FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

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Versailles Ballroom I-III
Holiday Inn Bethesda
8120 Wisconsin Avenue
Bethesda, Maryland

FRIEDMAN & ASSOCIATES, COURT REPORTERS
11923 Parklawn Drive, Suite 203
Rockville, MD 20852
(301) 881-8132

IN ATTENDANCE:

CAROL A. TAMMINGA, M.D., Chairperson
Professor, Department of Psychiatry
University of Maryland at Baltimore
Maryland Psychiatric Research Center
Spring Grove Hospital, White Building
Baltimore, Maryland 21228

SANDRA TITUS, Ph.D., Executive Secretary
Food and Drug Administration
Center for Drug Evaluation and Research
HFD-021
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857

EDWIN H. COOK, JR., M.D.
Director, Laboratory of Developmental Neuroscience
Department of Psychiatry, MC3077
University of Chicago
5841 South Maryland Avenue
Chicago, Illinois 60637

ABBY J. FYER, M.D.
Anxiety Disorders Clinic
New York State Psychiatric Institute
College of Physicians and Surgeons
Columbia University
722 West 168th Street, Unit 82
New York, New York 10032

TANA A. GRADY-WELIKY, M.D.
Associate Professor of Psychiatry
University of Rochester Medical Center
300 Crittenden Boulevard
Rochester, New York 14642

ROBERT M. HAMER, Ph.D.
Associate Professor
Department of Psychiatry
R.W. Johnson Medical School, D-331 UBHC
University of Medicine and Dentistry of New Jersey
Piscataway, New Jersey 08854

IN ATTENDANCE:

RICHARD P. MALONE, M.D.
Associate Professor
Eastern Pennsylvania Psychiatric Institute
MCP Hanneman University School of Medicine
3200 Henry Avenue
Philadelphia, Pennsylvania 19129

DAN A. OREN, M.D.
Associate Professor of Psychiatry
Psychiatric Department
Yale University
9050 Campbell Avenue, Mail Stop 116A
West Haven, Connecticut 06516

IRENE E. ORTIZ, M.D.
Assistant Professor of Psychiatry
Veterans Administration Medical Center (116C)
1501 San Pedro S.E.
Albuquerque, New Mexico 87108

MATTHEW V. RUDORFER, M.D.
Associate Director of Treatment Research
National Institute of Mental Health
Division of Services and Intervention Research
6001 Executive Boulevard, Room 7163, MSC 9635
Rockville, Maryland 20892

ANDREW WINOKUR, M.D., Ph.D.
Director of Psychopharmacology
Department of Psychiatry-NTRTC
University of Connecticut Health Center
263 Farmington Avenue, MC 1517
Farmington, Connecticut 06030-1517

IN ATTENDANCE:

Voting Consultants (Cardiology)

ROBERT CALIFF, M.D.
Professor of Medicine
Director, Duke Clinical Research Center
2024 West Main Street, Box 31123
Durham, North Carolina 27707

JOANN LINDENFELD, M.D.
Professor of Medicine
Division of Cardiology
4200 East Ninth Avenue, B-130
Denver, Colorado 80282

Voting Consultant (Psychiatry)

STEPHEN MARDER, M.D.
Chief, Psychiatry Service
West Los Angeles Veterans Affairs Medical Center
Psychiatry Service (116A)
11301 Wilshire Boulevard
Los Angeles, California 90072

Nonvoting Consultant (Cardiology)

ARTHUR MOSS, M.D.
University of Rochester
P.O. Box 653
Rochester, New York 14642

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P R O C E E D I N G S (8:10 a.m.)

DR. TAMMINGA: I'd like to call this meeting to order. This is a meeting of the Psychopharmacological Drugs Advisory Committee. The topic of the meeting is NDA 20-825, ziprasidone hydrochloride, as presented by Pfizer.

What I'd like to do first is to welcome the committee to discuss the material that will be presented to us over the course of the day, and I'd like the committee to introduce themselves, please, and to say your name and your affiliation.

Perhaps we could start with you at the end of the table, Dr. Moss.

DR. MOSS: I'm Dr. Moss, Professor of Medicine and Cardiology at the University of Rochester School of Medicine and Dentistry. I've had a longstanding interest in long QT syndrome, both primary genetic and drug-induced.

DR. CALIFF: I'm Rob Califf. I'm a cardiologist at Duke University and director of the Duke Clinical Research Institute.

DR. GRADY-WELIKY: Tana Grady-Weliky, Associate Professor of Psychiatry at the University of Rochester School of Medicine and Dentistry.

DR. OREN: Dan Oren at Yale University and the Department of Veterans Affairs. I'm not representing the Department of Veterans Affairs.

DR. ORTIZ: Irene Ortiz. I'm with the University of New Mexico and the Albuquerque VA.

DR. FYER: Abby Fyer from Columbia University.

DR. HAMER: I'm Bob Hamer from Psychiatry and Biometrics at UMDNJ.

DR. MARDER: I'm Steve Marder. I'm from the Department of Psychiatry at the UCLA School of Medicine and the VA Greater Los Angeles Health Care System.

DR. LINDENFELD: I'm JoAnn Lindenfeld from the University of Colorado. I'm a cardiologist.

DR. RUDORFER: I'm Matthew Rudorfer, Associate Director for Treatment Research, Division of Services and Intervention Research, at the National Institute of Mental Health.

DR. TITUS: I'm Sandy Titus. I am with the FDA and the Advisory Committee staff, and I'm the Executive Secretary for this committee.

DR. COOK: Ed Cook from Departments of Psychiatry, Pediatrics, and Committee on Clinical Pharmacology at the University of Chicago.

DR. WINOKUR: Andy Winokur, Department of Psychiatry, University of Connecticut Health Center.

DR. MALONE: Richard Malone, Department of Psychiatry, MCP Hanneman University.

DR. KORVICK: Joyce Korvick, medical officer,

infectious disease specialist from Division of Special Pathogens, FDA.

DR. CHOWDHURY: I'm Badrul Chowdhury. I'm with the Division of Pulmonary and Allergy Drug Products, FDA.

DR. THROCKMORTON: Doug Throckmorton. I'm with the Division of Cardiorenal Drug Products, Food and Drug Administration.

DR. DUBITSKY: Greg Dubitsky. I'm from the Division of Neuropharmacological Drug Products at the FDA.

DR. LAUGHREN: Tom Laughren, Neuropharm Division at FDA.

DR. KATZ: Russ Katz, Neuropharm, FDA.

DR. TAMMINGA: And I'm Carol Tamminga, and I'm the Chair of this committee, and I'm from the University of Maryland, the Maryland Psychiatric Research Center.

Now our Executive Secretary, Sandra Titus, will read the conflicts of interest of the committee.

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

Based on the submitted agenda and the information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no

potential for a conflict of interest at this meeting with the following exceptions. In accordance with 18 USC Section 208(b), full waivers have been granted to Dr. Guardia Banister, Dr. Robert Hamer, Dr. Stephen Marder, and Dr. Andrew Winokur.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, located in Room 12A-30 of the Parklawn Building.

In addition, we would like to disclose that Drs. Robert Califf, Carol Tamminga, and Stephen Marder have interests which do not constitute financial interests within the meaning of 18 USC Section 208, but which could create the appearance of a conflict. The agency has determined, notwithstanding these interests, that the interest of the government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Dr. Tamminga and Dr. Marder may participate fully in today's discussions and vote concerning Zeldox. Dr. Califf may participate in the discussions. However, he is excluded from any vote concerning Zeldox.

With respect to FDA's invited guest, Dr. Arthur Moss has reported an interest which we believe should be made public in order to allow the participants to

objectively evaluate his comments. Dr. Moss has been asked to consult with Eli Lilly on Zyprexa regarding QT wave prolongation. He will receive nominal compensation for his consulting.

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 such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask 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.

DR. TAMMINGA: We'll start our meeting with a welcome by Dr. Russell Katz, who is the Director of the Neuropsychopharmacology Drug Products.

DR. KATZ: Thank you. I really just want to be very, very brief and welcome you back again. We have a very long program, as you can see.

PARTICIPANT: We can't hear.

DR. KATZ: I gather you still can't hear me. Is that correct?

Anything now?

PARTICIPANT: Getting better.

DR. KATZ: Better. Anyway, I just really wanted to welcome you. We brought you back again to deal with an interesting and a particularly thorny problem, in particular the meaning of a particular degree of QTc prolongation. We know that the range of opinion on these matters is wide, ranging from folks who believe that any prolongation is problematic to those who feel that maybe there's a threshold below which we don't have to really worry too much, and I'm sure the range of opinion varies beyond that as well.

We also know that the definitive evidence that we would like to have to be able to address the clinical meaning of this is not available, so it's in that context that we come to you for your comments and your advice and guidance on what you think we ought to do in this particular case.

Having said that, I'd just like to welcome folks again. In particular, I'd like to welcome our invited consultants who we've asked here to add their particular expertise to the discussion, Drs. Califf, Lindenfeld, Marder, and Moss; and in particular also, our FDA colleagues from other divisions who are here to present to you how the agency has dealt with this problem across a wide span of drug products.

In addition, we have five new members of the

committee we'd like to welcome in particular. Hopefully, this will be the beginning of a long and fruitful relationship with the Division.

With that, I will turn it over to Tom Laughren, who will give the introductory remarks.

DR. TAMMINGA: We've been informed that they still can't hear in the back. So Sandra Titus has asked us to wait a minute.

If I could have your attention, the problem is actually -- it's determined that the problem is with these table microphones, but not with the podium microphones. So that gives us license to move ahead with Dr. Thomas Laughren's presentation, who is the team leader for the Psychiatric Drug Products Group, who will go to the lectern and present the historical review and issues for today's discussion.

Dr. Laughren?

DR. LAUGHREN: I'd like to also welcome everyone to the meeting today. My comments are also going to be fairly brief. Basically, what I'd like to do is to give a little bit of an historical perspective so you can understand how it is we got here today.

If I could have the first slide?

This NDA was submitted in March of 1997, and there was a non-approval letter sent in June of 1998. I'm

reading directly from that letter. The non-approval action was based on "the judgment that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular arrhythmias that is not outweighed by a demonstrated and sufficient advantage of ziprasidone over already marketed antipsychotic drug products." So that was the basis for the non-approval action.

If I could have the next slide?

That judgment was based on findings in the short-term, fixed-dose, placebo-controlled Phase II/III studies of a dose-related tendency for ziprasidone to increase the QTc. The size of that QTc increase was judged to be, compared to placebo, about 10 milliseconds in the 160 milligram per day dose, which was the top recommended dose.

An additional concern at that time was that that 10 millisecond increase may be an underestimate of the effect given the likelihood that the EKGs in those studies were probably obtained at trough, or at some time other than Cmax.

Next slide, please.

Now, the letter went on to talk a little bit about the issue of the extent of the prolongation and expressed the view that the size of the QTc increase is probably a factor in determining the degree of risk of

ventricular arrhythmias. Again, I'm reading directly from that letter. It suggested that "we would find QTc prolongation at maximum blood levels in the 5-10 millisecond range, with adequate assurances that there are very few outliers and that there are no factors that lead to substantially greater values in individuals (such as drug-drug interactions) sufficiently reassuring, in the absence of contrary evidence, to support the approval of a new antipsychotic such as ziprasidone."

Next slide, please.

The letter went on to recommend that the sponsor do an additional study to determine the QTc effect of ziprasidone at peak plasma concentrations in comparison with other atypical antipsychotics and with several standard antipsychotics.

Next slide, please.

Over the next few months, we worked with the company to design a study. That study was Study 054. It has been completed, and you will hear a lot more about that today. But basically, that is a study that looks at ziprasidone at its optimal dose in a head-to-head comparison with other antipsychotics at their optimal doses. The other drugs include two older drugs, haloperidol and thioridazine, and the three newer antipsychotics, olanzapine, risperidone, and quetiapine.

The EKGs in this study were done at the estimated Tmax for each drug. So the timing was worked out exactly for each drug. There was also a phase in Study 054 adding metabolic inhibitors to determine the additive effects on the QTc under the conditions of maximal inhibition of clearance of each of those drugs.

Next slide, please.

Basically, the point I want to make in this slide -- again, you're going to hear a lot more about the details of this study -- is that we are in agreement with the company on the basic outcome, and that is the positioning of ziprasidone relative to the other drugs in terms of QT prolongation. That is basically that ziprasidone had an approximately 10 millisecond greater effect than that observed with four of the other drugs, with haloperidol and the three atypical antipsychotics, and an approximately 10 millisecond lesser effect than thioridazine. So it was right in the middle.

What was not clear to us was how to interpret the apparent increase from baseline for the other drugs, for haloperidol and the three atypicals. There was no placebo in the study for comparison. The reason that we tend to perhaps doubt that the change represents a real change for the other drugs is that in many other studies in which haloperidol has been the active control, we've seen

no difference at that same dose between haloperidol and placebo on the QT. But this is an issue that I think we'll have some additional discussion about over the course of the day.

Next slide, please.

Other areas of agreement. We are in agreement with the company that they have demonstrated that ziprasidone has an antipsychotic effect. This is based on both the short-term fixed-dose studies, and also one longer-term study. However, it's important to note that there's no evidence from these trials that ziprasidone has a superior antipsychotic efficacy to these other drugs.

We also are in agreement that the other risks associated with ziprasidone can be handled in labeling and would not be a barrier to approvability.

Next slide, please.

I want to comment briefly on the consult from the Cardiorenal Division. We asked them to review Study 054 and its findings, and they did. They reached a conclusion that the greater QTc effect for ziprasidone predicts excess risk of potentially fatal ventricular arrhythmias, and they went on to recommend that without a demonstrated greater benefit, they would recommend either non-approval of this application or a second-line status.

Now, I want to point out that clearly that's

one of several conclusions one might reach from that study. The Division and the Office have not yet reached a conclusion on this matter, and it's precisely for that reason that we're bringing it to you to get your advice.

Next slide, please.

The program for today's meeting will, first of all, include a presentation by Pfizer. They're going to give a brief overview of the overall safety and efficacy of ziprasidone, clearly with an emphasis on the QTc findings. FDA's presentation will follow. That will focus exclusively on the QTc issue. What we're going to try to do is review the CDER experience with drugs that have this problem, and then you'll have a chance to discuss those issues.

Is there a final slide? Okay, go ahead.

Our questions for you will be the questions that we always ask about the overall safety and efficacy of the application. In particular, of course, here we're concerned about the relevance of the 10 millisecond prolongation in the QTc observed for ziprasidone and not seen for several other drugs in Study 054 on the approvability decision for this drug.

I'm going to stop at this point, but I will be returning just before the FDA presentation to talk in a little bit more detail about what we hope to accomplish in

the FDA presentation, and also I want to talk in more detail about some additional questions beyond the two general questions that we'd like the committee to address. I'm going to stop at this point.

DR. TAMMINGA: Thank you, Dr. Laughren.

Now we will begin the Pfizer presentation, and the Pfizer presentation will begin with Dr. Ed Harrigan, who is the Executive Director of Pfizer Global R&D, CNS Therapeutics, who will talk about the safety and efficacy of Zeldox.

DR. HARRIGAN: Thank you and good morning, Dr. Laughren, Dr. Katz, Dr. Tamminga, members of the committee, and FDA staff. My name is Ed Harrigan, and I'll be introducing the sponsor's presentation today.

But before beginning the presentation, I'd like to introduce to the committee the consultants who have helped us to understand the issues with ziprasidone and who were able to be here today to help us to address your questions.

What follows on the next slide is an outline of our presentation, which we've divided into six sections. As Dr. Laughren has pointed out, the Division and the sponsor agree that the efficacy of ziprasidone has been demonstrated in the NDA. So I'll spend more time reviewing the effect of ziprasidone upon the ECG. To provide some

context for judging the clinical significance of this effect, I will contrast it with terfenadine and cisapride. I'll then review the clinical safety experience to date with ziprasidone and close with a review of the favorable effects of ziprasidone compared to other antipsychotics on three well-established cardiovascular risk factors: namely, body weight, lipids, and diabetes.

Before beginning the review of the benefit/risk of ziprasidone, Dr. Daniel Casey of the Oregon Health Sciences University and Portland VA Medical Center will describe for the committee the unmet medical need which is currently recognized by patients, caregivers, and prescribers who are confronted with this illness.

Dr. Casey?

DR. CASEY: Thank you, Dr. Harrigan. I appreciate the opportunity to meet with the committee today and the agency to briefly provide an overview of the key issues about the epidemiology and unmet treatment needs for schizophrenia.

There are three points I'd like to make about the epidemiology. First, that schizophrenia is a highly prevalent disorder. It occurs in 1 percent of the population throughout the world. Thus, approximately 3 million people in the United States suffer from this illness. It accounts for 25 percent of all hospital bed

days in the U.S.

Secondly, this is a difficult and challenging disease to treat. Twenty to 30 percent of our patients respond poorly or not at all to our current pharmacopeia for the treatment of this illness. We have distressingly high relapse rates. Twenty percent of patients will relapse while they continue to take their medicine, and for those who discontinue their medicine, 70 percent will relapse within one year.

We also have disturbingly high non-compliance rates. Forty percent of patients are not taking their medicines as prescribed at six months. Finally, we have adverse effects that are affecting compliance and outcome. The old drugs, called the typical antipsychotic agents, primarily had neurological side effects affecting the motor system, and the new compounds bring an additional side effect profile, affecting weight and metabolic parameters.

Finally, the third point is that schizophrenia is a highly lethal illness, and this is much under-appreciated. Patients with schizophrenia die at excess rates of natural diseases such as cardiovascular illness, and they die at excess rates from unnatural causes such as suicide, where 10 percent of patients with schizophrenia commit suicide. So it is clearly a highly lethal illness.

The typical neuroleptic drugs -- haloperidol or

Haldol, chlorpromazine, thorazine, thioridazine, Mellaril -- have been the mainstay of treatment for the past several decades. Their efficacy was better in treating the positive symptoms of schizophrenia -- hallucinations, delusions, disorganized thinking -- and they were less effective in treating the negative symptoms of withdrawal, apathy, and anergia.

Additionally, they had the neurological syndromes as adverse effects that were very common and intolerable for many patients. The extrapyramidal syndromes of akathisia, Parkinsonism and dystonia occurred in 50 to 100 percent of patients, particularly in the elderly and high-risk groups, requiring additional medicines as antidotes, and those medicines had their own complications. Tardive dyskinesia, a potentially irreversible neurological syndrome of choreoathetoid dyskinesias occurred on average in 20 percent of patients, and occurred in up to 70 percent of high-risk patients such as the elderly. So the typical drugs clearly had limitations.

Over the past few years, we've had the advent of the atypical antipsychotic drugs, as they've been come to be known. They have become first-line treatments in most medical settings, and that's because of improved efficacy in positive symptoms, negative symptoms, affective

symptoms, and improved treatment of the cognitive disabilities that are associated with schizophrenia.

They also have an adverse effect profile that's improved by decreasing the neurological syndromes of EPS and TD, but they do bring additional challenges in terms of adverse effects. So limitations clearly do remain. The new drugs bring increased emphasis and focus on the issues of weight gain and the consequent metabolic abnormalities associated with weight gain. It's not uncommon for our patients to gain 10 to 20 pounds within the first year of treatment, and it's fairly common for patients to gain 30 to 40, sometimes 50 pounds within a year or more with an extended treatment. This weight gain is turning out to affect compliance for many patients, so we're seeing that our new drugs that have brought many opportunities and improvements also bring new challenges.

The weight gain issue can be summarized on the slide from a meta-analysis by Dr. Allison, published in the American Journal of Psychiatry last year that looked at increases in weight during the first 10 weeks of treatment. The color code for understanding this graph is that the blue bars represent the typical neuroleptic drugs, and the individual colors represent the atypical drugs.

Our traditional neuroleptics are typical agents such as chlorpromazine or thorazine do show that there was

a weight gain profile to some of the compounds. Even haloperidol had some weight gain. But as you look at this, you see that the atypical antipsychotic drugs tend to cluster toward the higher end of the weight gain continuum, and this is during the first 10 weeks of treatment, and this weight tends to increase or stay at this level during long-term treatment.

In contrast, ziprasidone, the compound of interest today, is weight neutral during the first 10 weeks of treatment, and as you'll hear from Dr. Harrigan, during longer-term treatment as well.

In any consideration of the long-term treatment of a chronic illness like schizophrenia, we have to look at other comorbid illnesses and risk factors. So we look at both the risk factor prevalence and our ability to intervene in risk factors of comorbid illnesses. Patients with schizophrenia are clearly overweight. When one looks at the body mass index or BMI, and set the cutoff at 27, clearly in the overweight category, 42 percent of patients with schizophrenia are overweight, compared to 25 percent of the general population. Smoking is alarmingly high in patients with schizophrenia. Seventy to 90 percent of patients with this disorder smoke cigarettes, versus 25 percent in the general population.

When we turn to our ability to intervene with

these risk factors, it's also an important consideration to recognize that patients with schizophrenia do less well with our proposed interventions. We have poor compliance rates, in part due to the impaired insight in people with schizophrenia, which is part of the illness. We have compliance issues that are related to the adverse effects. With the typical neuroleptic drugs, we have the neurological problems of EPS and tardive dyskinesia. With the atypical agents, we're struggling in many patients with weight gain and metabolic changes.

When we look to see what kinds of medical treatments patients with schizophrenia are getting, we also see consistently that patients get under-treated. In a study looking at the treatment of patients with high lipid levels, 25 percent of patients with schizophrenia, compared to their matched controls, received lipid-lowering prescription drugs. So they clearly are not getting treated for high lipid levels.

When we look at treatment for post-MI care, we see that 40 percent of patients with schizophrenia are getting the standard of care that the matched cohort is receiving. So clearly, patients with schizophrenia have high risks and have less participation in our interventions. This means that we're seeing higher death rates in patients with schizophrenia. The evidence is that

patients with schizophrenia have a 20 percent shorter life span.

A meta-analysis recently published looking at studies at the beginning of the modern antipsychotic era, starting in 1952, has showed that the death by natural causes in schizophrenia is 34 percent higher than expected. So for every 100 expected deaths, there are 134 deaths in patients with schizophrenia. Deaths by cardiovascular disease, which is a high cause of death to begin with, is 10 percent higher in schizophrenia.

This meta-analysis is likely to conservatively underestimate the morbidity and mortality because ascertainment rates in cause of death during the 1950s, 1960s and 1970s were much less precise than our current interest and focus on these issues. So a recent study that is available from the Saskatchewan Health Database, a province in Canada which has a single-payer system and a uniform method for collecting data, has shown that the mortality rate for schizophrenia overall has a relative risk of 2.7, and when we look at cardiovascular death, 2.0 or doubling the relative risk of death from cardiovascular disease.

When we look at the prevalence issues of diabetes, we see a relative risk of 1.9, confirming very nicely what we have seen in several other studies, that

patients with schizophrenia have nearly twice the prevalence of diabetes, and the risk of developing new cases of diabetes is a relative risk of 1.6.

So we're currently faced with the challenging situation in treating schizophrenia of our new medicines bringing some improved efficacy, but still many patients inadequately responding to current treatment options, whether it be in the treatment of their acute exacerbation of psychosis or during the important long-term phases of relapse prevention.

Safety issues are important in emphasizing the high medical risk liabilities that are comorbid with schizophrenia and are limited risk factor interventions. It's important to emphasize that the new antipsychotic drugs, as well as the old agents, may exacerbate these underlying medical morbidities in schizophrenia.

So we clearly need additional medicines in our armamentarium to address both the unmet psychiatric and medical needs in patients with schizophrenia to offer valuable new options for treatment for patients who suffer from this highly prevalent, highly morbid, and highly lethal illness that causes immense pain and suffering in patients and their families.

Dr. Tamminga, Dr. Laughren, Dr. Katz and the committee, thank you very much for allowing me the time to

present the current challenging situation in the treatment of schizophrenia. I'll turn the program over to Dr. Harrigan. Thank you.

DR. HARRIGAN: Thank you, Dr. Casey.

I'll now proceed to introduce ziprasidone, which is a benzosothiasol, a structurally unique member of the generation of so-called atypical antipsychotic agents. The pharmacology of these drugs is somewhat complex and varied, as shown on the next slide. This class of drugs is often referred to as 5-HT2A/D2 antagonists, and they do have that pharmacology in common; that is, antagonist activity at the serotonin Type 2A and dopamine Type 2 receptors. However, a comparison of the broader pharmacology of these compounds reveals a number of properties which distinguish them from each other.

Clearly, some of these differences may increase or decrease liability for certain adverse events, such as alpha-1 adrenal receptor antagonist activity in hypotension, or activity at the muscarinic M1 receptor in gastrointestinal symptoms. Whether these or other properties might have psychotropic implications is more speculative. But it is widely recognized that, on the basis of pharmacology alone, it's an oversimplification to lump these agents together. It is inaccurate to consider ziprasidone as simply another atypical.

The pharmacokinetics of ziprasidone are fairly straightforward, as shown on the next slide. Here's a high-level summary of the clinical pharmacokinetics, which are linear. All of the clinical trial protocols have called for administration of ziprasidone with food in view of the increased absorption, which would be expected. Ziprasidone is extensively metabolized. I'll have more to say about that in a few minutes. At this time, however, I'd like to briefly review the evidence for efficacy, describe the effective dose range and the design of the trials which have established that dose range.

In order to establish the claim of efficacy in the treatment of acute exacerbation, ziprasidone was studied in four trials in a population of nearly 1,000 recently hospitalized patients. As described in your briefing document and as we'll see in a moment, daily doses of 80 to 160 milligrams were most consistently effective in the treatment of acute exacerbation. Relapse prevention, on the other hand, was studied in a single trial of 294 chronically and continually hospitalized patients. In this trial, a daily dose as low as 40 milligrams was effective at preventing relapse.

One word about dose. I'll be stating total daily dose, which the label would recommend be divided into two equal doses and taken with meals, as was done in nearly

all ziprasidone clinical trials.

First, a summary graphic of the treatment effects in the short-term studies. This figure illustrates the placebo-corrected change from baseline with 95 percent confidence intervals for each fixed-dose treatment group studied in these trials. It is proposed that the 40 milligram daily dose is insufficient to treat acute exacerbation. Efficacy has clearly been demonstrated at daily doses of 80 to 160 milligrams. The 200 milligram per day dose appeared to offer no advantage in terms of efficacy. It was associated with increased adverse events. So the recommended effective dose range is 80 to 160 milligrams daily.

Efficacy data from a long-term trial is presented in the next slide as a Kaplan-Meier graph, showing time to relapse, which was the primary pre-defined endpoint. As you can see, all three ziprasidone dose groups -- 40, 80, and 160 milligrams daily -- were effective in preventing relapse, suggesting that there is room for individualization of treatment during maintenance therapy.

To provide a general sense of the side effect profile of the compound, this is a list of adverse events which occur with a frequency of at least 5 percent, and greater incidence in ziprasidone-treated patients than in

placebo-treated patients. Somnolence was described in approximately 14 percent of patients, most cases being mild and transient. Respiratory disorders, the other term here, which is statistically significantly more commonly occurring in ziprasidone-treated patients than placebo-treated patients, this term includes investigator terms or symptoms such as nasal congestion and carisa, generally mild and symptoms which are commonly reported in other drugs of this class as well.

As noted in the briefing document, 4 percent of ziprasidone-treated and 2 percent of placebo-treated patients discontinued from these studies for adverse events. As you can see, the mean treatment duration in these 4- to 6-week trials was approximately four weeks, across the second row here, which is quite different from the adverse event collection period in the relapse prevention trial. The adverse event picture in the long term shows only insomnia to occur with a frequency of greater than 10 percent, but insomnia occurred with fairly high frequency in placebo-treated patients as well.

Only asthenia occurred with significantly higher incidence in ziprasidone-treated compared to placebo-treated patients. The primary investigator term coding to asthenia is fatigue. Overall, ziprasidone was well tolerated during this mean treatment period of over

seven months.

So far, this introduction to ziprasidone has focused on areas which were agreed between the sponsor and the agency at the time of the original NDA. As stated in the not approvable letter and again noted in the agency's briefing document, the efficacy of ziprasidone has been established. I'll now take the bulk of the presentation to review data which we have collected in order to better characterize the effect of ziprasidone on the QTc.

In the course of this review, we'll address the following questions.

What is the effect of ziprasidone on the QTc?

Have there been clinical manifestations of an effect?

What can we learn by considering ziprasidone in the context of the terfenadine and cisapride experience?

Finally, what other properties of this drug should be considered in a determination of benefit-risk?

It's likely that no one in this room is completely naive to the QT interval, and I'll spend only a short time on some general orientation. This is a stylized ECG complex, with a P wave, QRS complex, and T wave. The QT interval, of course, is measured from the beginning of the Q wave to the end of the T wave, representing the time required for depolarization and repolarization of the

ventricles at a standard paper speed of 25 millimeters per second.

One of these small boxes illustrated up in the corner of this slide is equal to 40 milliseconds, one millimeter in width. So 10 milliseconds would be equal to the width of one-quarter of one box. The QT interval on this slide is 10 millimeters long, or 400 milliseconds, 10 boxes in width.

The duration of the QT interval is affected by a number of physiologic and pathologic factors, including importantly by the heart rate at which the QT interval is measured. As you can see in the six seconds of ECG displayed in each of these two sample tracings, the presence of more complexes per unit time will simply have the effect of shortening the intervals between each complex. In addition, however, the QT intervals within each complex are shortened as well. So a perfectly normal heart has a longer QT at a lower heart rate than it does at a higher heart rate.

The one option for expression of QT might simply be to state the heart rate at which it is measured: a QT of 420 milliseconds at a rate of 66 beats per minute, for instance. However, by convention, the QT interval is instead corrected for heart rate by application of a mathematical correction formula. This formula incorporates

terms for heart rate and QT, and produces a QTc or corrected QT. The correction formula first proposed by Bazett in 1920 became the standard used in the literature and remains the most commonly employed. However, there are others, and I'll later review the effects of correction formula upon the results and the findings of our QTc study 054.

While it is true that an average QTc in an average population is a difficult number to pin down, 400 milliseconds is a reasonable estimate. It is consistent with much of the epidemiological literature. Nonetheless, there is a considerable amount of variability between individuals which we can illustrate using the ziprasidone Phase II/III database.

What we've done here is simply counted the number of QTc measures at baseline. This is pre-randomization in patients enrolled in Phase II/III studies. We placed QTc in 10-millisecond bins; that is, counted the number of QTc's in each 10-millisecond bin. Then we've drawn a curve over the top of the distribution columns. For this population, the shortest QTc was 314 milliseconds, the longest QTc was 494 milliseconds, and the median was, in fact, 400 milliseconds.

One of the reasons for this variability across a population is variability within each person. The three

carefully conducted studies have examined this by measuring QTc a number of times within individuals. This slide summarizes the findings of these three studies. As you can see, the range of QTc -- that is, the longest minus the shortest -- for individuals within these populations ranged from 66 to 95 milliseconds and is partially dependent upon the number of times the observation is made. So in the third study on the list here by Molnar, the range of 95 milliseconds was found in patients when measures were taken every five minutes for 24 hours using a Holter technique.

In addition to diurnal influences, it has also been demonstrated that the QTc will increase following a meal by approximately 20 milliseconds. There are therapeutic drugs which prolong the QTc, as shown in this list, which was compiled from two Websites, the Canadian Adverse Drug Reaction Newsletter and a site maintained by the Georgetown University Department of Pharmacology. As you can see, there are a number of psychotherapeutic agents on the list highlighted in light blue on this slide. I'll soon be providing you with a quantitative estimate of the effects of four of those named antipsychotic agents. But such precise data is generally not available on the other psychotherapeutic agents on the list, and many non-psychotropic agents on this list as well.

In addition to those drugs listed here, there

are other agents that have been associated with QTc prolongation. During my presentation, I'll be contrasting the effects of ziprasidone to those seen with the antihistamine terfenadine, the gastrointestinal motility agent cisapride, and an antipsychotic.

Let's look first at the ziprasidone QTc data which caused concern at FDA. Recall the four short-term, fixed-dose, placebo-controlled studies in hospitalized patients which underwrite the claim of efficacy in the treatment of acute exacerbation. This table displays the mean change in QTc in the right-hand column at least visit compared to baseline for placebo in each fixed-dose ziprasidone group, and for haloperidol comparative group. As you can see, ziprasidone, in doses up to and including 40 milligrams, was associated with little or no change.

However, across the 80 to 160 milligram dose groups, one can see a prolongation of 6 to 10 milliseconds, which does not increase further at the highest dose studied. Based upon this evidence, FDA asked Pfizer, as Dr. Laughren described, to measure the effect of ziprasidone on the QTc in a comparative clinical trial with ECGs timed to match the maximum concentrations of ziprasidone and comparators.

Study 054 was an ECG study which enrolled 183 patients. By protocol, 30 ECGs were obtained per patient.

Tracings were obtained in the fasting state, timed to capture the Cmax of each agent, both in the absence and presence of a metabolic inhibitor which was selected specifically to match the metabolic pathway of each antipsychotic. ECGs were stripped of patient and treatment identification and sent to a blinded central reader.

I'd like to take a short side-step now to consider the metabolic inhibitor phase of this protocol. The objective was to select a metabolic inhibitor which would perturb the metabolism of parent drug and be informative of potential drug interaction risks. An inhibitor was therefore selected with the principal metabolic pathway of each antipsychotic in mind.

Looking more closely at ziprasidone, this chart illustrates the fate of ziprasidone following oral administration in humans, which, as you can see, is determined by two principal enzymatic pathways. The first is cytochrome P450 3A4, CYP3A4, which is ultimately responsible for the production of three metabolites which we have designated M1, M2, and M10. The numbering system reflects only the sequence of elution in a chromatographic analysis. It has no other significance.

The second enzymatic pathway is mediated by aldehyde oxidase, a non-P450 enzyme, which is the first step in the formation of M9 and is responsible for

approximately two-thirds of ziprasidone metabolism. These four compounds -- M1, M2, M9, and M10 -- are the principal metabolites of ziprasidone and circulate with ziprasidone after oral administration.

For Study 054, we selected ketoconazole for co-administration with ziprasidone. As the most potent known inhibitor of CYP3A4, ketoconazole represents a worst-case surrogate for the large number of drugs which are known to inhibit this system. CYP3A4 interactions have been quite prominent in the evaluation of QTc prolongation with a number of agents, including terfenadine and cisapride.

I'd like to point out again this second aldehyde oxidase-mediated pathway for ziprasidone metabolism. It plays an important role in the clinical behavior of ziprasidone. The literature provided no clinical examples of drug interactions with the aldehyde oxidase system, suggesting that this metabolic pathway is robust and resistant to induction or inhibition. Importantly, ziprasidone, M9 and M10 have been found to have potassium channel -- that's IKr -- blocking properties in preclinical models, while ziprasidone and M9 additionally have modest L-type calcium channel blocking properties. M1 and M2 are inactive in these models.

For now, I'd like to maintain the focus on the QTc measures in the clinic, though we're prepared to

provide more details on the preclinical findings if the committee requests later on.

This kinetic is identical with the previous slide. It illustrates that ketoconazole inhibition of CYP3A4 would be expected to shift more of the metabolism of ziprasidone through the aldehyde oxidase pathway, leading to an increase in M9 at the expense of M1, M2, and M10.

Perhaps also of importance in the context of CYP3A4 inhibition is the degradation of M10, illustrated here and here. This is also mediated by CYP3A4 and suggests the potential for an increase in M10 in spite of inhibition of its formation. As we describe the results of Study 054, we will report the effect of ketoconazole administration upon serum levels of ziprasidone, M9, and M10.

Back to Study 054. Schematically, the study looked like this. Previous antipsychotic treatment was tapered as appropriate for the individual prior to randomization at the initiation of a five-day, single-blind placebo washout. During that time, nine baseline ECGs were obtained, time to match the Cmax of the drug to which the patient had been assigned. Patients were then titrated to a target dose according to the package insert and held at that target dose long enough to reach steady state.

Three ECGs per day were obtained on three

consecutive days at each of the three principal time points: baseline, steady state, and again, in the presence of metabolic inhibitor. At the request of the agency, three ECGs were also obtained on the second day of the dose titration period.

Here's a profile of the patient population enrolled into the trial. Note that the treatment duration varied according to the approved dosing instructions for each antipsychotic agent. Ninety percent of the patients who enrolled in this study completed the trial.

Now I'd like to take a moment to review the specifics of the treatment groups. Ziprasidone has a mean Tmax of six hours. So ECGs were obtained at five, six, and seven hours post-dose, fasting, on three consecutive days. This was done again at baseline, steady state, and steady state in the presence of ketoconazole. As you can see, ziprasidone was studied at the highest recommended dose of 160 milligrams daily. Risperidone, olanzapine, and quetiapine were also titrated to maximum recommended doses, while haloperidol and thioridazine were studied at doses of 15 milligrams and 300 milligrams respectively. Finally, we also incorporated the agency's suggestion to study risperidone at two doses. So ECGs were also obtained at 6 to 8 milligrams daily.

This slide shows the mean increase in QTc

measured in each treatment group at steady state. As you can see, thioridazine at 300 milligrams showed the greatest change at approximately 36 milliseconds. Other mean changes were ziprasidone at 20 milliseconds, quetiapine at 14.5, risperidone at 11.6, olanzapine at 6.8, and haloperidol at 4.7. This graph illustrates the point estimate of the mean with 95 percent confidence intervals. The study was in fact powered to measure a mean change with a 95 percent confidence interval of plus or minus 7 milliseconds, as stated in the protocol and agreed with the agency during protocol design. In fact, the confidence intervals are approximately plus or minus 5 to 6 milliseconds.

This trial was not powered to provide a precise estimate of the incidence of uncommon events, such as 60-millisecond increases in QTc, a point I will return to shortly.

Recall again our discussion from the schematic of Study 054, that after obtaining three days of ECGs at steady state, a metabolic inhibitor was added to the study drug. As you can see here, the metabolic inhibitor was selected for each study drug according to its principal P450 metabolic pathway. As we described for ziprasidone, a CYP3A4 substrate, the inhibitor was ketoconazole, as it was for quetiapine.

Paroxetine, a CYP2D6 inhibitor, was chosen for risperidone and thioridazine; fluvoxamine, a CYP1A2 inhibitor, for olanzapine; and both CYP3A4 and CYP2D6 were inhibited for haloperidol, as it is a substrate for both enzyme systems.

This slide is a reproduction of Table 30 from the briefing document. The last row of each column presents an estimate of the effect of metabolic inhibitor on antipsychotic drug concentration. So for ziprasidone, M9 and M10, increases of 39, 55, and 8 percent in mean serum concentrations were measured. Concentrations increases in the other treatment groups ranged from 4 percent for thioridazine to 400 percent for quetiapine.

Here is a graphic display of the overall results. This slide includes the findings at steady state as presented earlier. Those are the yellow point estimates with confidence intervals. And alongside each of those is the mean change from baseline in the presence of metabolic inhibitor. As you can see, the effect of ziprasidone on the QTc interval, measured at steady state, at Cmax at the highest recommended dose, remained essentially unchanged despite co-administration of the potent CYP3A4 inhibitor ketoconazole. For thioridazine and risperidone, slight decreases were measured. For haloperidol and quetiapine, slight increases were noted.

Now, the QTc values that we've presented so far have been calculated using the Bazett formula. As I mentioned earlier, there are a number of other formulas which have been proposed to correct the QT interval for the heart rate at which it is measured. What distinguishes one formula from another is the way in which the heart rate term is handled. So in the Bazett formula, the QT interval is divided by the square root of the RR interval, or the RR interval to the 0.5 power.

The Bazett formula may have been the first, but there are at least 17 unique QT correction formulas which have been published over the years, and we're showing you six of those formulas here. Since each handles the RR term differently, then a QT measured at a heart rate of 80 will calculate to a different QTc with each formula. Among this group of formulas, the Bazett formula will give you the longest QTc for a heart rate above 60 and the shortest QTc for a heart rate below 60. To understand the effects of the correction formula upon the magnitude of the QTc changes seen in Study 054, we'll look first at the effects of the study drugs on heart rate and QT.

As you see in this table, each compound has its own pattern of effects on the heart rate and the QT interval. Thioridazine 300 milligrams, haloperidol 15 milligrams, and ziprasidone all effect the QT interval, but

have more modest effects on heart rate than quetiapine, risperidone, and olanzapine. Haloperidol was associated with a decrease in heart rate, the minus 2.9 on the last column.

Now I'll go back to our graphic illustration of the QTc findings from Study 054. For this slide, we've taken all the mean changes that you've seen already and pushed them over to the left-hand side of the slide. So you see thioridazine with the greatest effect, haloperidol with the least effect. This is measured at steady state using the Bazett correction formula.

Next we'll add on this slide the mean QTc change in the presence of metabolic inhibitor. Again, the results you've already seen using the Bazett correction formula. Thioridazine, risperidone and olanzapine show a slight decrease in QTc effect; quetiapine and haloperidol an increase; ziprasidone unchanged. So ziprasidone the yellow dots, haloperidol light blue, quetiapine in white. Thioridazine, the greatest change, in red.

Here I've added two alternative correction formulas, one derived from our own patient population at baseline, the other published a number of years ago by the Framingham investigators. I won't try to describe the migration of each individual data point, but I will point out that the difference between the Bazett formula and the

others is that the QTc with the other formulas will be smaller for drugs that increase the heart rate, and larger for drugs that decrease the heart rate. In this study, most notably that's haloperidol. Overall, I would suggest that there is no one correct correction formula, and I would point out that QTc prolongation appears common. All point estimates of the mean are above zero. They're not scattered above and below zero. Thioridazine 300 milligrams remains on top regardless of the correction formula selected.

The difference between ziprasidone and these other approved non-thioridazine agents varies somewhat according to the correction formula used and the absence or presence of a metabolic inhibitor. Remember, non-Bazett formulas reduce the magnitude of the effect of ziprasidone and several other drugs. However, whichever formula you select, the effect of ziprasidone in the absence of metabolic inhibition is within 6 or 9 milliseconds of quetiapine or haloperidol respectively. So with the Bazett formula, ziprasidone in yellow, within 6 milliseconds of quetiapine in white, with either of the other correction formulas, ziprasidone in yellow, within 9 milliseconds of haloperidol in light blue.

In the presence of metabolic inhibitor, the difference between ziprasidone and quetiapine is zero

milliseconds with the Bazett formula; between ziprasidone and haloperidol, 3 milliseconds using either of the other two correction formulas illustrated here. There are a number of other correction formula calculations presented in the briefing document as well.

The briefing documents provided by both the sponsor and the agency report the incidence of incremental increases in QTc in this study. This slide displays the incidence of 60-millisecond increase in each treatment group at steady state and with metabolic inhibitor, side by side, same order, ziprasidone on the left, risperidone, olanzapine, quetiapine, thioridazine, and haloperidol. As you can see, because this trial was not powered to provide a precise estimate of the frequency of relatively uncommon events, there is considerable variability in these estimates.

For the ziprasidone group, as we just saw, the mean effect on QTc was unchanged with metabolic inhibition. However, the incidence of 60-millisecond increase fell from 7 out of 31 individuals, or just over 20 percent, to 3 out of 31 individuals with the addition of metabolic inhibitor, the rate with metabolic inhibitor in the ziprasidone group lower than that seen in the quetiapine or the thioridazine group. Again, this is with the Bazett formula.

In fact, none of the apparent differences

between these treatment groups in the incidence of 60-millisecond increase are statistically significant. This is true whether the Bazett formula is used on that slide to calculate QTc or whether the baseline correction formula is used as illustrated on this slide. I'm showing you again the incidence of QTc prolongation above 60 milliseconds with 95 percent confidence intervals.

If we now consider the broad objectives of Study 054, I would suggest that this is the most rigorous examination of the effects of antipsychotic drugs on the QTc under controlled conditions, at Cmax, at steady state, at relevant doses, with metabolic inhibition, and with the results expressed using a number of different correction formulas. With regard to the second objective, I believe the experiment has perturbed ziprasidone metabolism in the most appropriate way to look for evidence of risk of drug interaction. I'll now show you additional data collected in our Phase II/III development program which contributes to an examination of the risk of drug interaction.

In the course of conducting our clinical trials, we obtained almost 10,000 serum ziprasidone measurements from over 3,000 individuals. Overall, the mean concentration was 70 nanograms per milliliter. In addition, over 2,000 measurements of metabolites M9 and M10 were obtained, ziprasidone measurements M9 and M10. The

third column of this slide notes the highest concentrations of ziprasidone, M9 and M10, which were measured in Study 054. As pointed out in the briefing document, 61, 13, and 9 patients respectively had measures which exceeded the highest serum levels of ziprasidone or those two metabolites in Study 054.

Our focus, of course, remains on ECG data. Within that data set, we have 1,359 individuals for whom a QTc was obtained within one hour of the ziprasidone serum measurement, creating a data set of over 2,400 QTc concentration data points. The mean concentration in this data set was 63 nanograms per milliliter, very similar to that seen in the overall data set. Over 700 QTc concentration data points are available for each of the metabolites M9 and M10, as well. There are 12, 5, and 4 individuals in this data set with serum values above the highest level measured in Study 054 for ziprasidone, M9, or M10.

This figure is in the briefing document. It plots the change in QTc on the vertical axis and concentration on the horizontal axis for these 2,435 ziprasidone concentration QTc data points. For this display we're using QTc calculated according to the baseline correction formula, which is QT divided by RR to the 0.38 power. The vertical line on the right-hand side

marks the highest concentration seen in Study 054 with ziprasidone. That's 380 nanograms per milliliter. The concentration axis on this slide is truncated at 400 nanograms per milliliter.

The data overall are very consistent with ECG data that were seen in the short-term, fixed-dose, placebo-controlled trials in Study 054. At the concentration range where most patients spend most of their time, the mean QTc effect is less than 10 milliseconds. If we look at the highest recommended dose at Cmax in the absence or presence of ketoconazole, the mean change measured in Study 054 is 15 to 20 milliseconds, depending upon the correction formula.

Clinically, one might reasonably have the greatest interest in those individuals with the highest exposure. These 12 patients with serum measurements exceeding 380 nanograms per milliliter are indicated on the right side of the figure, three of them just above the vertical line at 380 nanograms per mil, the other nine indicated at the appropriate level on the vertical axis to match the QTc change which was associated with that serum level in nanograms per milliliter.

The next slide provides a closer look at these individuals. These 12 individuals, along with four additional patients who had concentrations of the M9 or M10

metabolites which exceeded those seen in Study 054, are presented on this table. We're showing you the age, gender, baseline QTc, treatment day, QTc change associated with serum concentration of ziprasidone, M9, or M10. The highest serum ziprasidone concentration of 955 nanograms per milliliter was seen in a 44-year-old woman who had a QTc change from baseline of plus-2 milliseconds. Her baseline QTc was 423 milliseconds, and her QTc at the time, within one hour of that serum measurement, was 425 milliseconds.

The three greatest QTc changes seen on this table -- 60, 57, and 50 milliseconds -- were measured in patients with baseline values of 380, 385, and 346 milliseconds. I'll mention the relationship between baseline QTc and change in QTc in just a moment. For these 16 individuals who represent the top of the ziprasidone-treated patient population by exposure, the QTc measures obtained within one hour of serum measurement are still contained within the range of those QTc measures seen in the overall ziprasidone database. There are no QTc values exceeding 500 milliseconds among these 12 individuals, 12 patients with the highest serum levels.

One important issue we're addressing today is not whether ziprasidone lengthens the QTc slightly, but whether that effect predicts a measurable increase in

clinical risk. In addition to reviewing the clinical experience with ziprasidone, we have looked for ways to assess the clinical relevance of modest QTc changes. We have consulted experts with regard to the ways to link QTc prolongation to risk. We will shortly be contrasting ziprasidone with other well-studied agents such as terfenadine and cisapride. Later today you'll hear of a formula to assess QTc risk which was obtained and developed by identifying patients with congenital long QTc syndrome who suffered a clinical event. These affected patients, along with unaffected family members, form the database from which this formula was developed or calculated.

We ask you to carefully assess the validity of this formula as we do not feel it is appropriate to apply this formula to the modest QTc changes seen with many drugs.

In the recent past, there have been several drugs which have caused problems with drug interaction and QTc prolongation. The fact that terfenadine was withdrawn from the market because of its potential to prolong QTc and cause torsade and sudden death is well known and might lead one to expect that ziprasidone might have some increased risk of such events. On close examination, however, the evidence suggests a different conclusion.

This concern was raised in the 1997 review of

the original ziprasidone NDA, articulated here by the consulting cardiologist from the Cardiorenal Division. In his summary and impressions of his consultation on the ziprasidone NDA, he pointed out that "Although the mean increase in QT interval appears minimal and clinically unremarkable, on the order of 10 milliseconds with 160 milligrams per day, it should be recognized that the ECG data were obtained at trough and the magnitude of the increase is similar in magnitude to what is observed with therapeutic doses of terfenadine. Under circumstances where metabolism is impaired, terfenadine has been associated with torsade de pointes. The same could be expected with ziprasidone."

First, some background on terfenadine. Seldane was prescribed well over 100 million times between the time of its launch in 1979 and its withdrawal from many markets more than 15 years later. The mean effect of terfenadine, or Seldane, on the QTc has been characterized by a number of investigators as approximately 6 to 8 milliseconds. As described in the briefing document, a close review of our ECG data, obtained in a trial conducted by Dr. Craig Pratt and colleagues, reveals that terfenadine was associated with a prolongation of 18 milliseconds when measured at peak; that is, at one hour after dosing.

Importantly, examination of considerable

epidemiological evidence has failed to demonstrate that terfenadine alone was associated with an increased risk of sudden death, despite its ability to prolong QTc in this fashion. However, as FDA's Cardiorenal review mentions, the profile of terfenadine changes considerably in the presence of CYP3A4 inhibition. Honig et al. measured the QTc effect of terfenadine administered with ketoconazole as 82 milliseconds. The QTc in that trial was measured at trough, that is on ECG tracings taken in the morning before the first dose of terfenadine, and so may not be representative of the effect at Cmax.

Concomitant administration of terfenadine and CYP3A4 inhibitors such as ketoconazole has been associated with increased risk of sudden death.

Data from Study 054 now directly addressed the concern raised by the Cardiorenal reviewer. The profiles of terfenadine and ziprasidone -- terfenadine illustrated here on the left, and ziprasidone on the right -- similar in the absence of metabolic inhibition, become quite different in the presence of CYP3A4 inhibition. The mean effect of terfenadine is at 82 milliseconds, unchanged mean effect of ziprasidone. The potent CYP3A4 drug interaction liability present with terfenadine is not present with ziprasidone.

In addition to terfenadine, cisapride is

another agent where QTc prolongation was exacerbated by a significant drug interaction. Cisapride is a gastric prokinetic agent which increases acetylcholine release. It is primarily metabolized by CYP3A4. Launched in 1993, cisapride was widely used throughout the world. However, cisapride blocks IKr as a CYP3A4 substrate, and became associated with the occurrence of torsade. In this context, a drug interaction study was carried out with cisapride and fluconazole, an antifungal agent.

In this trial, 20 volunteers were randomized for treatment with placebo or fluconazole. After one week, cisapride 20 milligrams was added to each treatment group. In the cisapride plus placebo group, QTc changes were 12 milliseconds when averaged across the dosing interval, and 23 milliseconds at peak cisapride concentrations. Twelve milliseconds averaged across the dosing intervals at non-peak, 23 milliseconds when measured at peak cisapride concentrations.

In the cisapride plus fluconazole group, the peak QTc effect of 50 milliseconds was measured, in association with an approximately three-fold increase in cisapride concentrations. These findings are consistent with a separately conducted clarithromycin interaction study. Both of these agents -- that is, clarithromycin and fluconazole -- are modest inhibitors of CYP3A4.

Ketoconazole, however, is a potent inhibitor. As reported in the U.S. package insert, it's causing an eight-fold increase in cisapride AUC, compared to the three-fold increase seen with fluconazole, which was associated with a 50-millisecond peak QTc effect. The QTc effects in the ketoconazole interaction study are not described.

The experience with terfenadine and cisapride is a reminder of the potential importance of metabolic inhibition in the assessment of drugs which have the potential to prolong QTc. This issue has been directly and carefully addressed in Study 054. It is clear that ziprasidone does not have the potent CYP3A4 interaction liability seen with terfenadine and cisapride. Broader conclusions regarding drug interaction liability are supported by the understanding of the critical role of aldehyde oxidase in the metabolism of ziprasidone, and most importantly, by the Phase II/III database.

There is no universal definition of QTc outlier. The incidence of QTc values crossing a number of different thresholds is presented in the briefing document. However, a frequently used cutoff for clinically significant prolongation is 500 milliseconds, and this is a threshold value which has been discussed before this committee in the past. Within our Phase II/III database, Pfizer has collected 7,876 ECGs on 3,095 patients treated

with ziprasidone. Two of these patients had a QTc in excess of 500 milliseconds. One patient had a baseline clinical diagnosis of long QT, a screening QTc of 489, baseline QTc of 466 milliseconds. On treatment, QTc of 503 milliseconds led to discontinuation.

The other was a patient whose QTc was not prolonged while taking ziprasidone, but who then discontinued ziprasidone and was treated with thioridazine prior to the emergence of QTc prolongation.

Overall incidence. Two patients of 3,095, 0.06 percent. There was one patient in the placebo group of 440 with a QTc of 500 milliseconds.

At this point, I'd like to speak to the comparison between ziprasidone and sertindole, which was mentioned in the FDA briefing document which was provided to the committee. The 21-millisecond mean effect of sertindole which was described as 20 to 30 milliseconds before this committee in the past, in 1996, was not measured at Cmax in a controlled trial such as Study 054. That estimate was derived from therapeutic clinical trials and may be more analogous to the data acquired of hospitalized patients in the ziprasidone short-term, fixed-dose, placebo-controlled trials, which showed a mean effect of ziprasidone of approximately 10 milliseconds.

Even more importantly, the incidence of QTc

over 500 milliseconds was reported to this committee as 7 to 8 percent at therapeutic doses of sertindole of 20 and 24 milligrams daily. As I just pointed out, 2 of 3,095 patients in the ziprasidone database, one of whom had discontinued ziprasidone and begun treatment with thioridazine, experienced a QTc of 500 milliseconds. We don't have access to sufficient data to characterize the reasons for the difference, but it is possible that sertindole, a 2D6 and 3A4 substrate, may be more susceptible to drug interactions than ziprasidone.

Even though a proportion of patients with individual QTc changes of 60 milliseconds is small, how do these occur if the QTc effect of ziprasidone remains stable even in the presence of metabolic inhibition? And how could there have been increases to this extent in the ziprasidone database without QTc values exceeding 500 milliseconds?

This figure provides the answer to those questions. It displays QTc change across the entire Phase II/III database, the entire population of the Phase II/III database, by QTc at baseline. So QTc change from baseline with a zero line, by baseline QTc. This figure includes every post-baseline tracing across the entire program, excluding the one individual who experienced a profound increase in QTc after treatment with thioridazine. The

data from that patient would include a baseline of 409 milliseconds. The post-baseline QTc in that patient was nearly 600 milliseconds. So the change would have been off the scale at 180 or so milliseconds. There is no evidence of that kind of effect with ziprasidone, even in the same individual, whose final QTc on ziprasidone before she was treated with thioridazine was 392 milliseconds.

Clinically, one would be interested in points in the upper right-hand corner. That is, these would represent large QTc increase in patients with a long baseline QTc, with a longer baseline QTc represented out here. This figure, however, shows that the individuals with the greatest change in QTc tend to be those with the shortest baseline QTc. Within the ziprasidone database, therefore, there's no evidence that a patient with a higher baseline QTc will have a larger change from baseline. It's quite the opposite.

I'll now move on from a description of the QTc effect of ziprasidone to an examination of the ziprasidone clinical database for any evidence to suggest that this effect may be clinically meaningful.

First of all, there have been no reports of torsade. Other areas of particular relevance are mortality, syncope, and the overdose experience. This graph presents the all-cause mortality rate of 1.6 per 100

patient years for ziprasidone alongside the comparator groups in the ziprasidone development program: placebo, haloperidol, and risperidone, with 95 percent confidence intervals. Patient years exposure and number of events are noted on the left-hand side.

Now, on the lower half of the slide, we see as well the all-cause mortality rates for three recently approved antipsychotic agents, each with its own patient years of exposure at the time of marketing approval in the U.S. Meta-analysis, the bottom row, refers to a recent publication by Brown in which an all-cause mortality rate among patients with schizophrenia was calculated to be 1.9. While the data upon which this was calculated included a wide variety of populations, the mortality rate again appears consistent with that observed in contemporary antipsychotic development programs, and, as reported in the briefing document, there is no suggestion of an increase in mortality in the ziprasidone treatment group.

It is recognized that torsade is not always fatal but can present clinically as a syncopal event. This slide shows the incidence of syncope in our Phase II/III development program, up to the original NDA filing across the top half of the slide, and cumulative up to the recent safety update across the bottom. As you can see, there is no excess of syncope in the ziprasidone group measured as

percent incidence or as syncopal events per 100 years of exposure in the ziprasidone group relative to the comparator groups.

The overdose experience with ziprasidone includes 10 individuals who have ingested doses of up to 4,600 milligrams. There have been no significant cardiovascular adverse events. Unfortunately, we do not have serum ziprasidone levels measured coincident with any of these overdose events. But for two of them, we do have ECGs which were obtained around the time of the overdose.

One patient in Australia reportedly ingested 3,240 milligrams of ziprasidone. Symptoms included and were limited to sedation and slurred speech. ECGs were obtained approximately 4, 6, and 9 hours after the overdose and reveal a prolongation of approximately 20 milliseconds, compared to the three available pre-randomization QTc values. The other individual had an ECG approximately two-and-a-half hours following a reported overdose of 1,880 milligrams of ziprasidone taken with alcohol and paroxetine. Post-overdose QTc was 372 milliseconds. Pre-randomization QTc's were 331 and 385 milliseconds.

I'd like to just summarize now the ziprasidone data concerning QTc and safety. Studies conducted during the NDA development program and during the last two years since receipt of the non-approvable letter have well

characterized the QTc effect of ziprasidone. It is modest, with a 6- to 10-millisecond change found in random ECGs obtained throughout the dosing interval at the therapeutic dose range of 80 to 160 milligrams daily.

A peak effect of 15 to 20 milliseconds has been measured at the highest recommended dose of 160 milligrams per day. The QTc effect appears to be limited as a function of its pharmacology, and importantly, due to the stability of the metabolism of ziprasidone. There have been only two of 3,095 patients, with over 7,800 ECGs, two patients with a QTc of 500 milliseconds. Unlike terfenadine and cisapride, the co-administration of ketoconazole with ziprasidone does not cause an increase in QTc prolongation. In over 1,700 patient years of experience, there is no increase in mortality or syncope, and no cases of torsade.

Finally, among 10 individuals who have reported overdoses with ziprasidone, there have been no significant cardiovascular adverse events, and no excessive QTc prolongation was found in two of these individuals.

Having reviewed the effect of ziprasidone on the QTc and considered the clinical relevance of that effect, I'd now like to spend a short period of time discussing the effect of ziprasidone upon three major, well known cardiovascular risk factors: body weight, lipids,

and glucose.

The U.S. package inserts for antipsychotic drugs have, for a number of years, reported the incidence of clinically significant weight gain, defined as 7 percent of baseline body weight, in short-term placebo-controlled trials. As shown on this slide, just under 10 percent of patients treated with ziprasidone experience this gain, compared to approximately 4 percent of placebo-treated patients. The right-hand side of this slide shows the same information for the development programs for risperidone, quetiapine, and olanzapine, as reported in their U.S. package inserts. Incidence rates of 18 percent, 23 percent, and 29 percent were reported in association with those compounds, with rates in their placebo-control groups of 9 percent to 2 percent.

Mean weight gains in the same patient populations are presented on this slide, the vertical axis on the left being marked in kilograms, on the right in pounds. These mean weight changes, mean weight gains, range from 0.9 kilograms in ziprasidone-treated patients to 2.8 kilograms in patients treated with olanzapine. This is in short-term placebo-controlled trials. Mean weight changes over longer treatment periods are shown on this slide; again, kilograms on the left, pounds on the right, number of kilograms indicated on the tops of the columns.

For ziprasidone patients, there's very little mean weight change, 0.2 kilograms. The mean treatment duration is 83 weeks. The haloperidol and risperidone data on the left side of this slide were obtained in the ziprasidone clinical development program, where increases of approximately 1 kilogram and 3 kilograms were measured over mean treatment periods of about a year. The right-hand side of this slide displays data from U.S. package inserts or product monographs for risperidone, quetiapine, and olanzapine, with mean weight increases of 2.3, 5.6, and 5.4 kilograms, over 6-, 12-, and 8-month treatment periods, respectively.

In terms of body weight gain, ziprasidone appears weight neutral, a property which contrasts strongly with several recently approved antipsychotic agents.

A measure of the effect of ziprasidone upon lipids was obtained in Study 054, where fasting lipid profiles were obtained. This slide displays change from baseline, median change from baseline, with favorable changes highlighted in green, unfavorable changes in red. Six treatment groups in Study 054 are ziprasidone, risperidone, olanzapine, quetiapine, thioridazine, and haloperidol.

Although the treatment periods were short, as described earlier, decreases in serum cholesterol, LDL

cholesterol, and especially triglycerides, were seen with ziprasidone. These favorable effects contrasted with several of the comparative drugs, where increases in triglycerides in particular were observed. This pattern of change with ziprasidone can be confirmed over longer treatment periods with cholesterol. Routine laboratory safety testing in our clinical development program included measurement of total cholesterol and samples obtained randomly in relation to meals. This slide shows the median change in total cholesterol in patients receiving 28, 40, and 52 weeks of treatment, these three columns for the ziprasidone group.

The picture in the ziprasidone-treated patients is fairly consistent with a median decrease of 10 to 12 milligrams per deciliter observed. Haloperidol and risperidone treated patients did not show this favorable change.

Finally, I'd like to consider the properties of ziprasidone in relation to glucose intolerance. As Dr. Casey mentioned, the prevalence of diabetes in the population with schizophrenia is higher than that in the general population. There is some literature to suggest that this predates the usage of many of the newer atypical agents. However, in the past several years, there's been a notable increase in case reports linking antipsychotic drug

therapy to diabetic ketoacidosis and new-onset diabetes, including the case series noted here, where previously non-diabetic patients in this series by Henderson from Mass General Hospital, previously non-diabetic patients were observed to develop diabetes over a five-year treatment period with clozapine, or to convert from a normal to an abnormal fasting blood sugar, as in Dr. Casey's patients at the Portland, Oregon VA Medical Center, with clozapine and olanzapine.

These reports have caught the attention of the FDA. Dr. Elizabeth Koller of the Endocrine Division reported what she described as unusually severe cases of hyperglycemia and diabetes in association with clozapine, and quite recently the Neuropharmacology Division cited these reports when requesting sponsors of atypical antipsychotic drugs to submit all data "which may assist us in more fully evaluating the possibility that atypical antipsychotics may produce disturbances in glucose regulation."

In response to this request from the agency, Pfizer has recently submitted a summary of all data relevant to the issue of glucose intolerance. Beyond randomly obtained glucose, two ziprasidone studies have included measures of fasting glucose, insulin, and related variables. I am presenting laboratory data collected from

patients in Study 054, as well as data from an interim analysis of an ongoing, six-week, double-blind olanzapine comparative trial. These data are not included in the briefing document.

This slide shows the median change from baseline in body weight, triglycerides and insulin associated with both treatments. Study 054 on top, Study R0548, the double-blind, six-week olanzapine comparative trial on the bottom. As you can see, the increases in each of these three measures -- body weight, triglycerides, and insulin -- seen in association with olanzapine treatment, are not seen in ziprasidone-treated patients. A consistent pattern of increasing body weight, triglycerides and insulin is suggestive of the insulin-resistant syndrome. It is not seen with ziprasidone.

To summarize these benefits, the effects of ziprasidone upon body weight and lipids have been observed consistently over short- and long-term treatment periods and contrast favorably with the adverse effects of several treatment alternatives. Furthermore, there is no evidence of an association between ziprasidone and an insulin-resistant syndrome or glucose intolerance.

The QTc effect of ziprasidone has been closely examined. The effect of ziprasidone upon the QTc is well characterized and appears to be limited as a function of

its pharmacology and the stability of its metabolism. Examination of over 2,000 QTc concentration data points reveals no suggestion of increased risk which might be associated with a subset of high exposure individuals. In the 1,700 patient years of exposure to ziprasidone, there have been no reports of torsade and no suggestion of increased risk of arrhythmia-related clinical events.

Ziprasidone is an effective and well tolerated treatment for a severe illness, and in contrast with the adverse effects of many other approved treatments, ziprasidone has favorable effects on well documented cardiovascular risk factors. I propose that ziprasidone represents an important treatment option for patients with psychosis.

Thank you, Dr. Tamminga and committee members, Dr. Katz and Dr. Laughren. The sponsor is available to answer questions.

DR. TAMMINGA: Thank you, Dr. Harrigan, for your presentation.

I'd like to do a short test of the microphone system before the committee starts asking its questions.

THE REPORTER: I think if participants speak close to the microphone, we'll be in good shape.

DR. TAMMINGA: Close to the microphone.

Thank you, Dr. Harrigan and Pfizer, for your

presentation.

The committee is welcome to ask Dr. Harrigan and any of the Pfizer people questions about their presentation. It might be useful for us to limit our questions now to questions of clarification and not to necessarily get into the discussion of issues, which we can get into in more detail this afternoon.

Dr. Lindenfeld?

DR. LINDENFELD: If I could start, I have just a few questions for Dr. Casey.

Could you tell us the gender distribution of schizophrenia? I'm sorry, but the cardiologist doesn't know that.

DR. CASEY: I'd be glad to. Gender distribution is equally distributed in both men and women.

DR. LINDENFELD: I will come back to this point because I think a far greater number of the patients in these studies were men than women.

Smoking. Do the typical antipsychotics alter the incidence of smoking in these patients?

DR. CASEY: There's mixed evidence about that. Some studies suggest they may modestly decrease smoking rates, and other studies show that there's no decrease.

DR. LINDENFELD: I guess we'll come back to that, because I'm wondering if this has any influence on

the weight change in these patients, if there's a differential incidence of smoking.

Could you give us some idea of the number of other medications the average patient with schizophrenia is taking, and what general classification those would be? Just roughly. In other words, antihistamines. I know Benadryl is used with these patients not infrequently.

DR. CASEY: I'm not able to recall a comprehensive survey of the total medicine regimen that patients with schizophrenia take, but they often take at least one antipsychotic, perhaps an antidepressant. One-quarter to 50 percent of patients will be taking an antidepressant at one time or another. If they're taking the typical neuroleptic or antipsychotic drugs, they'll be taking an anticholinergic drug, 50 percent of the patients. Then they're likely to be taking other medicines for concomitant illnesses, such as diabetes or hypertension or other illnesses that the general population receives.

DR. LINDENFELD: I want to come back to this with Dr. Harrigan to just ask if the patients in 054 were on this typical range of medications.

Let me ask you one other question, again from a cardiology viewpoint. In a patient who doesn't have a good response to one of these atypical antipsychotics that's currently available, what is the incidence of an improved

response if one switches drugs, on the average?

DR. CASEY: There are very few studies to guide us to precise numbers. The general clinical impression is that one should not reach therapeutic nihilism by people failing one drug and should continue to try with different medicines, as people do respond to one medicine when they fail to respond to another. There is a substantial proportion of patients, 20 to 30 percent, who appear to repeatedly fail to respond to a series of medicines, indicating that we don't yet have a fully effective pharmacopeia for a large group of people.

DR. LINDENFELD: Do you have a rough idea of the incidence of response to one drug when you've failed another? High? Low? Medium?

DR. CASEY: I'd put it in the medium category.

DR. LINDENFELD: Okay, good. Then you said that 40 percent of these patients are not taking their medicines as prescribed. Could you give me a rough idea of what that means? They're overdosing themselves? Underdosing themselves? Or do we know?

DR. CASEY: The compliance studies usually assess whether people are taking their medicines or not, and the compliance numbers usually mean not taking the medicines. The compliance studies are mostly verbal reports, and sometimes reporting accuracy is somewhat

imprecise, as I imagine it is in hypertension and other areas.

DR. LINDENFELD: And then just a couple of quick questions for Dr. Harrigan. You showed us the overall QTc data. Could you divide that up between men versus women? We know there's a propensity for women to have torsade, and I'm interested if there's a difference. There's a small number of women here.

DR. HARRIGAN: Sure. If we could look at Slide M43, what we're showing you here is the mean change from baseline. This is the short-term, fixed-dose, placebo-controlled. So we're looking at change from baseline by dose in men versus women, with males in blue and the green bars being female. You see it in the legend here. So a dose is less than 40, 40, 80, 120, 160, and 200 milligrams or more per day.

There appear to be no consistent suggestions of a greater increase in females compared to males. This is using the Bazett formula.

DR. LINDENFELD: How many women in this group?

DR. HARRIGAN: In this group, the N of females -- let's see, we could add them up -- is 173.

DR. TAMMINGA: Dr. Harrigan, are these data from the Phase II/III studies or from Study 054?

DR. HARRIGAN: Phase II/III studies.

DR. TAMMINGA: Do you have the same data from Study 054? Do you have gender data from 054?

DR. HARRIGAN: M181. In Study 054, the number of females was, of course, smaller. But here it is for all of the treatment groups. This is mean change at steady state by gender. Again, male is blue and female is green. For ziprasidone, nine females, 22 males, as you see for the other antipsychotic groups as well.

DR. LINDENFELD: Slide number 61, where you showed us the distribution of the change in QTc according to the baseline QT, that was not the Bazett correction, right?

DR. HARRIGAN: Correct. That's the baseline correction.

DR. LINDENFELD: So we might see a slightly different distribution if we had the Bazett correction in there. The reason I ask that is because that's sort of the standard way that most people evaluate the QTc still, we look in the literature.

DR. HARRIGAN: We could show you that if you'd like to see it.

DR. LINDENFELD: That would be great.

DR. HARRIGAN: The Bazett formula.

DR. TAMMINGA: While you're looking for that slide, Dr. Harrigan, would you like to comment on Dr.

Lindenfeld's other question? Would you like to remark on the gender distribution in these studies?

DR. HARRIGAN: The gender distribution in these studies is probably close to 70 percent male, 30 percent female.

DR. LINDENFELD: I thought you said 75 percent for 054.

DR. HARRIGAN: For 054, yes.

So this is, again, change from baseline, baseline, and this is using the QTc correction formula of Bazett.

DR. LINDENFELD: Thank you.

DR. TAMMINGA: Dr. Oren?

DR. OREN: One question for Dr. Harrigan. You presented data on the particular effect of ziprasidone on lipid levels. Do you have any additional data dividing that by baseline levels of lipid levels?

DR. LINDENFELD: The same slide as for the QTc?

DR. HARRIGAN: Right. No, we don't.

DR. TAMMINGA: Dr. Califf?

DR. CALIFF: Dr. Lindenfeld took most of the questions right out of my mouth. I guess it's evidence of having been on the same committee for a few years. But I think what she was getting at, I'd really hope to find out a little bit more about whether the patients that you've

enrolled in these studies represent the patients who are likely to be treated in practice. I think she was getting at it in several different ways.

Were the number of medications these patients were on the same as what you would see in clinical practice? Was the age distribution the same? And I'm particularly interested in the mortality rate. I think the mortality rate you have in your studies is quite a bit lower than what's in the general population of people with schizophrenia, but I'm not sure about that. Do you have data that would allow us to compare the patients that are in your studies, both with regard to baseline characteristics, treatment, and outcome, with what's seen in the general population of people with schizophrenia?

DR. HARRIGAN: In terms of the mortality rate in the general population with schizophrenia, I think the Brown meta-analysis and a very similar meta-analysis written by Harris using pretty much the same data came out with the 1.9 figure, and that data is fairly similar. I don't know of any other mortality studies other than the Saskatchewan data that Dr. Casey presented.

In terms of the population in the ziprasidone clinical trials, if we could look at G11 and G12, we did look at the incidence of three cardiovascular conditions at baseline in the ziprasidone Phase II/III program. So the

number of patients entering studies with hypertensive disease, ischemic heart disease, and other forms of heart disease, for hypertensive disease, 8.4 percent of the population in the ziprasidone clinical trials had a history of hypertensive disease at baseline.

If we could look at the next slide, we went back and looked at the Saskatchewan database that Dr. Casey described, those 3,022 patients in the Saskatchewan public health database who have schizophrenia. The incidence of hypertension in that group is 9.9 percent, compared to the 8.4 percent seen in the ziprasidone clinical trial population. So the clinical trial population is just a little bit younger than that Saskatchewan population. It's similar to the age distribution of the clinical development programs for the other antipsychotic drugs and the tendency to enroll patients who are somewhat younger, unless the drug is being developed for dementia as well, in which case older patients are in the trials.

DR. CALIFF: Do you have a list of the inclusion and exclusion criteria from these studies?

DR. HARRIGAN: Yes, we do. G19. G9.

This N doesn't add up to the full N of the development program. We really selected a subset of trials with at least 100 patients to get an estimate. Clinical exclusion criteria were fairly broad. Clinically

significant and/or relevant physical illness for some of the European studies, significant cardiovascular disease, including uncontrolled hypertension, hypotension, congestive heart failure, angina, myocardial infarction within the past six months.

The QTc issue in terms of enrolling patients, almost 90 percent, 89 percent of patients were enrolled in the ziprasidone clinical ECG database prior to the request by FDA that QTc's be screened and 450-millisecond QTc's be identified prior to enrollment. So there were no enrollment restrictions on baseline QTc for the vast majority of EKG data you're seeing.

DR. CALIFF: Were there concomitant medication exclusions?

DR. HARRIGAN: There were in the efficacy trials. Certainly, some of the psychotherapeutic agents were excluded. Lorazepam and benzotropine were the sedative and anticholinergic agents of choice in those double-blind efficacy trials. The exclusions widened or broadened as you got into the longer-term studies, particularly the open-label extension studies.

Table 35 on page 95 of the briefing document presents a list of selected concomitant medications to give you an idea of how many patients on different concomitant medications were enrolled in the ziprasidone development

program, and I think it provides the QTc changes in those patients as well.

DR. TAMMINGA: Dr. Moss has a question.

DR. MOSS: Were any Holter recordings obtained during the course of any of the studies? And were QTc measurements made during any Holter recordings or during exercise testing?

DR. HARRIGAN: No Holter recordings, and no specific exercise testing of patients.

DR. TAMMINGA: Dr. Winokur?

DR. WINOKUR: A couple of questions. First, going back to data you presented earlier on the dose range for efficacy, you mentioned a range of 80 milligrams to 160, and it looks like, if I read the figure on 17 correctly, that there were two studies that you've indicated at 80 milligrams, one of which shows improvement, one which doesn't, the 104. I'm wondering if there's a reason why the 80 milligram dose is viewed as being clinically effective even with one of two trials not showing that.

DR. HARRIGAN: I guess there are two parts to the answer. The 80 milligram dose in Study 104 was not more effective than placebo. None of the three ziprasidone doses in that study -- that was essentially a failed study. There was no active comparator. The data I think is

described in a little more detail in the briefing document, as you know. So we do have one study with an 80 milligram per day dose, Study 114, with fairly robust efficacy. There was also Study 115 with a 40 milligram per day dose being more effective than placebo, significantly more effective.

So as a sense of the data and having to interpret sometimes inconsistent data across different studies, it seems that the most prudent choice for acute exacerbation would be about 40 milligrams per day, ineffective in two out of three trials, but at 80 milligrams per day.

DR. WINOKUR: And the other question I had, I think you made reference to, among other factors that can affect QTc is circadian factors, and I think you've already answered this, but was there any assessment in this study, for example with Holter monitoring, for sleep-related changes?

DR. HARRIGAN: No.

DR. TAMMINGA: Dr. Rudorfer?

DR. RUDORFER: Just to clarify the concomitant medication issue, the taper and washout only applied to existing antipsychotic drugs in Study 054?

DR. HARRIGAN: No. Patients were tapered pretty much from all concomitant medications. There is

some lorazepam that was permitted, and benzotropine was permitted for extra-prandial symptoms, if necessary.

DR. RUDORFER: Okay. So at the time of baseline ECG, patients had been totally med free for five days? Is that correct?

DR. HARRIGAN: No, for at least two days. There is a five-day placebo washout. It was on the last three of those days that ECGs were obtained. So the patients were tapered prior to the beginning of the washout, as much as was felt to be appropriate by the investigator for that patient. They then began the single-blind placebo washout. So there were two days of pure washout, and then the next three days we obtained ECGs on each of those three days.

In analyses that we don't have, there didn't appear to be any evidence of QTc change over those last three days of the baseline period.

DR. RUDORFER: Thank you.

DR. TAMMINGA: Dr. Fyer?

DR. FYER: I just have one quick clarification question. You cited this figure looking at all the patient years and the number of people with heart rate greater than 500, QTc interval greater than 500. I know in the 054 study, you did things at the maximum drug level. That's sort of putting everything together, not just the 054. I

wondered if the other reportings, they were not done at the maximum level. Is that correct? They were just done whenever they were done, or mainly during the trial period?

DR. HARRIGAN: No, they were done pretty much at random. I mean, some were from hospitalized patients with dose-administered BID. There may have been slight consistencies in the time of the ECGs relative to dose, but overall they were random, and many of the studies were outpatient studies. So there's no timing in relation to dose, with the exception of Study 054.

DR. FYER: So it doesn't reflect the maximum level, like the 054.

DR. HARRIGAN: The 054 is the only study that was specifically designed to reflect the Cmax.

DR. TAMMINGA: Dr. Marder?

DR. MARDER: I just have one question. If you could go back to Study 054, what proportion of patients who were screened were excluded for having a prolonged QTc?

DR. HARRIGAN: Zero. We had no one excluded from Study 054 for prolonged QTc at baseline.

DR. TAMMINGA: Dr. Lindenfeld?

DR. LINDENFELD: Just one other question. You said aldehyde oxidase, there were no metabolic interactions that had been reported. Is that affected by alcohol?

DR. HARRIGAN: I might ask Dr. Christine

Beedham to address that question.

DR. BEEDHAM: Good morning, ladies and gentlemen. Aldehyde oxidase does metabolize acetaldehyde, which is generated from alcohol. But it's not thought to contribute to the metabolism of ethanol in vivo. Aldehyde dehydrogenase is usually the enzyme that is thought of as the main contribution. So ethanol is not reported to have any effect on aldehyde oxidase activity, either as an inducer, because it does induce some forms of cytochrome P450. But it's not been shown to induce aldehyde oxidase, and it is not thought to inhibit aldehyde oxidase either.

Does that answer your question?

DR. TAMMINGA: Could you further clarify for us if there are common inhibitors of aldehyde oxidase?

DR. BEEDHAM: There are a few inhibitors that have been identified in vitro. Menadione is the one that is usually used to characterize aldehyde oxidase in vitro, and you can see later that ziprasidone metabolism was inhibited by menadione in vitro. But there are no reported drug interactions in vivo with aldehyde oxidase.

Phenothiazines are actually in vitro inhibitors, but there are no reported drug interactions in vivo with this enzyme.

There's very little known about it as far as the in vivo studies that have been done so far, so there

isn't an inhibitor that one could choose that would perturb the system.

DR. TAMMINGA: Dr. Moss?

DR. MOSS: This is for Dr. Harrigan. Did anyone look at the morphology of the T waves? All we've heard about is the QT interval, but was the configuration of the T waves altered at all by the medication?

DR. HARRIGAN: The ECGs in the ziprasidone development program were all submitted through a central reader for interval measurement. The local readings were in the protocols in the U.S., which is probably two-thirds of the total database, by protocol required a board-certified internist or cardiologist to do the reading, and we collected that data. There was data collection on T wave inversion in the clinical development program. There's no evidence of T wave inversion in any particular treatment group.

The morphology of ECGs in the individuals who experienced death were reviewed by Dr. Craig Pratt. I'd like Dr. Pratt to help with this answer.

DR. PRATT: In the EKGs that pertained to the patients who had unexpected sudden death, we looked at all ECGs pre and post. No T wave abnormalities. In the one patient in Table 38 with QT prolongation at all was a patient off ziprasidone for two days and on thioridazine.

DR. TAMMINGA: Dr. Laughren?

DR. LAUGHREN: I have a question for Dr. Harrigan, and this relates to the post-prandial effect on QTc that I didn't appreciate as much as I do now. From one of your earlier slides you suggested that the post-prandial effect is somewhere in the vicinity of 16 to 23 milliseconds. I guess my question is, in Study 054, as I understand it, the baseline was done in a fasting state. In the steady-state phase, I gather the patients -- basically, this was in a fed state, perhaps not post-prandial, but patients were allowed to eat their usual meals during that phase.

So I guess the question I'm asking is, is it possible that some of the QTc change that you're seeing, the change from baseline, is in part a food effect on the QTc?

DR. HARRIGAN: We believe we control for that. The patients were allowed to take meals certainly, but the timing of the meals was rigidly controlled depending upon the timing of the dose, and the timing of the ECGs, actually. All ECGs were obtained after at least three hours of fasting. So we deliberately timed the ECGs to avoid the post-prandial effect that you described.

DR. LAUGHREN: So you're confident that none of that change is basically a post-prandial event.

DR. TAMMINGA: Dr. Winokur?

DR. WINOKUR: I have a question for Dr. Casey. If you can think of any data or from clinical experience about the extent to which obstructive sleep apnea is an important clinical issue for the schizophrenia population.

DR. CASEY: As far as we know, it is not increased risk for patients with schizophrenia at normal weights, but as one increases weight, like the general population, one increases the risk, as best we know.

DR. TAMMINGA: Dr. Katz?

DR. KATZ: Also a question for Dr. Harrigan. You presented a number of slides talking about the long-term effects on what you called the cardiovascular risk factors, cholesterol and that sort of thing, maybe even weight gain and triglycerides. Of course, the numbers decreased as time went on.

I'm just wondering if you can comment about how many folks dropped out of those cohorts, why they dropped out. I assume it's not complete follow-up on everyone who started.

DR. HARRIGAN: No. The long-term measurements of cholesterol that we presented were in patients who had completed at least 28 weeks of treatment, and there you saw, whether we looked at 28, 40, or 52 weeks in those sets of patients, the change was fairly consistent, at 10 to 12

milligrams percent. As you know, the dropout rate in trials in this area is generally over 50 percent, and that's been true of virtually all the trials that we've run.

DR. TAMMINGA: Dr. Harrigan, in this regard, don't you have data from a 12-month inpatient study where you had a much lower dropout rate?

DR. HARRIGAN: Yes, Study 303. That was the relapse prevention study. We do have data from that, but cholesterol was not measured in those patients.

DR. TAMMINGA: Dr. Cook?

DR. COOK: Getting back to the question about inhibitors of aldehyde oxidase, it was mentioned that there were in vitro inhibitors, specifically phenothiazine, but there was no in vivo inhibition, and I wanted to clarify whether it has actually been sufficiently tested in vivo to rule that out.

I might as well ask the second question, which is any other evidence of concomitant use or sequential use close in time of thioridazine and ziprasidone, considering the fact that this might be given concomitantly, or certainly patients might be switched.

DR. HARRIGAN: We've generally excluded the concomitant antipsychotic medication in our clinical trials, including thioridazine.

I might ask Dr. Beedham to address the aldehyde oxidase part of the question.

DR. BEEDHAM: Could I have Slide 43 from the CP slides, please?

The studies that we carried out with chlorpromazine and other inhibitors in vitro have generally been carried out on oxidation reactions that are catalyzed by aldehyde oxidase. This tells you a little bit about the enzyme here. It's a little less known than cytochrome P450, but it has a very wide substrate specificity. As you can see from here, it's a molybdenum-containing enzyme, very high concentrations in the liver. There's less found in the lung and the kidney. It catalyzes the oxidation of a very wide range of nitrogen-containing heterocycles, compounds like zaladines, perimadines, purines, quinazolines, and quaternary compounds like nicotinamide.

As you can see, it also catalyzes the oxidation of aldehydes. But in addition to that, it will also catalyze the reverse reaction. Once the enzyme has been reduced, it can transfer the electrons to a compound such as containing a nitro group, sulfoxides, isoxizoles, and in this case ziprasidone. So it reduces ziprasidone, whereas most of the studies that have been carried out up to now have been on the oxidation of other substrates.

Now, there are relatively few drugs that are

primarily cleared by this enzyme. The one that we know most about is famciclovir. Famciclovir is, in fact, a pro-drug.

Can we go to slide 51, please, in this series?

Famciclovir has been on the market I think around seven years. Famciclovir itself is not active. It has to be activated to the quanime nucleoside. It undergoes two hydrolysis steps, one in the gut and one in liver, followed by an oxidation reaction that is catalyzed by aldehyde oxidase, and this produces the active moiety penciclovir. So this has been on the market for around five to seven years. There is no clinically significant drug interactions that have been observed with famciclovir over all that time.

Cimetidine, which is a weak inhibitor of aldehyde oxidase, as indeed it is a weak inhibitor of cytochrome P450, actually causes an increase in the area underneath the curve. Allopurinol, the reason this drug was tried in vivo is because this is a xanthene oxidase inhibitor, but it actually has no effect on aldehyde oxidase activity.

So if we then go back to slide 43, there are no clinical drug-drug interactions resulting from the alteration of human aldehyde oxidase activity. Athenoziasines inhibit oxidation in vitro. In fact,

they're a potent inhibitor. When they were tested with ziprasidone, they were weak inhibitors in vitro. This is probably because you've got a reductive pathway rather than an oxidation pathway, and the substrates are acting at different sites on the enzyme. So you would not necessarily expect that in vitro inhibition to be seen in vivo.

I think there's a further point that could be made on the slide there, that there's very little variation that is known in humans. For all the studies that have been done with famciclovir, there aren't any indications of any poor metabolizers, so you could get high concentrations of ziprasidone. So there are no perturbations of the system that we're aware of at the moment that would either inhibit, induce, or interfere with the metabolism of ziprasidone by aldehyde oxidase.

DR. COOK: One follow-up question. Could you comment more specifically on Sonata potential interactions, and also whether that was given concomitantly, although I suspect not. I'm just curious, because that would be more likely, I suppose.

DR. BEEDHAM: Sonata is metabolized -- can you just go back to that slide, please, 43? It's not completely cleared by aldehyde oxidase. In fact, I think it's a 3A4 pathway plus an aldehyde oxidase pathway, so

it's similar in that respect to ziprasidone.

They did I think a cimetadine interaction study, which caused very weak inhibition. It had very little effect. But the enzymology of the actual interaction hasn't been absolutely clear with Zalapron anyway, and as you can see, it's an oxidative reaction, not a reductive reaction, so you would not necessarily expect the same spectrum of inhibitor.

DR. LINDENFELD: Could I ask one more question?

DR. TAMMINGA: Yes, Dr. Lindenfeld.

DR. LINDENFELD: Because bradycardia is a predisposing factor for torsade, I wonder if Dr. Harrigan could tell us if there was a heart rate exclusion from these studies.

DR. HARRIGAN: There was no heart rate exclusion, no.

One other additional point. The package insert for Sonata mentions potential interactions with diphenhydramine and cimetadine, as Dr. Beedham I think mentioned. We have conducted interaction studies with both of those compounds diphenhydramine and cimetadine, and found no significant interaction, no meaningful interaction between those drugs.

DR. TAMMINGA: The committee would like to thank Pfizer for their presentation, and we'll take a

break. Before our morning coffee break, Sandra Titus has an announcement to make.

DR. TITUS: If there's anyone else who would like to participate in the open public hearing which will take place right after the noon hour, please come up and speak to me during this break.

DR. TAMMINGA: I'd like to ask people to come back at about 10:35, please, to take a 15-minute break. Thank you.

(Recess.)

DR. TAMMINGA: I'd like to start the second half of the morning. This will include the FDA presentations.

To begin the FDA presentations, we'll start with the introduction by Tom Laughren, who is the team leader for the psychiatric drug products.

Dr. Laughren.

DR. LAUGHREN: I just want to make a few brief comments to introduce the FDA presentation. If I could have the next slide?

There are two parts to the presentation. We've asked Dr. Moss to give a general overview of the QTc, talk about what it is, why one needs to be concerned about it, what sort of data are available to lead one to conclude that it's a problem and so forth, and then we're going to

have a number of speakers from the Center talk about the drugs in each of their areas that have a QT problem and the kind of thinking that's gone into working those drugs up and making decisions about them, so that you can get an overall perspective on how the Center has dealt with this issue.

There isn't any clearly articulated policy about how to deal with the QTc issue, but I think what you'll see emerging from these talks is a series of principles that are looked at in working up drugs and making decisions.

If I could have the next slide, what I'm going to do is try to take a stab at summarizing what I think these principles are so that as you hear these talks you can focus on these issues.

One issue is the indication itself and the availability of treatments for the indication. A second issue is the observed QTc effect. A third is other evidence suggestive in the database of a serious outcome associated with the QTc effect. Finally, this issue of a drug having a metabolic problem.

If I could have the next slide, please.

First of all, the indication itself. One thing that I think you'll hear is the seriousness of the indication is one thing that factors into the thinking

about how to deal with the QT issue. How effective are available treatments? How many alternative treatments are available? How does the new treatment compare with other treatments in the class with regard to efficacy, and also with regard to safety?

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The second issue is the actual size of the QTc effect, both in terms of the mean effect in the dose range that's proposed, but also the proportion of outliers, any way that you look at outliers, whether you look at the proportion of patients who have a change of a particular size from baseline, or the proportion of patients meeting some threshold criterion such as 500 milliseconds.

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A third issue is whether or not there's any other evidence of a drug with a QTc effect having any effect on either overall mortality or any evidence suggestive of sudden, unexplained deaths, whether that's in the NDA database or from some other source. Another way of looking at that is actual cases of torsade or some other serious ventricular arrhythmia occurring again within the NDA database or from some other source. Finally, as was pointed out earlier, sometimes torsade may present with syncopal episodes, so one would be interested in looking at syncope as a surrogate.

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Then finally this issue of the metabolic problem, and that is basically the vulnerability of a particular drug to have its plasma levels increased by virtue of its metabolism being inhibited by a co-administered drug that interferes with its clearance or its use in some subpopulation who don't have the ability to metabolize that drug very efficiently.

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Now I want to turn briefly to the questions. As I mentioned earlier, there are the two general questions that we always ask you to discuss. First of all, has the sponsor provided evidence from more than one adequate and well-controlled clinical investigation that supports the conclusion that ziprasidone is effective for the treatment of schizophrenia? Secondly, has the sponsor provided evidence that ziprasidone is safe when used in the treatment of schizophrenia? Of course, the QT issue is embedded in the safety question.

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Now, if you respond positively to the two general questions, there are a number of additional questions that we'd like you to discuss. There isn't any need to actually have a vote on these additional questions, but we would like to have them fully discussed.

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This is really the hardest question: Do you think that ziprasidone's risk of serious ventricular arrhythmias and sudden unexplained death is greater than that of most other drugs in this class, even if that excess risk cannot be quantified?

Now, there are several ways you can think about this question, and it depends on really what your belief is about whether or not there's a continuum of drugs in this class and their effects on QT or whether in some sense ziprasidone stands apart. From Study 054, there was a suggestion of a change from baseline in the four other drugs that it was compared with. There was no placebo in that trial, so it's hard to know what that means. In other settings, we've never seen a difference between haloperidol and placebo. But if you think that this is a continuum, then the question is does this somewhat greater effect on the QTc with ziprasidone convert into some real greater risk of serious outcome? So that's really the question.

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If you believe there is some excess risk, even though it's not quantified, associated with this drug in terms of risk of ventricular arrhythmias or sudden unexplained death, and you nevertheless believe that the drug can be approved, the question for us is how should

this risk be handled in labeling? That's a very difficult problem.

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One way of handling this -- and, as you well know, from our recent action on thioridazine, I think the "Dear Doctor" letter probably went out last week, for that particular drug with its effect and the fact that there are cases of torsade reported with that drug, we've chosen to make it a second-line drug. So that's the first question, whether or not the QT effect you're seeing here warrants a second-line status or if it can be a first-line status drug.

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Another issue is how should the warning be conveyed in labeling? Basically, what we're talking about here is a choice of two, either a black box or a more typical warning statement.

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Finally, for drugs that have serious side effects, in recent years we have often prepared a patient package insert to inform patients and families about the risks of using the drug. This is particularly important if there are conditions to be avoided. So another question here is whether or not there should be some kind of patient material that would accompany the labeling of this drug.

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Finally, I want to talk about the possibility of asking for additional studies, focused both on safety and on efficacy. A further question is if we were to ask for these studies, when should these studies be done? Should these studies be done before any approval decision, or would this be a Phase IV commitment?

If I could have the next slide, please.

Assuming that there is some unquantifiable risk associated with this greater effect on the QTc, the next logical question is how would one go about quantifying that? It would be a very difficult study to do, but one possible study would be to do a large comparative trial to try to estimate or rule out at some level a risk of excess sudden unexplained death associated with the use of the drug. If there's interest, we can talk more about this. As I say, it would be a difficult study to do. It would have to be large, and there would have to be some further explanation of a number of kinds of information that would have to go into the design of that trial that are not easily available.

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Finally, there's the question of whether or not there is something on the efficacy side to balance the excess risk that may be associated with the QTc effect. So

the next question that comes up, should there be some kind of study to look to see if there is some extra benefit in terms of efficacy associated with the use of this drug? The only other example that I can think of recently where we've done this is with the drug clozapine, where patients who were refractory to standard therapy were studied and it was shown that clozapine had an advantage over standard therapy. So the question is, should this kind of study be done for a drug with this effect?

I will stop at this point, and I think Dr. Moss is going to be the first speaker.

DR. TAMMINGA: Dr. Moss is professor of cardiology at Rochester Medical Center.

DR. MOSS: Dr. Tamminga, Dr. Katz, Dr. Laughren, members of the Advisory Committee and attendees, I've been asked to give an introduction to the QT issue problem, and I'll do so with some slides.

If we could see the first slide? I wonder if somebody could just turn on the slide machine?

PARTICIPANT: The carousel is empty.

DR. MOSS: The carousel is empty? Well, there should be a carousel over there.

That's what's called a double-blind presentation.

(Laughter.)

DR. MOSS: We may need the lights down just a little bit on this first slide and not on the rest of them. This is really an overview of the whole relationship between the electrocardiogram with the QT interval, and what you can't see is that in the dotted line, the prolongation of the interval, the action potential -- that is, the characteristic cellular action potential -- and the prolongation of the action potential that occurs that is probably responsible for the manifest QT prolongation on the electrocardiogram, and the channels that are involved in the action potential, with particular focus on the potassium channels that are responsible for the repolarization phase.

It's the repolarization that is the energy-requiring process, and the drugs that have some concern are drugs that seem to interfere with the potassium delayed rectifier occurrence. As shown in a little bit more schematic over here on the right side, there are, in essence, two major groups of potassium channels that are currently well described. There are many more potassium channels, but two are the so-called IKs, the slowly-activating potassium repolarization current, and it does not appear that there are a lot of drugs that have a lot of effect upon this potassium channel.

But the other channel, the HERG channel, which

is co-assembled with another protein that is referred to as the IKr channel or the rapidly-activating delayed potassium repolarization channel, is the one where the drug seemed to have some effect in a variety of different studies. It's this alteration that changes the kinetics of this channel that prolongs the action potential and is responsible for the QT prolongation.

At the present time, one is simply measuring the QT interval, but these drugs and genetic disorders that affect the HERG channel also change the morphology of the T wave.

Now, in terms of ionic channel dysfunction, there are genetic mutations involving the IKs, IKr, and the sodium channel. We're not in any way interested in the sodium channel at this time. The focus is on the IKr channel or the HERG gene, the gene that's altered genetically, and this is the genetic disorder. Relative to drugs that bind the channel and modify their function, the classical one is terfenadine in a dose-response curve, and you've heard a lot about that. Erythromycin and other antibiotics can also affect the HERG function in this acquired drug manner, and such classical drugs as quinidine are known to have significant effects on HERG, as well as on the sodium channel.

But today, we're really talking about drugs