannabinoid system is beneficial, antagonizing it with CB1 blockade is not necessarily detrimental.

In addition, another noteworthy point is the effects of chronic CB1 blockade are sometimes the exact opposite of acute CB1 blockade, presumably due to slowly developing changes, such as the question of inflammation.

An example of this are neuropathic inflammatory pain models where acute administration of rimonabant causes hyperalgesia, yet, chronic administration of rimonabant is analgesic.

Thus, care must be used in extending

animal studies investigating the acute effects of rimonabant to the human situation where the drug is dosed chronically.

[Slide.]

So, let's change direction now a little bit and look at the role of endocannabinoid system in obesity. It has been known for some years now that activation of the central endocannabinoid system, acting both in the hypothalamus and limbic forebrain, increases food intake and promotes weight gain.

However, recent evidence has emerged suggesting that the peripheral endocannabinoid system is a key player in human obesity.

As shown on the left, circulating levels of two endocannabinoids, anandamide and 2-arachidonoylglycerol, are increased in obese compared to lean women. The middle slide shows that if you break down the type of obesity between primarily visceral fat to subcutaneous fat, levels of circulating are even more increased in subjects with visceral obesity.

Finally, moving to type 2 diabetes, in subjects that are matched for age and BMI, but have type 2 diabetes, both anandamide and 2-arachidonoylglycerol levels are increased, suggesting that across both obesity and type 2 diabetes of the endocannabinoid system is overactivated.

[Slide.]

So, additional evidence for the role of overactivated endocannabinoid system and obesity comes from population studies. Fatty acid aminohydrolase, shown here as a crystal structure, is the primary enzyme that degrades anandamide.

A mutation here, proline 3 at 129 decreases the enzyme activity by decreasing stability and decreasing enzyme levels, which results in a decrease in activity, which is shown here, looking at enzyme activity in lymphocytes from patients with this mutation.

This is a naturally occurring mutation, relatively low percentage of the population. But you can see that there is an association of this

polymorphism with obesity shown here for caucasian Americans, but also in the African-American U.S. population.

[Slide.]

So, a number of preclinical studies have shown that the reduction of food intake with rimonabant is transient, returning towards baseline levels after days or a few weeks.

Despite the transient reduction energy intake, weight loss is consistently found to be sustained, suggesting that weight loss is due to additional metabolic mechanisms.

An example here is an experiment where mice made obese by diet were treated either with vehicle or 10 mg/day of rimonabant. And you can see, over the course of 4 weeks, they lost approximately 20 percent of their body weight.

As one measure whether this is purely mediated through decreased food intake, a control group that was fed the same amount of calories as the high fat diet mice and studied at the same time only lost about two-thirds of that weight, or about

14 percent.

These results strongly support an effect of rimonabant on body weight that goes beyond the reduction of food intake. But this is a true peripheral effect or mediated by the CNS.

[Slide.]

Evidence for a peripheral set of action comes from this experiment. On the left panel is shown an experiment where cultured adipocytes were incubated with rimonabant, which increased the level of adiptonectin mRNA expression in a time-dependent fashion.

A longer term experiment is shown on the right looking at secreted adiptonectin in the media where cultures are treated for 4 days with rimonabant at these 2 concentrations. And you can see that this treatment results in a fairly marked increase in secreted adiptonectin.

So, these results show that rimonabant stimulates both adiptonectin mRNA expression and protein secretion and adiposed cells in culture clearly a system totally devoid of any CNS

influence.

So, what significance these find is demonstration of functional endocannabinoid system solely in a peripheral tissue. Moreover, the established role of adiptonectin on lipid metabolism and influence sensitivity provides a plausible biological basis for some of the clinical effects of rimonabant that we will hear about later.

[Slide.]

So, animal studies are useful for looking at mechanism, but can they inform us at all about outcome? in this experiment, Zucker rats defective in leptin were studied. The leptin deficiency leads to hyperphasia, obesity, dyslipidemia, type 2 diabetes, chronic renal failure culminating in an early death.

In these experiments, four groups were used. Obese rats, shown in red here, obese rats that were treated with rimonabant, shown in yellow, obese rats that were pair fed the same amount of calories as rimonabant to get an idea of caloric

restriction, and then, as a control, lean heterozygous animals which still have leptin.

In this experiment, treatment began at 12 weeks, shown here, so when they are 12 weeks of age, it corresponds to zero time in the experiment--and then just followed for the next year.

Starting at 9 months, here with the untreated obese rats, the early mortality becomes apparent. By 12 months, only 40 percent of the obese non-treated rats were alive, while about 80 percent of the obese-treated rats were still alive. Of note, none of the rimonabant treated rats over this long-term study had seizures.

Correspondingly, the rimonabant group showed an improvement versus a vehicle-treated obese rats in most metabolic primers related to glucose metabolism, lipids, inflammation and renal function.

Thus, rimonabant treatment in this rat model of obesity clearly improved survival.

[Slide.]

To sum up the preceding slides and studies, unfortunately, I didn't have time to present, this is a schematic view of a current understanding of the mechanism of action of rimonabant in decreasing body weight. Rimonabant decreases food intake both through central actions in hypothalamus and limbic forebrains, and by significant peripheral actions on sensory nerves innervating the gut.

It also acts on peripheral tissues including adipose tissue, liver, skeletal muscle and gut. The culmination of these actions is to decrease food intake and decrease fat storage. This dual mode of action both central and peripheral contributes to the observed metabolic effects of rimonabant including improved insulin resistance, increased HDL cholesterol, decreased triglycerides, increased glucose uptake and increased adiponectin.

[Slide.]

To summarize, the endocannabinoid system is an endogenous physiological system which

integrates nutrient intake, metabolism and energy storage.

At clinically relevant concentrations, rimonabant acts as a neutral antagonist of the CB1 receptor.

Chronic overactivation of endocannabinoid system is associated with obesity and type 2 diabetes. Rimonabant decreases body weight, in effect partially explained by reduced food intake and increases adiponectin, suggesting that it may have beneficial metabolic effects.

Chronic rimonabant treatment improves metabolic parameters and survival in a rat model of obesity.

Thus, the CB1 receptor antagonist is a valid therapeutic target for the treatment of obesity and type 2 diabetes. So, the next step was to assess if rimonabant would have the same beneficial effects in humans.

Thank you.

[Slide.]

DR. GURAL: Thank you, Dr. Mackie.

I would like to now introduce Dr. Pierre Rosenzweig, Vice President of Internal Medicine and Clinical Development with Sanofi-Aventis.

Dr. Rosenzweig will present on the medical need and the clinical efficacy of rimonabant.

Dr. Rosenzweig.

Medical Need and Clinical Efficacy of Rimonabant

DR. ROSENZWEIG: Good morning, Mr. Chairman, members of the Committee.

[Slide.]

After reviewing the medical need, I will present the efficacy results, first, as related to treatment of obesity, and then in type 2 diabetes.

Finally, I will present our understanding of the relationship between the metabolic improvement and the body weight loss.

[Slide.]

The epidemic of obesity is a major public health concern in the United States. It is estimated that over 30 percent of the people in the U.S. are obese and that over 60 percent of the total population is overweight or obese.

[Slide.]

In parallel to the epidemic of obesity, an increase in type 2 diabetes is also observed. Over 20 million U.S citizens are diabetics and, in fact, type 2 diabetes and obesity are closely associated. As shown, in a man with a BMI above 35, the related risk of diabetes compared to normal BMI is 42, and up to 93 for a woman.

[Slide.]

What is the perspective of the obese patient? First, obesity can be a painful condition on a daily basis. The quality of life of the obese patient is impaired due to social discrimination, restricted activity, low self esteem, and social isolation.

Second, obese patients are frequently suffering from comorbidities that are due to or aggravated by their obesities, such as sleep apnea or osteoarthritis, back pain, and infertility.

Finally, many obese patients are suffering from dyslipidemia, or cardiovascular disease, or are concerned about the risk of developing such

comorbidities.

[Slide.]

In reaction, many patients are trying to lose weight, but, unfortunately, most weight loss intervention fails. One reason for these failures is the unrealistic weight loss goals that patients set for themselves as shown by the investigation on the right.

Patients with an average body weight of 218 pounds dream of losing 38 percent of their body weight and would consider 17 percent loss, representing 38 pounds, as a disappointment.

Frustration and disappointment lead many of these patients to products not approved for weight loss. Of $1 billion spent annually on weight loss, 90 percent is for dietary and herbal supplements. Only 10 percent is for FDA-approved prescription drugs.

Bariatric surgery may be looked as a last resort. It is effective, yet carries risk and complications.

[Slide.]

Moving from surgery, what is the medical perspective? The goals for the medical treatment of obesity are more realistic than some of the patient expectations.

It has been demonstrated that a modest body weight loss of 5 to 10 percent is associated with significant improvement in key cardiovascular risk factors.

Moreover, this range of body weight loss of 5 to 10 percent also improves several comorbidities including sleep apnea, osteoarthritis, and also has a significant impact and beneficial on the quality of life of the obese patient.

[Slide.]

In addition, weight loss can prevent the development of type 2 diabetes. As is shown here from Diabetes Prevention Program study demonstrates that change in lifestyle that results in a 4 to 7 percent weight loss decrease the full year accumulative incidence of diabetes by 58 percent in overweight or obese patients with impaired glucose

intolerance that is pre-diabetes.

What are the therapeutic options?

The NIH guidelines for treatment of obesity is based on BMI and the presence of comorbidities, such as diabetes and hypertension. The guidelines state diet, physical activity, and behavioral therapy is the first-line therapy. Pharmacotherapy is to be started from BMI of 27 with comorbidity and in all patients from a BMI of 30.

Surgery is to be considered from a BMI of 35. The guidelines also state that since obesity is a chronic disease, short-term therapy is not useful. Rather, long-term therapy is needed always in conjunction with diet and physical activity.

[Slide.]f

What are the choices of FDA-approved drugs for the treatment of obesity? In addition to phentermine and other amphetamines approved in the '60s, which are still used today, physicians can prescribe either sibutramine or orlistat, the later being recently approved as OTC for the lower dosage

form.

[Slide.]

To sum up, obesity and type 2 diabetes is a growing epidemic.

Many patients use unapproved weight loss products and resort to bariatric surgery, effective but with risk and complications.

Modest 5 to 10 percent weight loss provides important medical benefits.

Pharmacotherapy is a recognized treatment from a BMI of 27 with comorbidities and from a BMI of 30.

[Slide.]

Moving now to the clinical development of rimonabant, I will start with the efficacy data supporting our proposed indication for the treatment of obesity.

[Slide.]

This shows the first pharmacodynamic study performed in humans. Twenty overweight patients were treated for one week with rimonabant 20 mg and placebo using a crossover design in a Phase I

Center.

As shown on the panel, they lost 1.5 pounds during this week of treatment on rimonabant over the placebo effect. In conjunction, there was a decrease in hunger as shown here, as well as a decrease in caloric intake as shown on the right.

[Slide.]

The next step was Phase II. A dose-ranging study was performed in 60 to 70 patients per group with 3 doses: 5, 10 and 20 mg compared to a placebo given for 16 weeks. All doses were significantly better than placebo and body weight loss and were well tolerated.

The effect of 5 and 10 mg were very similar, around 5 to 6 pound, as you can see on the slide, and 20 mg induces the greatest weight loss of 8.4 pounds as shown here.

Based on these results, the Phase III clinical program was designed with two doses, 5 and 20 mg.

[Slide.]

The Phase III RIO program, RIO meaning

rimonabant in obesity, comprised 4 pivotal studies conducted in over 6,600 patients, two, 2-year studies, RIO-North American and RIO-Europe, and two, 1-year studies, RIO-lipid and RIO- diabetes.

[Slide.]

RIO-North America and RIO-Europe were conducted in obese and overweight patients with comorbidities excluding diabetes. RIO-lipid included obese or overweight patients with untreated dyslipidemia excluding also diabetes.

RIO-diabetes was conducted in obese or overweight type 2 diabetes patients, not well controlled by metformin, also sulfonylurea.

The design of the 4 RIO studies was very consistent. The 4 RIO studies were randomized parallel, double-blind, placebo-controlled studies evaluating rimonabant 5 and 20 mg.

After screening, patients were prescribed a mild hypocaloric diet and exercise. These recommendations were continued throughout the study.

The placebo run-in period of 4 weeks

preceded the randomizations. As I said, both RIO-lipids and RIO-diabetes were one-year trials.

[Slide.]

RIO-Europe, now shown, had a duration of 2 years.

[Slide.]

RIO-North America had also a duration of 2 years, but with re-randomization scheme after the first year of treatment when the patients on Active were re-randomized either to stay on their active treatment or switch to placebo.

[Slide.]

The baseline demographics are presented in this table. The patients were in their mid-40s in all studies except in RIO-diabetes where they were in their mid-50s.

Most of the patients were females in RIO-North America and RIO-Europe, but the gender ratio was more balanced in RIO-lipids and RIO-diabetes.

The weight range varied from 208 to 230 pounds. The BMI was high across all studies

particularly in RIO-North America. All together, these 5 contained over 1,300 patients with BMI over 40.

The elevated weight circumference, high prevalence of abdominal obesity and, as expected, there was a high rate of co-morbidities as seen on the next slide.

[Slide.]

This shows the baseline cardiovascular and metabolic risk factor of the RIO Population. The most frequent metabolic abnormality was dyslipidemia, either high triglycerides or lower HDL cholesterol or high LDL, or a combination of these.

In RIO-lipids, dyslipidemia was presented in 100 percent of the patients and not treated per protocol.

In RIO-diabetes, more than 60 percent of the patients were dyslipidemic, were on a drug and generally a statin. By protocol, all patients of RIO-diabetes were diabetes. The pre-diabetic patients shown here represented a quarter of the

population of the three other studies.

Hypertension was present in 30 to 60 percent of the population and was frequently treated as shown here.

At total, 90 percent of the RIO population qualified for the trial had at least one co-morbidity. Thus, the population of the RIO trial was an at-risk obese population.

The completer rates were those expected in long-term studies in obese patients with overall no difference between the rimonabant 20 mg and the placebo group. More patients discontinued the study for subject request in the placebo group, possibly because their expectation of weight loss were not met, as just discussed.

More patients discontinue rimonabant 20 mg for adverse events, and this will be further discussed in the safety presentation.

[Slide.]

The results of the 4 RIO studies are shown the same way on this slide and on the next one.

The top part represent the

placebo-adjusted results using the ITT:LOCF approach, which was the primary analysis of all trials. At one year the placebo adjusted weight loss was rimonabant 20 mg was 10.5 pounds and was identical in RIO-North America and RIO-Europe presented here.

[Slide.]

Coming to the curves which represent the observed case, the time course and extent of body weight loss was very similar in the two studies, leading to a body weight loss for the completers of 19 pounds after one year of treatment with rimonabant 20 mg.

In addition to these 19 pounds, can consider adding the 4 to 5 pounds lost during the run-in period that I just point out, thus reaching close to 25 pounds at total as a mean body weight loss for the completer during the whole procedure.

RIO-lipids show now nearly identical results with a placebo-adjusted weight loss of 12 pounds in the primary ITT:LOCF analysis. It is notoriously difficult to achieve any significant

weight loss in type 2 diabetes patients.

It may have to do with less exercise, concomitant antidiabetic treatment that puts on weight or other mechanisms. It is therefore not surprising that the weight loss with rimonabant in this population is somewhat less than in the non-diabetic population, but still reaching 8.6 pounds in the ITT:LOCF and to adjusted data, and 13.5 pounds from baseline for completers.

[Slide.]

Here we see the placebo-adjusted weight and waist loss of the 4 RIO studies, and these highlight the consistency of the efficacy of rimonabant 20 mg and weight and waist loss across the study.

The results on the waist to conference parallel the results of the weight loss and points out the benefits of rimonabant for the treatment of abdominal obesity.

As for guidelines for treatment of obesity, another important analysis was to look at the rate of patients who have a good response of 5

or 10 percent weight loss or more of their baseline weight.

At both thresholds, the respondent rate was significantly higher with rimonabant 20 mg compared to placebo in all studies. The 5 percent threshold data are presented in the briefing package.

The 10 percent responders presented.

[Slide.]

As we saw in the three non-diabetic population, RIO-North American, RIO-Europe and RIO-lipids, rimonabant 20 mg tripled the effect of diet and exercise alone.

For reasons already outlined, the rate of responders in diabetes population are lower, but still there was an 8-fold increase in the respond rate with rimonabant compared to placebo as shown here.

[Slide.]

Let's now move to the metabolic effects of rimonabant. As we saw in the baseline characteristics, low HDL and elevated TG is a

frequent finding in obese and overweight patients.

Here are the results of RIO-lipid, the study with untreated dyslipidemic patients.

As shown on the top left, using the ITT-LOCF, there was an increase in HDL of 8 percent over placebo and here, on the observed case of 23 percent over baseline in the completers.

On the right panel, rimonabant 20 mg induced a reduction of triglycerides of 12 percent over placebo in the ITT-LOCF analogies and of 15 percent reduction versus baseline in the completer population.

[Slide.]

Here we see again the consistency of the effect of rimonabant 20 mg represented as placebo adjusted data across the four RIO studies. HDL rate by 8 percent across the four studies, triglycerides decreased from 12 to 16 percent across the four studies.

Non-HDL cholesterol decreased by 2 to 4 percent across the four studies and there was no effect on the LDL cholesterol as shown here.

These results were observed in a consistent manner in patients with or without diabetes and in patients with or without treated dyslipidemia.

[Slide.]

The durability of the efficacy of rimonabant was an important objective of the RIO program. This is why RIO- Europe and RIO-North America were designed as two-year trials.

In RIO-Europe, patients maintained a weight loss at 2 years of 9.3 pounds adjusted to placebo and 16 pounds compared to baseline.

[Slide.]

The durability of the effect was replicated in the RIO-North America study. In this particular study, I remind you that patients on active treatment were re-randomized after one year either to stay on their rimonabant treatment or to be switched to placebo for the second year.

As you saw in RIO-Europe, the patients who stayed on rimonabant for 20 mg maintained their initial weight loss up to 2 years. When patients

on active were switched to placebo, they progressively regained body weight without reaching their baseline body weight after one year on placebo.

This was an expected finding, this was expected.

[Slide.]

As with any chronic disease, when treatment is stopped, the disease reappears. When rimonabant was stopped, patients started to regain body weight.

[Slide.]

Let's now move to the efficacy data supporting our second proposed indication of glycemic control in type 2 diabetes.

RIO-diabetes studied two important groups of diabetics, though still not able to achieve adequate control when treated by metformin or by sulfonylurea as monotherapy.

SERENADE was conducted in a different diabetic population--that is, the treatment-naive patients. The design of the two studies shown here

were different. RIO-Diabetes was a 1-year trial with a placebo run-in, as you heard, and 2 doses of rimonabant versus placebo.

SERENADE was a 6-month trial without run-in and looking at rimonabant 20 mg versus placebo.

The baseline demographics of the diabetic patients are quite similar across studies. Patients in their mid-50s, race, gender ratio, body weight and BMI are the same. A1C was higher in SERENADE, but there was a run-in in Rio- diabetes where patients lost a little bit of A1C.

[Slide.]

Finally, as expected, for a treatment-naive population, the time since diabetes diagnosis was shorter in SERENADE.

RIO-Diabetes studied patients not well controlled by metformin, also sulfonylurea. The A1C change over time is shown here in the central panel. The effect of lifestyle changes were transient in the placebo and in the 5 mg group. Yet, there was a continuous decrease in A1C,

reaching 0.7 percent decrease in the ITT-LOCF on placebo adjusted data.

This improvement is confirmed by a reduction of the fasting glucose as shown on the right. At the same time, weight decreased as shown on the left. This is contrary to what is usually seen when, for example, sulfonylurea or glitazone is added to metformin. Therefore rimonabant is an oral diabetic therapy that has achieved significant glycemic control while also controlling or reducing weight.

Patients including the RIO-diabetes trial were stratified according to the background therapy, making this study as a type 2 studies in 1. Those will present a large sample of patients which could have been studied in two different studies. Here, the advantage is that patients in both strata were studied under the very same conditions. The same improvements were seen in both strata, for A1C and for weight loss.

[Slide.]

Rimonabant was equally and significantly

effective in both situations. SERENADE studied patients not previously on drug. There was continuously a decrease of 0.5 percent over placebo after 6 months of treatment. This improved glucose control is confirmed by a parallel reduction of the fasting glucose.

At the same time, weight decreased by 15 pounds versus baseline, and by 8 pounds over placebo. Thus, rimonabant is a oral antidiabetic has achieved significant glycemic control in treatment-naive patients while also reducing weight.

[Slide.]

As you heard from Dr. Mackie, rimonabant increases adiponectin in vitro production by adipocytes. During the SERENADE study, and that is shown here, adiponectin increased significantly in type 2 diabetes patients on rimonabant as compared to placebo. This increase in adiponectin is an interesting finding in light of its recognized antidiabetic and antiandrogenic properties.

[Slide.]

Let's now move to the analysis of the relationship between the metabolic improvement and the body weight loss.

From a patient and a physician perspective, the nature of this relationship may be not a critical matter since it is benefit of the treatment that matters and not whether it is fully explained by weight loss alone or not.

[Slide.]

We use the linear regression methodology to explore the relationship between metabolic effect and body weight loss. This was an exploratory prespecified method in the statistical analysis plan. Let me first explain the model.

The relationship of a given metabolic parameter with weight loss in the placebo group is estimated using linear regression. If the metabolic effect is fully explained by the weight loss, then, the same relationship will hold in the active group and the placebo group, and the two regression line would be a line as shown now.

Then, whatever treatment group, placebo or

active, a given weight loss respond to a single given improvement in HDL. Otherwise, as shown now on the right, the two regression lines are no more aligned but parallel. Then, the difference is an indication that the effect could not be fully explained by the weight loss alone.

[Slide.]

Let's now consider the linear regression model applied to HDL cholesterol in any of the RIO trials.

As shown on the left, since the regression lines for HDL are parallel, the improvement in HDL for the same weight loss is better on rimonabant as compared to placebo. For A1C represented on the right, the two regression lines are also different. Thus, for the same weight loss improvement in A1C is better on rimonabant as compared to placebo.

[Slide.]

Before concluding, I would like to share with you the results of the quality of life in the RIO trial. We used two instruments. In the SF-36 scale, the physical function improved on the

rimonabant while the score of the mental has decreased, which was explained by the subgroup of patients with mood disorders.

[Slide.]

We also used an obesity-specific validated instrument called IWQOL-Lite. This covered the domain of physical function, self-esteem, sexual life, public distress and work. Patients on rimonabant 20 mg reported significantly greater improvement in all domains of quality of life compared to patients on placebo.

[Slide.]

Finally, what is the appropriate patient in the view of the benefits of rimonabant?

It is adult patients ready to comply with diet and exercise, committed to a long-term treatment with a base or overweight with 1 or more of the following risk factors: hypertension, abdominal obesity, or dyslipidemia; or, who is an overweight or obese type 2 diabetes not well controlled by metformin or sulfonylurea, who is at risk to gain weight to attain some improvement in

his glucose control.

[Slide.]

It is now time to sum up. Rimonabant 20 mg induced a significant reduction in weight and waist, as well as a significant improvement in HDL cholesterol and triglyceride levels. These effects were maintained up to 2 years of treatment.

Rimonabant 20 mg significantly improved A1C and body weight in type 2 diabetes with different background therapies and in treatment-naive patients.

The metabolic improvement cannot be fully explained by body weight loss alone. With the obesity specific quality of life measurement tool, all domains of quality of life were significantly improved.

Importantly, the efficacy data were consistent in 5 clinical trials. Thus, the data support the proposed indication of rimonabant in the treatment of obesity and improvement of glucose control in type 2 diabetes.

I thank you for your attention.

DR. GURAL: Thank you, Dr. Rosenzweig.

I would now like to introduce Dr. Paul Chew, who is the Vice President for Metabolism, Diabetes and Thrombosis in Clinical Development for Sanofi-Aventis.

Dr. Chew.

Clinical Safety of Rimonabant

DR. CHEW: Thank you, Dr. Gural.

Good morning, Mr. Chairman, members of the Committee, ladies and gentlemen.

I am here this morning to present to you the safety experience with rimonabant in the clinical program. My name is Paul Chew and I head the Clinical Development for Metabolism, Diabetes and Thrombosis at Sanofi-Aventis.

[Slide.]

This presentation will focus on the Phase III program and specifically the obesity and type 2 diabetes programs as these are the requested indications.

Given our limited time, I will refer the Committee to the briefing book for data from the

Phase I and Phase II studies. We will begin the overall safety profile of rimonabant and then follow with a special focus on adverse events of interest including data from the completed and ongoing trials.

[Slide.]

These figures were reviewed earlier by Dr. Gural, so I will summarize them here.

We have over 15,000 individuals exposed to rimonabant as of March with 1190 in Phase I and 1008 in Phase II.

The Phase II program was conducted in various populations including obesity, smoking cessation, prevention of alcohol relapse and in schizophrenia. The far greater part of the exposure has been in Phase III where almost 13,000 patients have been enrolled with 7,447 with 20 mg from 1 day to 2 years at 20 mg. We have 3,478 patient years.

[Slide.]

During the conduct of Phase III, adverse events were routinely collected via open

questioning. The safety analysis followed guidelines from the International Conference on Harmonization, a project that achieves greater harmonization in the interpretation and application of technical guidelines and requirements for product registration.

Safety analyses were performed in these pools. Today's discussion will focus on the obesity and diabetes indications, and we will include the other population for very rare events, such as seizures or suicidality.

[Slide.]

The number of patients exposed for completed Phase III studies for an obesity and diabetes is shown here. Please note that RIO-diabetes was conducted as part of the obesity program. But SERENADE, its companion study, was analyzed also with the diabetes population.

As a cue in the future slides, you will see 2474 under the placebo group as a grouping for these 7 studies and 488 as a cue for the type 2 diabetes studies.

To obtain the most complete and transparent accounting of patient exposure, the sponsor counted patient exposure based on the treatment received.

For RIO-North America, as Dr. Rosenzweig had indicated, there was a re-randomization from 20 mg to placebo or maintaining 20 mg with the beginning of the second year. The same with 5 mg as well.

So, we retained the exposure after treatment received. So, patients who were on 20 mg for 2 years counted for the 20 mg exposure. Those who were randomized to a placebo on the second year were counted on the first year and 20 mg second year on placebo.

Moreover, our analyses comprised the 7 studies. These accounting conventions differ from FDA where the safety analysis included only the 4 RIO studies and moreover, re-randomized patients were not counted in the second year if they had been re-randomized downward.

The re-randomized patients who were

maintained in their analysis were those who maintained the same dose throughout and, if they were re-randomized downward, only the first year was kept.

It is important to articulate these differences now, so that you will be able to understand better the subsequent analyses I will present.

[Slide.]

This is the smoking program which will not be discussed today. But here are the total exposure listed here again in patients exposed.

[Slide.]

As of March 1st, there were 11 ongoing clinical studies with 14,280 additional patients included. Of course, these studies are blinded, but with a 1 to 1 randomization to 20 mg or placebo. This provides approximately 7,855 patient years.

As discussed earlier by Dr. Gural in the introduction, these ongoing clinical studies are focusing on patients at increased risk for

cardiovascular outcomes.

[Slide.]

We will first review the overall safety profile in obese and diabetes and the events that led to premature discontinuation.

Adverse events were collected, as I said, by investigators in an open questioning fashion at each visit, and by "open questioning," I mean a non-directed approach. Specifically, in light of the presentation by Dr. Posner, suicidality was not prospectively obtained. But I will say more on this later.

[Slide.]

Shown here are the common adverse events in the obesity studies occurring in at least 2 percent of rimonabant-treated patients and more than 1 percent over placebo.

They were GI, nervous system and psychiatric disorders. The most common GI event was nausea, occurring in 13.6 percent versus 4.7 percent, with a difference of about 9 percent between the groups, compared with approximately a 2

percent difference with diarrhea and vomiting.

For nervous system disorders, dizziness was the most common, with approximately a 3.2 percent difference between the groups.

For psychiatric disorders shown here, anxiety was 5.9 versus 2.1, and, with insomnia, mood alterations, and depressive disorders as shown.

[Slide.]

In the diabetes population, the events were similar overall, as you can see, however, there were events of hypoglycemia and muscle spasms that were more associated with the diabetes population and, relative to the obesity population, there was a somewhat greater incidence of paresthesias.

Almost all of the hypoglycemic episodes occurred in the RIO-diabetes program, a trial with background sulfonylurea or metformin and, in that study, hypoglycemia was reported with both background therapies.

In SERENADE, a study with the