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CENTER FOR DRUG EVALUATION AND RESEARCH
Psychopharmacologic Drugs Advisory Committee

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8727 Colesville Road
Silver Spring, Maryland

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P R O C E E D I N G S

DR. GOODMAN: Good morning, everybody. I'm Wayne Goodman, and I'll be chairing today's FDA Advisory Committee. I'd like to first remind you to silence your cell phones, Blackberries, I-phones, other devices, if you haven't done so already. I would also like to identify the FDA press contact, Ms. Riley.

If you're here, please stand up; identify yourself.

Two people have waved and identified themselves.

MS. RICE: I'm Crystal Rice --

DR. GOODMAN: Okay, very good.

I just thought we'd start by going around the table and introducing everybody. As I mentioned, I'm Wayne Goodman. I am at the National Institute of Mental Health, where I'm director of Division for Adult Translational Research.

Why don't we start at that end over there.

DR. LAUGHREN: I'm the Director of the Division of Psychiatry Products at FDA.

DR. MATHIS: Mitchell Mathis, Deputy Director,

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Division of Psychiatry Products.

MR. HENDREN: My name is Bob Hendren. I'm a Professor of Psychiatry at the University of California at Davis and President of the American Academy of Child and Adolescent Psychiatry.

DR. SLATTERY: I'm Marcia Slattery. I'm a Child and Adolescent Psychiatrist at the University of Wisconsin, School of Medicine and Public Health.

DR. DAY: I'm Ruth Day, Director of the Medical Cognition Laboratory at Duke University, with a

background in drug safety and risk management.
DR. BILKER: Warren Bilker, Professor of Biostatistics at the University of Pennsylvania.
DR. GRANGER: Chris Granger, Cardiologist, Duke University.
DR. WAPLES: Yvette Waples, the DFO for today's meeting.
DR. PINE: Danny Pine, Child and Adolescent Psychiatrist from the NIMH Intramural Research Program.
MS. GRIFFITH: I'm Gail Griffith and the Consumer Representative for this Committee, and I'm a writer and activist on mental health issues here in
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Washington.
DR. KELSEY: I'm Sherry Kelsey, Statistician, Professor of Epidemiology at the School of Public Health at University of Pittsburgh.
DR. HARRINGTON: Bob Harrington. I'm a Cardiologist at Duke University. I'm a standing member of the Cardio-Renal Panel.
DR. WINOKUR: Andy Winokur. I'm in the Psychiatry Department at the UCON Health Center.
MS. LAWRENCE: I'm Margy Lawrence. I'm a Patient
Representative and affiliated with NAMI, National Alliance on Mental Illness in Montgomery County here.
DR. MALONE: I'm Richard Malone. I'm a Professor of Psychiatry at Drexel University, College of Medicine.
DR. POTTER: I'm Bill Potter. I'm at Merck Research Labs, and I'm the nonvoting industry representative.
DR. GOODMAN: I want to thank all the distinguished members of this panel for being here today, and I want to thank everyone in the audience, as
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well as industry, who will be doing presentations today.
For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal at today's meeting is to be fair and open, have it be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.
In the spirit of the Federal Advisory Committee Act and the Government and the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the Committee is

reminded to please refrain from discussing the meeting topic during breaks or lunch.

Thank you very much, and let me turn the mic over to Yvette Waples.

DR. WAPLES: Thank you.

The Food and Drug Administration, FDA, is convening today's meeting of the Psychopharmacologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members are special Government employees, SGEs, or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with Federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C., Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, FD&C Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have potential financial conflicts when it is determined that the Agency's need for particular individual services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussion of today's meeting, the members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and for purposes of 18 U.S.C., Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussions of the safety and efficacy issues regarding new drug application, NDA 20-644, Serdolect, sertindole tablets, sponsored by H. Lundbeck A/S in collaboration with Abbott Laboratories, proposed for the treatment of schizophrenia. This is a particular matters meeting where specific matters related to Serdolect, sertindole, will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the Committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. With respect to FDA's invited industry representative, we would like to disclose that Dr. William Potter is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Potter's role at this meeting is to represent industry in general and not any particular company. Dr. Potter is employed by Merck & Company.

We would like to remind members and temporary

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voting members that if the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships that they may have with any firm at issue. Thank you.

DR. GOODMAN: Okay. Thanks, Yvette.

I see that somebody else has joined us.

Dr. Temple, could you introduce yourself?

DR. TEMPLE: Yes. Bob Temple. Sorry I was late parking. I'm Director of the Office of Drug Evaluation I.

DR. GOODMAN: Okay.

Do we still have somebody missing? My eyes aren't as good as they used to be. From our side over there?

Oh, that's Marc Stone, FDA. Okay. So that's fine.

But everybody is accounted for, Yvette, from

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our panel?

Okay, very good.

I'd like to remind public observers at this meeting, that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. And there is a specific time allotted later for public testimony.

Now, one of my jobs is to keep us on time, and we're ahead by about two or three minutes, so we're making progress.

The first presentation will be from the FDA, which I shall introduce Dr. Laughren.

DR. LAUGHREN: Good morning. I'd like to welcome everyone to the meeting today. Today, the focus of our meeting is going to be on the safety and efficacy issues for new drug application for sertindole for the treatment of schizophrenia. Now, sertindole, as you know, is an atypical antipsychotic agent, and the sponsor is seeking claims, both for the treatment of schizophrenia, generally, but also specifically for

reducing the risk of fatal and nonfatal suicide attempts in patients with schizophrenia.

Now, we have provided you with various FDA review documents for this application, including both the current application that we are considering, but also several review documents from the previous applications for this product. We've also provided you the sponsor's background package for sertindole.

Now, I can tell you that the division has concluded that the sponsor has submitted sufficient data to support the conclusion that sertindole is effective for the acute treatment of schizophrenia, and that the overall safety profile for this drug, with the exception of a potential to prolong the QTc interval, appears to be similar to that observed with other atypical antipsychotic agents. There remains, however, a concern about a possible risk of sudden cardiac death with this drug, related to its potential for QTc prolongation.

To address this question, the sponsor has conducted a large, simple trial, the sertindole cohort prospective study, or what we will refer to as the SCoP study, comparing sertindole to risperidone, another atypical, antipsychotic on all-cause mortality. In addition to examining mortality, this study has also compared these two drugs on suicidal behavior.

Now, if sertindole does turn out to have a benefit on suicidal behavior in this population, this would be an important advantage for this drug over most other antipsychotic drugs that have not been shown to have this specific benefit. Suicidal behavior is, of course, an important aspect of schizophrenia and a common cause of death in this population.

The formal presentations today will include a summary of the safety and efficacy data for this drug by the sponsor. The FDA's presentation will focus more specifically on the cardiovascular risks for sertindole, including both the QTc data and the mortality data from the SCoP study. We will also present the data pertinent to the claim for a reduction in suicidal behavior. We will also include a presentation on what are known as REMS or risk evaluation and mitigation strategies. The REMS issues will be pertinent for sertindole if it were to be approved.

I'm sure you've discerned from FDA's review documents that we continue to have concerns about sertindole's potential to cause excess cardiac deaths compared to other drugs in this class, and that we also have concerns about the sufficiency of the data the sponsor has provided to support the claim of a benefit for suicidal behavior in this population.

Regarding cardiovascular risks, we don't think that the SCoP study meets the non-inferiority criterion

of 1.5 on all-cause mortality. It's close, but the upper bound of the 95 percent confidence interval exceeds 1.5 in our view. In addition, it's not clear that the standard of being as much as 50 percent worse than a comparator on mortality is necessarily acceptable. In addition there is a clear excess of sudden cardiac deaths in sertindole patients.

Regarding the data supporting a benefit on suicidal behavior, we feel they are suggestive but fall short of meeting a regulatory standard for this claim. There's only one other drug, as you know, that is approved for a benefit on suicidal behavior in schizophrenia, the drug clozapine. And that approval was based, in part, on a robustly positive control

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trial, but also on a strongly suggestive observational study that utilized the clozapine registry. Nevertheless, the Division has not yet reached a final conclusion on this application, and we seek your advice before we do reach a conclusion.

After you've heard all the findings and arguments, we will ask you, first of all, to discuss and comment on several questions of particular concern regarding the safety and efficacy of this drug. Then we will ask you to vote on three questions.

So, first, the issues that we wish to have you discuss and comment, I believe you have these in front of you -- first of all, has the cardiovascular risk for sertindole been adequately characterized? And if so, does this risk pose an obstacle to the use of this drug in the treatment of schizophrenia?

Secondly, has sertindole been shown to have an advantage over other antipsychotic drugs with regard to reducing the risk of suicidal behavior in this population?

If you do end up concluding that sertindole is a drug with sufficient benefits to justify its

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availability despite its risks, we would like you to discuss the public health consequences of having this drug available, as well as possible strategies for mitigating the risk if this product were to be approved.

Then we'll have three questions that we want you to vote on. First of all, has sertindole been shown to be effective for the acute treatment of schizophrenia? Secondly, has sertindole been shown to be effective for the treatment of suicidal behavior? And then, finally, has sertindole been shown to be acceptably safe for the acute treatment of schizophrenia?

Now, you should not feel constrained by this set of questions. In other words, if you feel that it's necessary to modify the questions, you should feel free to do so. We want you to vote on questions that you think are meaningful. And if you have additional issues or questions that you wish to discuss, you, of

course, may do so. And I'll stop there. Thank you.
DR. GOODMAN: Okay. Thanks, Tom.
Now, we'll hear a series of presentations from
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the sponsor.
DR. PEDERSEN: Good morning, Chairman Goodman, Members of the Committee and the FDA. My name is Anders Pedersen, and I'm the Executive Director of Lundbeck, responsible for drug development. We're here today to present our data on the antipsychotic medication, sertindole, and to request your positive recommendation for sertindole for the treatment of schizophrenia and for reducing the fatal and nonfatal suicide attempts in patients with schizophrenia.
The reduction of suicide attempts is a significant need in patients with schizophrenia, in particular, in patients with a known history of suicide attempts.
Let me tell you a bit about sertindole's pharmacology. It has unique limbic selectivity, which may account for its low-level, extrapyramidal syndrome, EPS, or movement disorders. This is brought about by a balanced effect on the dopamine D2 receptors, as well as effect on select other receptors. Importantly, sertindole has no antihistamine or anticholinergic activity. This translates into a low potential for
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sedation and cognitive disturbances, which are major issues in this disease.
Schizophrenia is a chronic and severely disabling disease with early onset. Patients with schizophrenia have a two to three-fold increase in mortality compared to the normal population, and suicide is an important contributor to that increased mortality. Close to half of all patients attempt suicide and many of them have fatal outcomes. Thus, any treatment that reduces suicide attempts in patients with schizophrenia is meaningful. It is also important to recognize that no treatment is effective in all patients, so there is a medical need for additional treatment options for this disease.
We agree with the FDA that sertindole has demonstrated efficacy with an effect size similar to that of other antipsychotics in adequate, well-controlled studies. Patients treated with sertindole have a response rate of 40 to 50 percent in dosages between 12 and 20 milligrams. Sertindole has an extensive body of nonclinical and clinical data, as well as data from a very large, randomized, simple
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study. Sertindole is currently approved in Europe, Asia and Latin American countries, altogether providing us more information on clinical use than most other drugs under NDA review. It has a well-characterized safety profile and is well tolerated. Importantly, it has placebo level incidence of EPS. And as we'll show you, the risk associated with a QT prolongation is more

and well defined and can be managed through proper labeling and patient selection.

Sertindole was discovered by Lundbeck and developed in collaboration with a U.S. partner. Our partner filed the first NDA in 1995, and sertindole received a positive vote on both efficacy and safety from the FDA Advisory Committee meeting in 1996. Soon thereafter, the FDA issued two approvable letters; however, because of QT prolongation observed in the clinical trials, one of the conditions for approval was that our partner company was asked to conduct a large post-marketing safety study to assess mortality. Our U.S. partner chose to withdraw the NDA in 1998 and the rights were returned to Lundbeck in 2002.

Meanwhile, in Europe, Lundbeck launched

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sertindole between 1996 and 1998. In 1998, sertindole was withdrawn from the market due to a concern or an increased mortality in cardiac event reporting rate ratio in the UK. Lundbeck conducted extensive research and epidemiologic studies to address these concerns, and these studies could not confirm the above signal. After reviewing the results, European experts and regulators therefore concluded that the benefit/risk ratio of sertindole was positive, and they requested a large prospective study to confirm these findings.

The SCoP study was designed as an all-cause mortality trial, and after discussions with the FDA, we included suicide and suicide attempts as a prospectively defined endpoint. The results of the SCoP study led European regulators to approve sertindole, and it was relaunched in 2006. The SCoP study was a 10,000 patient, well-controlled prospective, randomized simple study against risperidone. In this context, the term "simple" means with limited intervention in order to mimic normal clinical practice. The SCoP study was, in fact, a massive undertaking and is one of the largest

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prospective randomized studies ever conducted in patients with schizophrenia.

All-cause mortality was considered the most objective endpoint to determine increased cardiovascular risk in an open-label comparative setting. There was a very high degree of follow-up to ensure we knew what happened with patients so that the endpoint could be accurately determined.

The SCoP study met its primary endpoint. It demonstrated that all-cause mortality with sertindole was comparable to that of risperidone. This conclusion was reached after European regulators reviewed the second pre-specified interim analysis after 100 events. They concluded that the data were convincing and provided enough reassurance to support the closing of the study before reaching its originally planned 150 events. It was considered that continuing the study would not yield significant additional information.

Importantly, sertindole was superior to risperidone in reducing the rate of suicide and suicide attempts, the results of the pre-defined endpoint. These events were prospectively identified and

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classified using MedDRA classification. A blinded safety committee reviewed more broadly safety data from the study. During the NDA review, the FDA requested that all suicides, suicide attempts, ideations or tendencies, as judged by the safety committee, be blindly reviewed and classified by an independent expert group according to the Columbia Classification Algorithm for Suicide Assessment, the C-CASA.

Here we see the results of both assessments of suicide and suicide attempts from the SCoP trial, the unblinded MedDRA and the C-CASA. While we may differ with the FDA on the exact statistical interpretation of these data, we're in agreement that the point estimate of hazard ratios for suicide attempts, both fatal and nonfatal, under multiple recording periods regardless of the classification system, are all in favor of sertindole. These data will also be reviewed in more detail in a few moments.

Here is our agenda and our presenters. We'll begin with Dr. Carol Tamminga, Professor of Psychiatry at the University of Texas, Southwestern School of Medicine, who will provide her clinical perspective on

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the medical need for treating schizophrenia with particular attention to suicide. Then, Dr. Raimund Buller will present the clinical data on the efficacy of sertindole and describe the SCoP study and sertindole's reduction of suicide risk. Dr. Lasse Ravn will present data on the general tolerability of sertindole, the safety data on QT interval prolongation, and mortality with particular focus on the SCoP study. And, finally, I will return to wrap up our presentation.

We also have a number of additional experts with us today to answer your questions. Dr. Edward Pritchett is a cardiologist and clinical pharmacologist with expertise in arrhythmia. Dr. Charles Antzelevitch is an expert in experimental cardiology and cardiac electrophysiology. And also with us today is Dr. Judith Jones, clinical pharmacologist and pharmacoepidemiologist.

I will now turn the podium over to Dr. Tamminga.

DR. TAMMINGA: Good morning. My name is Carol Tamminga. I'm pleased to be able to talk with

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Dr. Goodman, the Committee and the FDA about the medical need in schizophrenia. I've been an academic psychiatrist for more than 20 years with an emphasis on clinical research and patient care in schizophrenia. It's my pleasure to be able to present the unmet clinical need for additional treatments for the

disorder. I will discuss the disease, our patients, and our need for more treatment options, with a particular emphasis on suicidality, defined today as risk of suicide and suicide attempts.

Schizophrenia is one of most serious of all psychiatric conditions. It affects about 1 percent of the population in the United States, and the average age of onset is in the early twenties. It strikes people right at the beginning of the most productive period of their lives. It's an illness that affects very broad aspects of human function. Most people are surprised to learn that less than 20 percent of people with the illness actually work productively, fewer than 1 percent ever marry, and for almost all patients, it's a very chronic, lifelong disorder with high relapse rates. All of this causes overwhelming hardship for

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patients and for families.

Schizophrenia is a complex, multi-symptom disorder with several different domains of dysfunction. It's most commonly known domain of dysfunction is psychosis, which is characterized by hallucinations, delusions and paranoia. But this is not by any means the only domain. There's negative symptoms, cognitive dysfunction, most commonly, dysfunctions in attention, executive function in memory, and mood dysregulation.

All of this leads to significant social impairment. Patients are usually unemployed. They're oftentimes homeless and sometimes incarcerated. And most people with schizophrenia are socially isolated and have a lack of access to quality health care. Because of these factors, our patients frequently have high levels of physical as well as mental illness, which must be considered in prescribing medication.

When assessing a person with schizophrenia for treatment, psychiatrists look at a number of different factors. We look at the individual risk profile of the patient, and these are based on patient characteristics such as age, medical health and mood regulation.

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Specifically for our discussion today, a psychiatrist asks if a patient has an elevated risk for cardiovascular disease and the characteristics that go along with that, or if a person raises a specific concern about suicidality. Characteristically, these two risk profiles will appear in different patients, oftentimes suicide in the very young and cardiac risk factors in older people. However, when these two risk factors are present in the same patient, psychiatrists must weigh the relative risk in an individual patient.

It's important to emphasize that psychiatrists in clinical practice have both the obligation and the experience to make these kind of risk-benefit choices in the context of personalized medicine, but we need more treatment options. Because the current treatments in schizophrenia are very limited, not all treatments are effective for all symptom domains. In fact,

psychosis is in the only symptom domain that has actual, adequate treatments. And not all treatments are effective in treating the multiple symptom complexes and the effectiveness is different by individuals, and patients do not respond to treatment,

and the effectiveness of treatment for individual treatment domains varies.

There are side effects of many antipsychotics, and they oftentimes lead to noncompliance. Many of the side effects include excessive sedation, somnolence, lethargy, motor side effects. These can be particularly troublesome to young patients who are likely to stop drugs due to these side effects. A number of medications carry the side effects of the metabolic syndrome, QT prolongation, and their associated cardiovascular risks.

For an older patient with cardiovascular risk factors, you would not prescribe the same medication as one would for a younger, more recently diagnosed patient with good premorbid function. For the younger patient I've described, you would be less concerned about cardiovascular disease and more concerned about suicidality.

The risk of suicide in people with schizophrenia, as an Australian study put it recently, is unbearably frequent, much higher than in the general population. In a Finnish study, which was recently

published based on a 10,000 person birth cohort, approximately 50 percent of all of the deaths between the ages of 16 and 39 were by suicide. So the birth cohort has gotten to 39 years, and 50 percent of all the deaths in this cohort have been by suicide, providing a rate of suicide of 2.9 percent in women but 9.2 percent in men.

In addition, one of the biggest risk factors for completed suicide is prior attempts. Ninety percent of patients who commit suicide have made previous attempts, so it's possible to find useful markers of treatment. Perhaps the most significant risk factor for suicide is hopelessness. Other risk factors include male gender, depression, substance abuse, good premorbid function, and young age. The average age of death for most people with schizophrenia is earlier than the usual population, but 60 years, whereas the average age of death by suicide is in the late thirties.

While we have very little knowledge about how to prevent suicide, targeting a patient with significant risk factors with a known treatment could

bring medical benefit. Given our lack of knowledge, it would be helpful to have additional treatments that might prevent suicide attempts in high risk people. But the only drug indicated for reducing suicidal ideation is clozapine, which is a difficult treatment

because of its significant side effects. These include serious side effects like agranulocytosis, cardiomyopathies, and seizures, and troublesome side effects like hypotension, blurred vision and excessive sedation.

These side effects make clozapine challenging for physicians to use and difficult for patients to tolerate. Moreover, it's important to realize that the sertindole evidence you'll hear today regarding suicide is based on a stricter outcome measure, the outcome measure of suicidal events, compared to the data which was used for the clozapine approval.

To summarize, the problem is clear. There's considerable unmet need for additional treatments in schizophrenia. Many domains of treatment are entirely unaddressed. Current drug therapies have incomplete efficacy and potency, coupled with limited

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tolerability. No one compound is best for all patients, and individual patients can respond to the same drug differently. The good news is that we do have enough knowledge to assess patients' profile against the risk-benefit for each potential treatment in order to maximize treatment benefit and minimize risk. If we have an opportunity to provide a new and efficacious treatment for schizophrenia, we should take it, especially if it has the potential to reduce risks of suicide, which is an aspect of the illness, which causes patient and family suffering.

Thank you for your attention, and I'll now turn the podium over to Dr. Raimund Buller, who will show the efficacy data on sertindole and its effect on suicidality.

DR. BULLER: Thank you, Dr. Tamminga.

Good morning. It is certainly an honor for me to address this committee. I'm a trained psychiatrist, and I've worked in the university hospital with patients for 10 years before joining the pharmaceutical industry. I will start with a global summary of sertindole's efficacy and then discuss sertindole's

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effect on the reduction of the risk of suicide attempts. I will also introduce the methodology of the sertindole cohort prospective study, a SCoP study, which provided the key support for this reduction of suicide risk.

The FDA has already agreed that sertindole has demonstrated efficacy in two adequate and well-controlled studies. Several supportive studies further illustrate sertindole's antipsychotic effect. The efficacy is similar to that of other first and second generation antipsychotics, like haloperidol or risperidone, and global antipsychotic effect usually measured with a PANSS total score and also in responder rates and time to response. Data also support long-term efficacy of sertindole.

As we have just heard Dr. Tamminga say, there

is a need for additional treatment choices in schizophrenia, particularly for drugs that reduce suicidality. The FDA has acknowledged this need and regard suicidality in schizophrenia as a valid target for drug development.

While the Agency has expressed concern about

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our data from a statistical perspective, I will show that there is a clinically relevant treatment effect with sertindole in reducing the risk of suicide and suicide attempts. Before presenting the data, I will review the key studies and the doses used.

Sertindole has been examined in more than 20 clinical trials. As the FDA agreed, the efficacy was demonstrated in two U.S. studies, the Landmark study and M93-098. Both were placebo controlled and used haloperidol as a comparator. These results were supported by two active control trials, the European and French studies. In an earlier U.S. study, M92-762, we saw that the 8 milligram dose was subtherapeutic. The U.S. one-year study was a double-blind active control trial with haloperidol that examined the long-term effects of sertindole.

Now, let's look at some key results.

Here are the results from the Landmark study. This placebo controlled study has a unique design as it also includes three dose levels of the comparator, haloperidol, including a low dose of 4 milligrams. Thus, it allows an unbiased estimate of sertindole's

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therapeutic effect versus placebo and also versus haloperidol, the standard treatment. Sertindole was similar to haloperidol in the reduction of the PANSS total score shown here on the Y axis. The PANSS scale is currently the most widely accepted instrument to measure efficacy in schizophrenia trials. All sertindole doses from 12 to 25 milligrams were significantly superior to placebo. These results were confirmed in the second pivotal study. Both the 20 and 24 milligram doses of sertindole was significantly superior to placebo.

In the French study, we used the flexible dose design. Sertindole was compared to risperidone. On the Y axis, the PANSS total score is plotted and the X axis represents time and weeks. Both treatments show a similar reduction in the PANSS total score at endpoint. The Landmark study also provides information on responder rates. Response is defined as a reduction in the PANSS total score of at least 30 percent, which is considered a clinically relevant measurement. Sertindole and haloperidol were comparable, and sertindole doses from 12 to 24 milligrams was

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significantly superior to placebo. Approximately 40 to 50 percent of those receiving active treatment responded while the placebo responder rate was only about 20 percent.

In the same study, the time to a clinically relevant response was also comparable between sertindole and haloperidol despite the fact that sertindole requires stepwise up-titration. Here, response was defined as at least 30 percent sustained reduction in the PANSS total score.

Looking now at dose range, the acute efficacy studies show that sertindole was effective in doses ranging from 12 to 25 milligrams. Here we see the placebo corrected change from baseline in the PANSS total score with a 95 percent confidence interval. The zero line represented here by a dashed yellow line indicates the mean response of the comparator. Doses of 20 and 24 milligrams have comparable efficacy and were significantly superior to placebo. Twelve milligrams of sertindole were superior to placebo in one study. As you can see, the 8 milligram dose at the bottom of the slide was not effective compared to

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placebo. So in the European study, shown in white lines, the 8 milligram dose was used as a comparator and 16 milligrams was significantly superior to 8 milligrams. Thus, we have demonstrated that doses from 12 to 24 milligrams of sertindole are effective. As you will see later in studies such as SCoP, where investigators are free to choose based on the patients' response, doses of 12 and 16 milligrams are preferred.

Turning now to long-term efficacy, we agree with the FDA that we do not have a formal relapse prevention study; however, we do have data on long-term treatment with sertindole. In the one-year U.S. study, stable patients were switched to either 24 milligrams of sertindole or 10 milligrams of haloperidol.

Both groups showed comparable PANSS total scores over 12 months. Not shown on this slide, the time to treatment failure and the retention rates were similar in both treatment groups as well. Later I will present data from the SCoP study for 12 months to further support this efficacy.

In addition to being efficacious in the treatment of schizophrenia, sertindole also reduces the

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risk of suicide attempts to a clinically relevant degree. We first observed this effect in our clinical program, then it was confirmed in our epidemiological studies. The SCoP study, while primarily designed to look at mortality, provided another opportunity to investigate of sertindole on the risk of suicide attempts.

I will begin by discussing data from the original NDA along with data from the olanzapine and risperidone NDA submissions, which were done approximately at the same time.

It appears that the estimate for the rate of completed suicides per 100 patient years of exposure is lower with sertindole. In the literature, the suicide rate in schizophrenia is approximately .7 per 100

patient years of exposure, and that's higher than what we have seen with sertindole.

Since outcomes from clinical trials are not always predictive for routine practice, we look to see if the epidemiological data would confirm the effect on suicidality. These large studies with several thousands of patients show even lower suicide mortality

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rates with sertindole in a naturalistic setting.

Here, we see results from the European Safety and Exposure Survey, ESES, and the Sertindole Safety Survey. In a crossover sub-study of ESES, we followed patients who were switched from sertindole to other antipsychotics. We saw a lower risk of suicide when patients were on sertindole.

We presented the clinical and epidemiological data on suicide attempts to the FDA in 2003, and after discussions with the Agency, we included the composite endpoint of suicide attempts, fatal plus nonfatal, in the SCoP study. This would allow us to confirm sertindole's beneficial effect in a prospective randomized trial.

The definition of a suicide attempt was acceptable to the FDA. Suicidal behavior had to be observable. Mere suicidal ideation and tendencies were excluded. Clinicians were asked to confirm that the patients actually intended to commit suicide. Information on previous attempts was collected on entry and used to define a high risk population. However, the SCoP study did not exclusively select high risk

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patients, unlike the InterSePT study, which I will mention later. Rather, the inclusion criteria were deliberately brought in order to inquire a sample representative of the subtarget population for sertindole.

I will now describe the SCoP design and methodology.

The SCoP study was a randomized, large simple trial in 38 countries in Europe and Asia that compared sertindole to risperidone in approximately 10,000 patients, which makes it one of the largest schizophrenia trials ever conducted. After randomization, patients received sertindole or risperidone as their only antipsychotic. Other medications could also be prescribed if not contraindicated on the label. Later, if the treating physician wished to prescribe an additional antipsychotic drug, they could. Treatment duration was not pre-defined.

I will now present the two main reporting periods.

The only randomized treatment period, or ORT,

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was the period when the patient received only risperidone or sertindole as the antipsychotic medication. ORT is used to examine suicidality to

avoid confounding factors. The other main reporting period, the whole randomized treatment period, or WRT, includes the ORT plus the time when patients received an additional antipsychotic. An additional antipsychotic was prescribed in roughly 7 percent of the patients either to augment efficacy or as a cross-titration to facilitate a treatment switch.

In the SCoP study, patients were randomized to avoid channeling bias that is differential selection for one of the treatments. The study was open label to reflect routine clinical practice. Consistent with a label for each compound, only sertindole patients had follow-up ECGs. Through the first three months, patients were assessed monthly for serious adverse events, suicidality, and non-serious cardiac events, and thereafter on a quarterly basis.

The study was conducted in accordance with good clinical practice and informed consent was obtained. The diagnosis of schizophrenia was based on

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clinical presentation rather than on DSM or ICD criteria, as the goal was to recruit as large and broad a population with schizophrenia as possible. Patients who entered the study were being taken off previous medication either because of problems with efficacy or tolerability. Patients had to be at least 18 years of age and meet criteria from both sertindole and risperidone labels, particularly in regard to contraindications and warnings. While both treatment groups had baseline ECGs before randomization, only sertindole patients were required to have follow-up ECGs.

There were only few exclusion criteria in addition to those mentioned in the label for both drugs. Patients could not be on sertindole or risperidone before entering into the study. They could not be antipsychotic drug naive, nor could they require treatment with more than one antipsychotic. They had to have an address where they could be reached for follow-up, and they had to be able to comply with the study protocol.

The total exposure in this SCoP study was

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almost 15,000 patient years and most subjects were recruited in Europe. Average treatment duration was around one year. Total exposure was lower with sertindole. Importantly, we see that there was no difference between groups in the percentage of patients who discontinued for lack of efficacy. The difference was seen in the category of non-serious adverse events. This was mostly related to asymptomatic ECG findings. And please remember, ECGs were required only for the sertindole group to identify patients with QT prolongations. Investigators tended to take a conservative approach. In some cases, patients were discontinued with QTc values below 500 milliseconds and for other non-specific ECG findings.

Now, looking at doses.
Approximately, 80 percent of the sertindole patients received doses within the recommended dose range, between 12 and 20 milligrams. As in clinical practice, investigators showed a preference for lower doses. The pattern remained stable throughout the first year, indicating that the chosen doses were well tolerated and efficacious over time. This provides

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further support of evidence for the long-term efficacy of sertindole. Similarly, for risperidone, approximately 90 percent of the patients received doses within the recommended dose range and with a preference for lower doses.
Here are the endpoints for the SCoP study. As I mentioned, the primary endpoint was all-cause mortality. This endpoint was fulfilled, as Dr. Ravn will show in his safety presentation. In the following slides, I will focus on the per-specified secondary endpoint of suicidality.
Suicide attempts, along with other serious adverse events, were reviewed in three separate steps. This chart shows the flow of that data. It was first assessed by Lundbeck and coded according to MedDRA, the routinely used classification system, and then by an independent safety committee, or ISC, composed of outside experts. Later, the FDA requested that all cases identified by the ISC be blindly reviewed and classified by another independent expert group according to the Columbia Classification Algorithm of Suicide Assessment, C-CASA.

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This classification was preferred by the FDA, which found the other two to have certain weaknesses. The MedDRA classification was not done in a blinded way, and the ISC classification was too broad, as it included patients who exhibited self-injurious behavior regardless of whether they intended to die, as well as suicidal ideation or tendencies. C-CASA is based on a blinded review and objective criteria. In fact, it has become the FDA's gold standard for the classification of suicidality. The C-CASA covers nine codes grouped in three categories: suicidal events, indeterminate or potentially suicidal events, and non-suicidal events.
The FDA requested a re-analysis of our data with a C-CASA code of 1, 2 or 3, that is, completed suicides, suicide attempts with an intent to commit suicide, or preparatory acts toward imminent suicidal behavior. The review and coding was performed by the Columbia Group under the supervision of Dr. Kelly Posner, the author of this instrument.
Given the FDA's preference for C-CASA, I will present that analysis first, then briefly cover the MedDRA analysis, and come back to the analysis from the

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FDA briefing book.
As I mentioned earlier, I will focus on events

that occurred while the patients were only on the randomized medication plus one day, the ORT plus one day period, to exclude possible confounding of treatment effects due to discontinuation or switching to other drugs. The FDA used a similar period to review suicidality for antidepressants and antiepileptics.

According to C-CASA, there were 36 suicide attempts in the sertindole group and 54 in the risperidone group. When we looked at how suicide was attempted, we found that the sertindole group had fewer violent attempts, 36 percent versus 52 percent in the risperidone group. Violent attempts are of clinical interest as they are more likely associated with severe injury or even death.

Before going to the results, I would like to address one point that was raised in the FDA briefing book. There was concern about potential confounding due to different exposure in the two treatment groups. This slide shows the number of suicides observed during

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the first three months after treatment discontinuation. In this period, the group previously treated with sertindole had a higher exposure, 500 patient years more. The number of completed suicides, however, is comparable, five in the sertindole group versus four in the risperidone group. Therefore, these data do not indicate a higher dropout rate of patients at risk for suicide from the sertindole group.

Our analysis of suicide attempts is based on a Cox regression. This slide shows the variables included in the model and pre-defined either in the protocol or in the statistical analysis plan, which was finalized before the end of the study and included in the NDA submission. In addition to those pre-defined variables, since the inclusion period was five years, we added a variable, date of entry into study, to adjust for changes in practice over time.

This slide shows the results of our analysis based on this model. During treatment, the risk of a patient attempting suicide with a fatal or nonfatal outcome was 30 percent lower with sertindole corresponding to the hazard ratio of .66. In my

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presentation, I will use numbers with only two digits after the decimal, whereas the briefing book presents three digits. I have rounded the numbers up for simplicity.

There were two additional sertindole patients for whom information on some of the prognostic variables was lacking, which prevented to include them in the model. The FDA has imputed these missing values and has come up with a slightly higher estimate for the hazard ratio, .703 instead of .66, and also with a higher p value, .1014 instead of .06. While all p values may not be below 0.05, there are consistent trends in the sensitivity analysis and in the hazard

ratios, which all indicate an advantage for sertindole. For example, the risk of completed suicide in the sertindole group was also lower. There were half as many completed suicides in patients treated with sertindole indicated by a hazard ratio of .50.

Here, we see that the treatment effect emerged soon after the start of therapy during the first year of treatment, where the hazard ratio is .54. The analysis of the first year was added because that's

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when about 80 percent of the events occurred. This also supports the robustness of the findings.

This Kaplan-Meier curve shows the events as they occur over time. The relevant information of the treatment effect is contained in the left part of the curve, shaded in blue, where most of the events occur. On the right part of the curve, we see about 10 more events. The sertindole effect was already visible after three months, and at 6 and 12 months, the hazard ratio is approximately .6, which means that we see a 40 percent lower risk of suicide attempts with sertindole. As you saw before, over the whole study period, the suicide risk with sertindole remained lower, the hazard ratio was .66, which translates into a more than 30 percent lower risk.

Now, let's look specifically at high risk patients, defined by having at least one suicide attempt during the five years before entering the study. This population was different from the total population. They were younger, and few of our chronic patients, a lower percentage of schizophrenia for more than 10 years. Thirty-five percent of these patients

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had actually attempted suicide during the year just before entry into the study.

In this high risk group, we saw more than a 40 percent lower risk of suicide attempts with sertindole, indicated by a hazard ratio of .58. As with the overall population, the effect became visible within the first year. Note that this group was only 7 percent of the total population, yet accounted for nearly half of the suicide attempts. This provides further confirmation that these patients were indeed high risk for suicidality, as well as further evidence for the clinical relevance of our findings.

To put the SCoP results into perspective, we also compared SCoP data to data from InterSePT. InterSePT is widely recognized as a pioneering study, assessing the pharmacological treatment of suicidality in schizophrenia, and it was the basis for FDA approval of clozapine for that indication. InterSePT was a multicenter, two-year trial, comparing clozapine with olanzapine in 980 patients at high risk for suicide. High risk was defined as having either a history of previous suicide attempts, or hospitalizations to

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prevent an attempt in the three years before

enrollment, or moderate or severe current suicidal ideation.

Here, we see that the InterSePT and SCoP studies show comparable risk reduction for clozapine and sertindole. Both studies had similar number of events; InterSePT, 34 and 55, and SCoP, 32 and 51. Both studies showed comparable hazard ratios after two years of treatment; that is, .76 and .61 and similar p values. The InterSePT study shows a hazard ratio above 1 for completed suicide; however, it was not designed to evaluate that effect. In the SCoP trial, sertindole showed a reduced risk for completed suicide with a hazard ratio of .05. And of note, the overall mortality was also lower in the SCoP study. Focusing on the high risk group in SCoP, which is closer to the InterSePT study population, the effect of sertindole on suicide attempts is retained and comparable to clozapine.

In the next slide, I will show you the sensitivity analysis that support the robustness of our findings.

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Here, we see the hazard ratios for various reporting periods, based on both the C-CASA and MedDRA approaches to classifying suicide attempts. As mentioned previously, both classifications are based on observable behavior associated with an intent to die, and both produce similar results, further supporting the consistency and robustness of our findings. The two FDA analyses for ORT plus 1 and WRT plus 30 also show hazard ratios below 1. Therefore, all results presented on this slide show point estimates of hazard ratios consistently in favor of sertindole.

To summarize, the SCoP study has demonstrated a clinically relevant reduction in the risk of fatal plus nonfatal suicide attempts with sertindole in a broad population of patients with schizophrenia and especially in high risk patients. This effect was observed early on during the first 12 months of treatment. Sertindole also reduced the risk of completed suicides. This confirmed previous observations of low suicide mortality in the clinical trials and in the epidemiological studies. The mechanism of this effect is unknown but may be linked

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to the robust efficacy of sertindole as well as to its good tolerability, and notably to the low level of akathisia, which in the literature is discussed as a risk factor for suicide.

To conclude my efficacy presentation, as demonstrated in well controlled studies and stated in the FDA briefing book, sertindole is effective for acute treatment of schizophrenia, and our data support a target dose range of 12 to 20 milligrams. We have shown you that the antipsychotic effect of sertindole is comparable to haloperidol and risperidone in improving the symptoms of schizophrenia. Sertindole

also showed clinically relevant efficacy of long-term treatment.

As Dr. Tamminga has pointed out, half of the people with schizophrenia will attempt to take their lives. Reducing the risk of suicide attempts is just as important as reducing the risk of completed suicide, and sertindole does both. This effect is especially beneficial for high risk patients.

Thank you for your attention. I will now turn the podium over to Dr. Ravn, who will present data on

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tolerability and safety.

DR. RAVN: Thank you.

Good morning. My name is Lasse Steen Ravn, and I'm the head of the Psychiatry Safety Department at Lundbeck. As we've heard today, schizophrenia is associated with significant morbidity for all patients. 1:02:24 what we want to treat, ideally, without introducing side effects that makes it difficult for patients to tolerate treatment. As we've also discussed, sertindole prolongs the QT interval, and while it's in the range of other current antipsychotic medications, we take this concern very seriously.

The FDA briefing document characterizes this risk by focusing on cause-specific mortality and risk of sudden death. We respect the FDA's efforts to try to come up with a meaningful analysis but are concerned about using cause-specific mortality for quantitative purposes. Assessing all-cause mortality is a more reliable endpoint. It's generally considered to be more objective, and when the endpoint is death, it's the most relevant. I'll expand on this later in my presentation.

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First, I'll begin by presenting data on all-cause mortality. I'll also discuss cause-specific mortality, arrhythmias, as we see them in our safety database, and the overdose experience with sertindole. To help us understand these data, I'll explain what we know about the mechanism behind the QT prolongation, and this will include what we have learned from nonclinical investigations, as well as from all clinical trials. I'll end my presentation discussing side effects that are particularly important to patients, such as extrapyramidal symptoms, akathisia or inner restlessness, and excessive sedation. As I'll explain, sertindole has a favorable tolerability profile which will have a positive impact on treatment adherence.

First, the mortality data from our clinical development program.

We used four large sources of data to evaluate mortality with sertindole. They include more than 20 clinical trials with almost 3,400 patients, a series of epidemiologic studies involving approximately 10,000 patients, and a sertindole cohort prospective study, or

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the SCoP study. In addition, we have the database of post-marketing reports collected from 38 different countries where sertindole has been used to treat patients with schizophrenia.

First, we'll look at all-cause mortality from the integrated, primary database, which supports the current NDA. In these clinical trials, we saw a mortality rate of 0.82 per 100 patient years of exposure and 1.47 when we include 30 days following stop of treatment. These rates are comparable to those presented in the approval packages for other currently used antipsychotics. And it's important to note that patients with preexisting cardiovascular disease, they were allowed in the clinical trials with sertindole. That was not the case in many of the studies for these other compounds.

Now, there's always a concern that mortality rates will be higher in everyday clinical practice than in clinical trials, and to address this concern, Lundbeck initiated three retrospective cohort studies. The mortality rates observed in these studies, they were similar to each other, and they were lower than

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what we have seen in the clinical trials. Finally, in order to investigate all-cause mortality in a setting that affects everyday clinical practice, Lundbeck initiated the SCoP study.

As Dr. Buller just explained, the SCoP study was a randomized, large simple trial, comparing sertindole to risperidone in approximately 10,000 patients. And just to remind you, the ORT period is a monotherapy period, and the WRT period also includes the time where some patients received an additional antipsychotic. One of the unique things about the SCoP study was that the patients, they stayed in this trial after stop of randomized treatment and were followed until completion of the trial. At that time, only 12 patients out of nearly 10,000 were lost to follow-up, and there were six in each treatment group.

Here, we see the results of the first primary endpoints, the all-cause mortality. Number of fatal events is low and similar in the two treatment groups. During the ORT, where the patients were treated only with risperidone or sertindole, the mortality rates were 0.6 for both groups and the hazard ratio was very

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close to 1.

Here are the Kaplan-Meier curves for the two treatment groups, and we clearly see that the two curves are overlapping. Again, this is a monotherapy period, the most informative period regarding the effect of randomized treatment.

Now, turning to the WRT period, which includes the time when some of the patients were on polytherapy plus 30 days after stop of randomized treatment. We see increases in mortality for both compounds, but still a hazard ratio 12 to 1.

Now, before considering cause-specific mortality, we'll discuss why this can be difficult to establish. Death is a reliable outcome, but cause of death is not often definitive. Few autopsies are performed and classifications are often based more on medical history than on clinical observation. For example, when a patient with concurrent cancer dies, this diagnosis will often override all the possible causes of death; whereas, with other medical conditions, such as untreated infection, sudden unexplained death may become the default

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classification; that is, if information about the circumstances is lacking. Thus, all-cause mortality is the most reliable endpoint.

We see this illustrated in the SCoP study, where the investigator and the ISC classified similar cases differently, particularly with sudden unexplained death. Since SCoP was an open-label trial with ECG monitoring during treatment only for sertindole treated patients, ascertainment bias regarding cardiac endpoint was inevitable.

Here's just one example. In the SCoP, we received these two reports on two patients, both of whom had seizures and died. One was reported as a myocardial infarction by the investigator and subsequently classified by the ISC as a sudden unexplained death. In the second case, the death was reported as a seizure by the investigator and classified as other by the ISC. Again, from a clinical perspective, the two cases were virtually identical, although the amount of information in both cases was limited. Several deaths of patients taking risperidone that were reported as other actually fulfilled the

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criteria for sudden unexpected death or unknown cause of death, but were classified differently.

Also, when using different methodologies in classifying deaths, you always have different results. On this slide, we see four different ways of classifying the SCoP mortality data and the corresponding rate ratios. The FDA, looking at the ISC classification, has come out with 13 versus 3. However, a more conservative approach would be to pool all cases of uncertain and sudden unexplained deaths, and then calculate the rate based on these numbers. In doing so, we have identified 23 cases in the sertindole group and 17 in the risperidone group, and see it's accrued rate ratio of 1.55 between the two groups. Again, this number is a more conservative approach to analyzing sudden and unexplained death in the database.

So in conclusion, the data shows that all-cause mortality for sertindole is comparable to risperidone as well as to other antipsychotics. As we've seen, assigning cause-specific mortality has significant limitations. In particular, the diagnosis of sudden cardiac death or sudden unexplained death

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require a level of detailed information that in many cases is not available.

I'll now discuss cases of arrhythmia and of torsades de pointes.

In our database, we find one fatal case reported as arrhythmia, one fatal case reported as torsades de pointes, and three nonfatal cases reported as torsades de pointes during therapeutic use of sertindole. Both fatal cases involved elderly patients. Both our confounded by medical history and/or by concomitant medication. And in both cases, the exact cause of death was not identified.

In the global safety database for sertindole, there are three cases reported as nonfatal torsades de pointes during normal treatment. Again, we see that these cases of reported arrhythmia are confounded by a number of factors. These include concomitant medication such as antibiotic, ajmaline, which is a Class 1a antiarrhythmic like quinidine, that confounded by traditional medicine, low potassium medical history such as palpitation and collapse, and by a family history of sudden death.

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Finally, I'll describe the overdose experience with sertindole. As with all other antipsychotics, cases of torsades de pointes have been observed in association with overdoses. Overdoses are important. They provide a way to investigate super therapeutic doses of sertindole and its association with torsades de pointes. In the global safety database for sertindole, there are 280 cases of reported overdose, 133 of these cases involved sertindole, 91 cases with an overdose of sertindole only, and 42 cases of a mixed overdose involving one or more other compounds in addition to sertindole.

For the overdoses involving sertindole, we have eight cases of reported arrhythmia. Three reports were related to an overdose with sertindole only and five were related to a mixed overdose. Torsades de pointes was reported in three of these eight cases. All three cases were suicide attempts, and in all three cases, the patient recovered. In two of the cases, the overdoses were high, 480 and 720 milligrams, respectively. In the third case, the dose was moderate. It was only 48 milligrams of sertindole, but

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it was combined with an unknown amount of thioridizine.

In conclusion, the overdose experienced with sertindole is extensive. Of 133 cases of overdose involving sertindole, there are only eight reports of arrhythmia, and the majority of these involve overdoses of sertindole mixed with another or more other compounds. Reports of torsades de pointes are rare. The rate reported in the clinical trials are three cases in more than 8,000 patients, corresponding to a rate less than one in 2,500. All cases were reported

in female patients. All patients were confounded by risk factors in the medical history and/or by concomitant medication.

We now turn our attention to the QT prolongation. As you know, the initial concern with sertindole was whether the QT prolongation would translate into an increased risk for arrhythmia and death. As we've seen, overall, mortality with sertindole is low and is comparable to that observed with other antipsychotics. Cause-specific mortality also appears to be low. The low number of arrhythmias captured in our global database during normal

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treatment, as well as those in association with overdoses, does not appear to confirm the concern initially raised.

In order to better understand why QT prolongation with sertindole would not translate into a higher death rate, we'll now look at the molecular properties of sertindole and its effect on different cardiac ion channels. Note that the preclinical experience with sertindole is massive. It may be one of the most extensively studied non-cardiac compounds regarding ion channel blockade and effect on the QT interval.

QT prolongation is the most commonly used biomarker for the risk of torsades de pointes; however, it does not always predict an arrhythmic event in a given patient. Furthermore, there is no correlation between the QT interval prolongation and risk of arrhythmia if there is a simultaneous blockade of the late sodium current. Sertindole possesses these multi-channel properties and has been extensively studied in various preclinical models and compared to compounds that selectively block the I KR current.

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On this slide, we see that the QT prolongation is dose dependent, up to the 16 milligram dose, where we see a plateau. On the Y axis, we see the mean QT change in milliseconds, and on the X axis, we plot the various sertindole doses from a clinical development program in the NDA for sertindole. Using current standards for reading and correcting the QT interval, the mean QTc interval prolongation seen with sertindole is 23 milliseconds at the 20 milligram dose.

To put this into perspective, we received data from the 054 study on QT prolongation with, from left to right, ziprasidone, risperidone, olanzapine, quetiapine, thioridizine, and haloperidol. On the right, we have data on sertindole from our own clinical trials, and what we see is that the QT prolongation with sertindole is in the upper end of the range of these other commonly used antipsychotics.

For the two pivotal studies, the ECGs from patients on the 20 milligram dose and on placebo were analyzed in accordance with today's standards. For the

20 milligram dose, 1.5 percent of patients had an ECG with a QTc longer than 500 milliseconds compared to

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none on placebo. Looking at the QT interval change by category, 35 percent of the patients treated with 20 milligram sertindole had an increase between 30 and 60 milliseconds from baseline to last assessment. Ten percent had an increase longer than 60 milliseconds. This is proportionately higher than placebo treated patients. So we know that treatment with sertindole is associated with prolongation of the QT interval up to a mean of 23 milliseconds at the 20 milligram per day dose. The prolongation is dose dependent, and it appears to reach a plateau at the 60 milligram dose.

Now, to gain more insight, we'll look at the preclinical data.

The primary mechanism by which sertindole prolongs the QT interval is reduction of the I current and subsequent prolongation of the cardiac action potential. This is the exact same mechanism as other compounds that cause QT prolongation, including several other antipsychotics.

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On this slide, you see the effect of four different antipsychotics on the I current. On the Y axis, you see the percentage of I current as a

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function of increasing concentrations of the drug, depicted on the X axis. And what we see is that any of these four compounds has the ability to totally block out the I current.

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The effect of sertindole on both the I and the late sodium current can be seen on this slide. Both currents are inhibited in a concentration dependent manner. The yellow line indicates the inhibition of the I current with an IC of 12 nanomolar. The orange line indicates inhibition of the late sodium current with an IC of 51 nanomolar. The blue bar represents the therapeutic plasmic concentration range, and clearly patients are expected to be influenced by the inhibition of both the I and the late sodium current at therapeutic concentrations of sertindole.

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This makes sertindole a mixed ion channel blocker, where the effect on the late sodium current mitigates the effect of the I blockade. This mitigation has been demonstrated in animal models of arrhythmia.

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First, I'll discuss the effect of sertindole

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on so-called early after depolarizations, or EADs. EADs are a phenomenon believed to proceed arrhythmia, acting as a trigger or a starting point for an arrhythmia. Using single fibers from a rabbit heart, we recorded the action potential at low and high heart rates. On the left in this panel, you see the fibers stimulated at 60 beats per minute, and on the right at 12 beats per minute.

At low heart rates, the action potential is prolonged in normal, healthy hearts. We added increasing amounts of astemizole, which is known to trigger EADs. And here in the orange, we see that astemizole prolongs the action potential, especially at low heart rates. Further addition of astemizole elicits EADs at low heart rates, and with increasing amount, we see triggered abnormal activity. For sertindole, we do not see this kind of arrhythmogenic activities, not even at low heart rates.

Transmural dispersion of repolarization is the other phenomenon that is necessary for an arrhythmia to occur. Transmural dispersion is the difference in the length of the cardiac acting potential recorded at the

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outer layers of the heart versus that recorded at the inner layers of the heart. As seen in the white bars on this graph, normal, healthy hearts always have some degree of transmural dispersion, but increasing dispersion will destabilize the myocardium.

On the X axis, you see cycle length, which is a measure of heart rate in this setting, where 300 milliseconds is a fast heart rate and 900 milliseconds corresponds to a slow heart rate. Addition of sertindole, in light blue, does not change transmural dispersion from baseline as compared to sotalol, in red, which is used as a reference in this model because it causes a high degree of transmural dispersion.

Now, to examine whether arrhythmia can be induced under extreme circumstances, we tested sertindole in diseased animal hearts. On the left, you see this G, from a normal heart in sinus rhythm. Following a surgical procedure of AV node ablation, biventricular hypertrophy was induced after eight weeks. The heart anatomy is grossly changed by this procedure, and the heart is no longer in sinus rhythm,

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but an idioventricular rhythm of a much lower rate.

These factors makes this model extremely vulnerable to drug induced torsades de pointes. We see that adding sertindole by a rapid intravenous dose, causing a steep rise in plasma concentration to the high therapeutic range, does not induce ventricular arrhythmias, even in these very vulnerable hearts. To induce arrhythmia with sertindole in this model, it requires not only a compromised diseased heart, it also requires a higher dose of sertindole to be administered

intravenously as a bolus to a level markedly beyond therapeutic concentrations.

So to summarize what preclinical data have taught us about sertindole, it prolongs the QT interval by blocking the I_{Kr} current, and it also blocks the late sodium current. This means sertindole is a mixed ion channel blocker, but the effect on the late sodium current mitigates the effect of the I_{Kr} current blockade. Sertindole does not lead to triggered activity or EADs, and it does not increase transmural dispersion of repolarization, the true phenomenon that are prerequisites for a QT prolongation to translate

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into arrhythmia. Arrhythmia is absent in very vulnerable hearts at therapeutic dosing and only seen with a combination of an extremely vulnerable heart and a rapid infusion of super therapeutic doses of sertindole.

These preclinical data may explain why we find a low number of arrhythmic events in our global safety database, a database comprising more than 40,000 years of patient exposure, including 133 reports of overdoses involving sertindole, some with very high doses of sertindole.

I'll now turn to the general tolerability profile of sertindole. I'd like to repeat what we heard early on today, and that is that treatment is necessary. And, therefore, it's critically important that patients are able to tolerate the treatment. Certain issues related to treatment are particularly important to patients with schizophrenia because they can have such a profound impact on their daily lives. That includes EPS, akathisia or inner restlessness, and excessive sedation. What we'll see is that sertindole has a favorable tolerability profile on these issues.

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The most common adverse events with sertindole are similar to those you see with many other compounds. They include headache, insomnia, nasal congestion, constipation, dizziness. Sexual side effects, which can be very bothersome to some patients, are uncommon with sertindole, except for reduced ejaculatory volume reported by 9 percent of male patients; however, this is rarely of concern if the patient is properly counseled. Importantly, the rates of discontinuation are less than 1 percent for the most common adverse events with sertindole. A thing of special interest is that sertindole has a high degree of limbic selectivity, which can explain the low incidence of extrapyramidal symptoms, such as Parkinsonism and akathisia and dyskinesia.

In the U.S. Landmark study, we saw improvement in EPS with sertindole, with significant superiority over haloperidol for Parkinsonism and akathisia, even at the lowest doses of haloperidol. For akathisia and

dyskinesia, there was greater improvement with sertindole than with placebo. These findings in the Landmark study were based on experts raising the

patient systems, but the results are confirmed by patients own reporting, as you see on this slide.

Here the so-called MedDRA SMQ search has been used to identify all reported adverse events related to EPS and akathisia from the pool of active control studies. We see that the incidence of these adverse events with sertindole was at the level of placebo and certainly lower than with haloperidol. Patients also reported a low level of sedation with sertindole, which, as we know, it's important for long-term treatment and rehabilitation. Sedation, somnolence and lethargy were all at placebo levels. This low level of sedation is attributable to the lack of activity by sertindole on histaminergic H-1 receptors.

Most antipsychotics are associated with weight gain, some with even dramatic increases in weight.

Here are the short-term data from our placebo controlled studies in the United States and in Western Europe, where the mean weight gain was 2.9 kilos over a period of six to eight weeks. Weight has always been a routine assessment in clinical studies, but metabolic effects have not been routine. So to address not only

weight gain, but the whole issue of metabolic syndrome during treatment with sertindole, we initiated a sub-study to the SCoP trial. The sub-study was also a head to head comparison with risperidone. It included more than 100 patients in each treatment group, and it was conducted between 2005 and 2007. Treatment for an individual patient was up to approximately 12 months. Here, we saw lower weight gain, even over a longer period of time than we did in the short-term trials. In this recent study, changes with sertindole in weight, BMI and weight circumference are modest and comparable to those seen with risperidone.

We also looked at long-term weight gain with sertindole in the U.S. and the Western population. And on a list on this slide, you see sertindole compared with haloperidol, and these data are from our own clinical trials. On the right, we have taken the data from the literature on risperidone, quetiapine and olanzapine in the United States, and these data indicate that long-term weight gain in this population would be comparable to risperidone, which is exactly what we saw in the SCoP study. Also in the SCoP study,

we looked at other parameters of the metabolic syndrome, including triglycerides, total cholesterol and HDL cholesterol, and for these parameters, we didn't see any clinically relevant changes from baseline.

In conclusion, in the SCoP sub-study, sertindole was associated with a moderate increase in

weight, but no clinically relevant changes in the other parameters of the metabolic syndrome.

So to summarize the tolerability data, we have shown that sertindole is well tolerated as placebo level sedation and EPS, including akathisia, and it's associated with a moderate weight gain but with no clinical relevant changes in the other parameters of the metabolic syndrome.

To conclude my presentation, sertindole prolongs the QT interval in a dose dependent manner with a mean increase of 23 milliseconds at the 20 milligram dose, and prolongation appears to plateau with the 16 milligram dose. Cases of arrhythmia are few during normal treatment, and the large overdose experience with sertindole supports that sertindole has

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a low risk of causing arrhythmia. During treatment with sertindole, all-cause mortality, the most unbiased endpoint, is comparable to other antipsychotics. And, finally, what we have seen is that sertindole is well tolerated on issues that are important to patients in order for them to be able to adhere to treatment.

So thank you for your attention. I'll now turn the podium back to Dr. Pedersen for concluding remarks.

DR. PEDERSEN: Thank you, Dr. Ravn.

I will now conclude our presentation by summarizing the salient information you have heard today and provide you with our perspective on the overall benefit/risk assessment supporting approval.

The efficacy of sertindole in the treatment of patients with schizophrenia is well established, and the drug is approved for this condition in many countries around the world. Our clinical trials have documented placebo level sedation and EPS. This makes sertindole a well tolerated drug for many patients. And very importantly, sertindole reduces suicide attempts in people with schizophrenia who are known to

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be highly predisposed to take their own lives. This benefit has consistently been observed in clinical trials, in epidemiologic studies, and most recently in the SCoP study where it was a pre-specified endpoint.

The robustness of the SCoP results is reinforced by sensitivity analysis with different observation periods and classifications which consistently point to a benefit of 25 to 40 percent in favor of sertindole. This effect was observed both in a general schizophrenia population and in patients with a high risk.

As Dr. Tamminga has explained, suicide remains one of the main causes of death for people with schizophrenia, and this is not sufficiently addressed by current antipsychotics. Currently, clozapine is the only antipsychotic agent approved in the United States for the reduction of suicide attempts in patients with schizophrenia.

As Dr. Buller has shown us, the InterSePT study allows us to put the findings of the SCoP study into perspective. We see that the rates in confidence intervals for suicide attempt reduction for sertindole

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are similar to that of clozapine over the course of the same two-year observation period that they used.

Sertindole is showing benefit in reducing the rate of completed suicides.

With respect to risk, I'd like to emphasize that we know more about sertindole than we know about most other drugs at the time of NDA review. We know that there is a risk of QT prolongation that may translate into a rare occurrence of torsades de pointes. As with other antipsychotics, torsades de pointes cases have been reported in patients using sertindole as of cardiac events, including sudden death.

The SCoP study, one of the larger ever conducted in people with schizophrenia, was designed in collaboration with regulators to address all-cause mortality in broad clinical practice as an objective endpoint. Therefore, the lack of detailed information on patient death precluded accurate adjudication of cause of death for many medical conditions. Rates of sudden, unexpected death, as we have conservatively reported, are high on sertindole than those reported on

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risperidone; however, not statistically different. And the 1:37:36 risk remains low and not higher than that reported in other large population analysis. However, as we're committed to safety, we will work with the FDA to develop a robust risk management program to accompany an introduction of sertindole in the U.S.

Our preliminary recommendations for risk management are based on the discussions with psychiatric and cardiological experts. The goal of this program is to reduce the cardiac risk for sertindole by educating and guiding physicians and patients so that the appropriate patients are selected and that they use sertindole in accordance with the approved labeling.

This labeling will contain a prominent black box warning, explicitly expressing sertindole's prolongation of QT interval, the risk for cardiovascular events, the need to contraindicate use in patients with known cardiac risk factors, and guidelines for continued safe use of the drug, including ECGs. To reinforce the label, we will also produce extensive educational material for prescribers,

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pharmacists and patients. Our active safety surveillance efforts will supplement these risk management tools, and we commit to evaluate the effectiveness of our risk management program on a regular pre-defined basis.

Sertindole displays a unique mode of action.

It is effective for the treatment of patients with schizophrenia and reduces suicide attempts in this population. The benefit is critically important, given the high percentage of patients, 50 percent, who attempt to take their own lives. The risk of suicide and suicide attempts are a large and quantifiable problem. Despite the potential of sertindole's prolonged QT interval, the risk of arrhythmia and cardiac events is rare. And, importantly, it is an identified risk that can be managed in the population through selection and screening patients. The mortality ratio for sertindole is no different than that of other antipsychotic agents, and the benefit/risk profile for sertindole is positive.

We believe this is an important drug for patients, and Lundbeck is, therefore, committed to

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addressing possible cardiac risk through a robust risk management plan with the FDA. Thank you for the opportunity to summarize our data and for considering the potential use of sertindole by patients in the U.S. who may benefit from this. We welcome any questions you may have to support you in reaching a decision on the considerations and the questions raised by the FDA. Thank you.

DR. GOODMAN: Thank you, Dr. Pedersen. And I want to thank you and your entire team for an excellent set of presentations and for actually putting us ahead of schedule.

I'm going to recommend a minor change in our schedule. I'd like for us to take a brief 10-minute break now. We'll return at 9:50, at which time we will start a set of clarifying questions, followed by presentations by the FDA. I think we'll be on schedule.

Let me ask a big favor of all the audience. Could you let us, the panel, slip out first to the restroom, so we can get back on time? Thank you very much.

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(Whereupon, a recess was taken at 9:40 a.m.)

DR. GOODMAN: Okay. What we're going to do in the next 35 minutes is give the Committee an opportunity to ask clarifying questions of the sponsor's presentations. Let's try to avoid getting into extensive discussion among ourselves on the Committee. We'll have plenty of time to do that later. So really try to keep it to clarifying.

I'm going to take chairman's prerogative here and kick it off with a few questions I have about the SCoP study. The SCoP study is obviously very critical to making the case that there's a protective effect for suicidality for sertindole. So I just want to make sure that I'm clear on some of the methodological issues and outcomes. This is a randomized study, but, as you mentioned, it's not double-blind.

How many patients -- if you'll bear with me,

just a few questions. How many of the patients refused the randomization?

DR. PEDERSEN: We don't have a total record of the number of refused randomization patients, and just sort of a record of non-included patients in this study, as part of the notion of a simple study. So if a patient was screened by a physician and did not meet the screening criteria to get into the study, we would not know that exact number.

DR. GOODMAN: So if a particular patient, one being assigned to risperidone, and they might have been hoping to get sertindole, you don't know whether they -- you didn't capture that data that they opted out?

DR. PEDERSEN: In terms of having patients who after they were randomized decided not to receive the treatment, I need to ask Dr. Buller that.

DR. BULLER: There were very few cases of patients who were randomized to one treatment and then didn't want to have --

DR. GOODMAN: Okay.

DR. BULLER: -- that treatment, we can give you the exact number, it's in our study report, but we don't have a slide on that. But it's approximately -- it's less than a hundred patients.

DR. GOODMAN: And it was similar in both groups?

DR. BULLER: And it's similar in both groups.

DR. GOODMAN: Okay. That answers my question.

Do you have a measure of adherence during the course of the study?

DR. PEDERSEN: Dr. Buller?

DR. BULLER: Could I ask you to classify what you mean adherence? Adherence by the patients --

DR. PEDERSEN: So you didn't do drug levels; there were no counts?

DR. BULLER: No. We didn't measure drug levels, but there's drug accountability. So patients were asked to bring back the medication. The medication was supplied by the sponsor, and patients were asked to bring back the medication, and there was drug accountability at the site.

DR. GOODMAN: Okay. Thank you.

You mentioned in one of your slides that twice as many patients were disqualified in the sertindole group because of mostly baseline ECG changes, 8 percent versus 4 percent.

Could you elaborate a little bit on that? My concern there is that that, then, changes, to some degree, the baseline characteristics now that you've screened out some patients from the sertindole group that may have had some ECG abnormalities at baseline.

DR. BULLER: Yes. Thank you for giving me the possibility to clarify this.

The label for sertindole requires that a patient that shows an ECG change in terms of the QT prolongation needs to be discontinued from treatment. And that was part of the study design as well.

Can I have the slide up, please?

DR. PINE: Can I ask you a question about this, because I think you --

DR. GOODMAN: Put on your mic, Dr. Pine.

DR. PINE: Yes. I think you're talking about two different things.

You asked about pre-randomization exclusion.

DR. GOODMAN: Right.

DR. PINE: Now, I didn't see a slide on that. He's talking about --

DR. GOODMAN: Post. That may be my misunderstanding.

DR. PINE: Yes, you got confused. You

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misunderstood.

DR. GOODMAN: Okay.

So at baseline, you didn't disqualify anybody on the basis of ECG?

DR. BULLER: Yes.

DR. GOODMAN: Oh, they did?

DR. BULLER: If a patient had -- patients for both groups, before randomization, had to have an ECG. And if there was a QT prolongation above 450 or 470, they could not be randomized.

DR. PINE: In either group.

DR. BULLER: For either group.

DR. GOODMAN: Either group.

DR. BULLER: That was before randomization.

DR. GOODMAN: Okay, good, good, good.

And then post-randomization --

DR. BULLER: This is after randomization.

DR. GOODMAN: Okay. Very good. That's helpful.

Let me turn to Dr. Pine, and then see who else has questions.

DR. PINE: I have three comments/questions, a

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couple of which will be very clear and straightforward, and a couple of which I think will come up when the FDA presents their view of things.

The first one has to do with page 28 of the document that you guys sent around, in Slide C-55 and C-56, with the issue of the high risk group.

So I did not hear any presentation of a moderator analysis. Just looking at the data, my sense is that there was no greater effect in the high risk than the low risk group, and that your main point for making this was to say that -- it wasn't only the low risk patients where you saw it, but it would be important to clarify that you don't think that any potential effect, even though we can debate whether it happens or not, varies as a function of risk status. So it would be important to clarify that you don't

think that.
Is that correct?
DR. PEDERSEN: That's correct.
DR. PINE: That's correct. Okay. So that's number one.
Number two -- and this will come up again, I

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think, in the FDA -- is there does seem to be a difference of either opinion or fact, and I'm not clear which it is, about the comparability of the analysis in the InterSePT study for clozapine and in the analyses that were done here.
I mean, we heard Dr. Laughren in the beginning emphasize the review for clozapine, and I was led to believe that you guys think a comparable analysis looks more convincing for clozapine than not. The way I heard the review of the InterSePT study is that the company does not feel that way. They feel that the data are comparable. So it would be good to hear that discussed in more detail.
DR. GOODMAN: That sounds like more of a discussion item.
DR. PINE: I'm clear on what their response is going to be to what was said there.
Then the last question had to do with page 38, Slide C-75, and that was from the SCoP study, looking at the sudden and unexplained death and looking at the rate ratios, and talking about kind of the different things that one could emphasize.

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So in looking at the one, two, three, four, five rate ratios, my recollection from the material that we were provided was that only one of those -- and that was the ISC subclassification -- was significant. It would be good to have the confidence intervals on all one, two, three, four -- on all five of those. It would be good to have the confidence intervals maybe later.
Then, also, by the same logic that you guys presented, one is struck by the fact that regardless of the p values, all five of them do go in the same direction. And so, again, it would be good to come back to that issue, of how significant is it when --
DR. GOODMAN: I think we should give them a chance to respond to that query.
DR. BULLER: Let me respond to the question concerning the InterSePT study.
We used the slide with the InterSePT study to give you a measure of effect, if you want. It is not meant as a direct comparison, but what we have done is if we had applied the same kind of duration of trial, for InterSePT it was two years, to our data, we would

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come up with similar numbers of events -- slide up, please -- we would come up with similar number of events observed in both treatment groups. So for clozapine, it was 34 events and 55 for olanzapine.

If you look one line below, in the SCoP study during that period of two years, it would be 32 and 51. That is approximately the same dimension. If you then focus your attention on the hazard ratios, it is .62 in favor of clozapine in the InterSePT study, and it's .61 in favor of SCoP, if you do that analysis on our data. And the p values are comparable.

We have then added the third line, which is just the high risk group. But here you have to remember that we see fewer results there, so that has an effect on the p value. But what is important is it shows a similar hazard ratio of .61. So that means this effect does not get lost in that high risk group.

Does that answer your question?

DR. PINE: Well, it does, although -- I mean, that's how I understood it, but I also understood it as differing from the sense that we got in the material from the FDA. And that's why I'm a little confused

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about whether the same -- if the same definitions and the same analysis yield the same results or not.

DR. GOODMAN: Okay. We'll let Tom respond.

DR. LAUGHREN: We didn't come prepared to talk in detail about the InterSePT study, but these data for the SCoP study, this is a post-hoc analysis here. You're looking at a different time period here. This was not the planned analysis. I mean, you're doing it for comparative purposes, but it was not the protocol specified analysis. That's the problem.

DR. GOODMAN: Dr. Winokur?

DR. WINOKUR: I have several questions. If I can just go through them one at a time.

The first is early on from Dr. Pedersen. He mentioned that in 1998, there was a signal raising concern about cardiovascular risks initially for sertindole, and that led to a number of subsequent studies, but I don't think we heard exactly the nature of that risk. I'd just be interested in getting a little better understanding about that.

DR. PEDERSEN: The risk constituted a -- there's a reporting system in the United Kingdom,

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which is called the Adroitte database, which reports relative reporting rates of adverse events at the entry of new drugs into the pharmaceutical market. And at that report -- that reporting rate ratio, as it is, has two important factors. First of all, if you're looking for a particular outcome, what is in the numerator and, secondly, what is in the denominator there. And also, when you have that reporting system, how complete are the reportings that you have in that.

The system reported a higher rate for cardiac death and mortality, as such, at the initial prescription period with sertindole, relative to other types of adverse events that were reported. So it also has a consequence that if you have a lot of other adverse events reported, then you have a lower

reporting rate ratio. So that's part of the uncertainty with that sort of signal.

The second question to that signal is how complete is that reporting. And what we were able to do is go out and look at comparable reporting rates for other antipsychotics in the introduction period and show that there was a much higher completion of

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reportings of cases related to sertindole than there were to other antipsychotics, for one thing. And secondly, other adverse event reporting elements were more frequent, so the ratio obviously has an impact.

I hope that helps.

DR. GOODMAN: Another question?

DR. WINOKUR: Yes, I have a few more, if I may.

The slide that we saw just before -- and I've lost the number; I apologize -- one of the datapoints on the slide showed low SAE rates for -- this is from the SCoP study -- for both sertindole and risperidone. But it was higher for the sertindole group, 2 percent versus 1 percent. And I was just wondering if we could get a sense of what actually went into the SAEs that were seen in that trial, to get more of a flavor for what was emerging as what was reported as SAEs.

DR. PEDERSEN: First of all, there is a -- the serious adverse event is, as a terminology, related to hospitalization as such, so by the fact that there were patients based on the nature of the protocol. Also, with the ECGs that have to be performed, there were

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higher numbers of individuals who would fulfill that definition of a serious adverse event reporting by virtue of having to have to go in and have an ECG done and being considered. That would immediately trigger as a serious adverse event. So that's part of the difference between the two groups.

DR. WINOKUR: So, actually, having to have the ECG done was constituted in that statement?

DR. PEDERSEN: If it meant that the patient was hospitalized in order to get that done, yes.

DR. WINOKUR: Okay.

DR. GOODMAN: I'll give you one more, Dr. Winokur.

DR. WINOKUR: This is one with a couple of components.

This is related to C-43, and it's the data we were shown on the QTc, and it put into context the data from the major ziprasidone study. I'm sorry. I got the wrong number. This is the one showing the different QTc interval following different atypical antipsychotics, plus haloperidol.

My question is, for the sertindole, how

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comparable was the experimental design to the design used in the ziprasidone study, which used the time of peak plasma concentration for each of the atypicals in

that trial. And I'm interested in whether for the sertindole determination with 23 milliseconds, did that use the comparable design?

A related question, of course, in the ziprasidone study, another key part of that analysis involved assessment of the antipsychotic administered along with an important metabolic inhibitor, and I was also interested in any data that we could hear about for sertindole studied in that kind of paradigm.

DR. PRITCHETT: Can we put that slide up, please?

I think this is the slide you're asking about.

DR. WINOKUR: That is, right.

DR. PRITCHETT: My name is Ed Pritchett, by the way, and I'm here as a cardiology consultant with Lundbeck.

The figures on the left are from the famous Pfizer 054 study, one of the great studies ever done of QT intervals. It is a thorough QT interval study, so

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that is as they're defined. And you very perceptively pointed out that those are placebo adjusted, changed from baseline, measured at peak change.

The sertindole figure is, in fact, the change from baseline. And to get the exactly comparable value, you'd have to subtract off another 5 milliseconds. And the FDA reviewers actually did this for you in their double delta calculation, which would move that up a little bit, about 4 or 5 milliseconds would move up. And then that is just a randomly timed variable. So it's not exactly comparable.

I look at it and say, well, it's in the ballpark. It's in the same range. I mean, ziprasidone and thioridizine contain warnings about QT prolongation and torsades de pointes. All of these drugs contain verbiage about premature death in patients with psychosis related to dementia, of old age, and that sort of thing. And these are not new ideas. Sertindole is in there somewhere, but you're correct, not as precisely measured as we have from the 054, a great study.

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DR. GOODMAN: Okay. Thank you very much.

DR. WINOKUR: Metabolic inhibitor --

DR. PRITCHETT: They're -- well, I'll let clinical pharm --

Somebody want to take on the metabolic inhibitor?

DR. PEDERSEN: The study on sertindole did not include metabolic inhibitor.

DR. GOODMAN: Now, I want to give some of the other committee members a chance just to ask questions.

Dr. Granger?

DR. GRANGER: Three questions.

First of all, the intent of the SCoP trial was to assess the drug under normal conditions of use.

Given that there were no U.S. patients, that it was mostly conducted it sounds like in Eastern Europe, India, Asia, can you comment on whether or not that, in fact, represents normal conditions of use for U.S. practice?

DR. PEDERSEN: The intention here was to make sure that it was not conducted under very restrictive conditions so that the way that physicians would

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normally treat patients, the way patients would be managed and supervised in the process, was being representative of that.

In terms of the schizophrenic patient in other countries, cross-border, the diagnosis is such that it's very robust in most places, so we do believe that the patients, as such, are similar. But it's obvious that even within the study, but also if you go across to the U.S. scenario, that there are variances between the scenario in patient conditions, the healthcare structure in European countries and in the United States, obviously, as in Asian countries. But in terms of the ability of us to follow up on patients, we believe it was very high and actually much superior to what you see in many well controlled, randomized studies, because it was something we knew would be critical.

DR. GRANGER: Okay, thanks.

One more question around the issue of the analysis groups. And I'm wondering, this whole randomized treatment, and the whole randomized treatment plus 30 days -- maybe Slide C-69, if you

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could bring that up. I'd just like clarification on was there kind of a true, pure intention to treat analysis. There was mention in some of the briefing work about a whole follow-up period analysis.

But, for example, if a patient stopped --

DR. GOODMAN: Do we have that slide?

DR. GRANGER: C-69 -- stopped study drug for some reason, say a week after initiating in the trial, and they died a year later, was that patient included in any of these analyses or not?

DR. PEDERSEN: Slide on. Well, we do have --

DR. BULLER: We have studied patients after the end of the randomized treatment, and we have followed up if they allowed us to follow up. So we have another period which we haven't reported here, which is called the whole follow-up period. So we know what happened to a large number of patients after the completion of the trial.

But to come back to your question, if a patient terminated treatment without having, for example, an additional antipsychotic, their events during the study would just be reported in what is

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called here the ORT period. If the patient, at some point in time during the study, received an additional

antipsychotic, that would be reported in the WRT period, the whole randomized treatment period. And for safety evaluations, we have added 30 days after the end of the randomized treatment to cover events that were occurring in that period.

DR. GRANGER: So just to make sure I understand, the randomized treatment period is for that individual patient or it's the duration of the --

DR. BULLER: It's for the individual patient, and then all events that occur in this period for an individual patient would then be reported together for that period. So an individual patient could have an ORT of one day, two days, two years, four years, and that would all be reported in that period as we report the results.

DR. GRANGER: So at some point, I'd like to see data on this whole follow-up period, as well as for mortality and suicide.

DR. GOODMAN: We probably shouldn't do it right now. I want to make sure I get to everybody's

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questions.

Dr. Lawrence?

MS. LAWRENCE: I wish I was a doctor, but that's okay. I'm --

DR. GOODMAN: Margy Lawrence.

MS. LAWRENCE: -- really a layperson.

I know in research with random studies, everybody's coming to the table with different backgrounds.

Are any diagnostic tests done on the patients before they're part of the study related to cardiovascular disease?

DR. BULLER: All patients before randomized had to have an ECG, and this ECG was evaluated to see whether the exclusion criteria from the study of having a prolonged QT interval was met or not met. The patients underwent the normal way of clinical investigation, but it was not standardized. So all patients were assessed psychiatrically, and they would have whatever happened in that routine clinical practice in terms of a medical exam.

MS. LAWRENCE: Thank you.

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DR. GOODMAN: Dr. Harrington?

DR. HARRINGTON: Thanks, Dr. Goodman.

Two questions for you.

SCoP, as I understand it, was a non-inferiority trial with regard to mortality. If you could explain to me the thought process that went into the selection of the boundary of 1.5 so that I can understand how you chose that. And second, could you give me some insight into why you chose a 90 percent confidence interval for the termination of non-inferiority, because that's going to play out, as you know, in the FDA discussion, where they apply the 95 percent.

So I'm just interested in how you selected those.

DR. PEDERSEN: First of all, the study was sort of created as part of a history in which we had data that were clearly indicating a low mortality in the clinical trial setting. The concern by the European regulators at that time frame was, well, that's a very controlled scenario; we'd like to know what happens in the real world.

Then we developed data from the epidemiologic studies, including the crossover study that was mentioned here. And the feedback was, this looks really reassuring, but could we avoid or could we make sure there's not any sort of channeling bias because people are concerned about this.

So the desire would really be to make as naturalistic as possible a study in terms of randomizing patients to receive either sertindole or risperidone under the respective labels as they would be used in a normal clinical setting. But, obviously, in order for us to avoid the point that was raised earlier by Dr. Goodman, that there were selections in that process, both treatment groups had to live up to the SPC of both drugs. So that was clarified before you randomized them.

In that scenario, the safety that was worried about was if there was an excess mortality on sertindole compared to risperidone. And that's why the one-sided test was there. And in terms of the sample size, the sample size was one that we discussed with the regulators. They felt that was a reasonable amount of confidence that you could expect to have, given the confidence, the marks that you normally put on large studies of this kind.

I don't know if Dr. Pritchett would comment on that because he's got a lot of experience in that.

DR. PRITCHETT: I think, Bob, that your question is quite an interesting one, and it really relates to how do we feel about what see out of this trial, where we've got a little bit of power. We've got randomized trial, we've got 125 events, so we've got a little bit of power and a little bit of precision. And we've got a point estimate that looks pretty good. Those slides are visually very appealing, a hazard ratio in the 1 to 1.0 range. And then we've got this upper confidence limit to deal with. The original trial was set up with the Europeans as a 90 percent upper confidence bound of 1.5. It would be good to beat that. And depending on what time period you use, and you use the 90 percent bound, you come in around 1.5.

The FDA reviewers prefer a two-sided 95 percent confidence interval, and that gives you somewhere between 1.5 and 1.6.

How do we feel about a confidence interval that big? Well, okay. This is not gusto with 43,000 patients and 3,000 deaths after 30 days. But for an antipsychotic drug, this is about as good as it gets. If we think we're going to find a mortality study with an antipsychotic that has more than 125 or thereabout deaths, we're going to wait a long time for it.

So a confidence interval in the range of 1.5 is in a range that we understand. I mean, the new guidance for Type 2 diabetes drugs talks about the potential approvability of compounds where the hazard ratio for total mortality is less than 1.3 and the confidence intervals are between 1.3 and 1.8. This is where we're living now.

DR. GOODMAN: Although I said I wanted to confine ourselves to clarification, this one's worth a little follow-up. So I'd be interested in Dr. Harrington's reaction.

DR. HARRINGTON: So I was going to ask you, Mr. Chairman, if we could have some discussion -- maybe this afternoon is more appropriate -- because, for me,

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the math is fairly straightforward to figure out. What's challenging is what's the acceptability of the margin. And in my world of cardiology, there are certain ways of determining what acceptability is, one of which includes the literature, one of which includes discussion with investigators. And so maybe my psychiatry colleagues around the table can help me understand that.

Then the second is that in my world, 95 percent boundaries are common, in which case we'll hear from the FDA. And, again, I'd like to hear from my psychiatry colleagues as to what's common in your world.

So that was the essence of my question. The math is fairly straightforward.

DR. GOODMAN: Hopefully, we have a lot in common, but we'll see.

So, yes, I think we'll put that in the parking lot and have a more extensive discussion.

Dr. Malone?

DR. MALONE: I have a question --

DR. GOODMAN: Bob Temple has a comment. We'll

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let him --

DR. TEMPLE: Well, I only wanted to throw into the mix that the recent DIVEES (ph.), a guidance that we put out, asks for -- and this isn't prejudice or anything; I just want to be sure we have the terms down -- asks for ruling out a hazard of 1.8, but not on mortality. It's on the sum of a wide variety of things, Mace plus, if you'd like, heart attack, stroke and death. And then, after approval, you have to rule out a hazard ratio of 1.3. Where the 1.3 came from, there's no rational basis, but we've been using 1.3 for the nonsteroidal, anti-inflammatory drug large studies,

trying to rule out that risk, also, not of mortality but of MACE. What you rule out for mortality is going to be considerably higher than that.

So just for context.

DR. MALONE: Very well.

DR. GOODMAN: Good.

Dr. Malone?

DR. MALONE: I have a question about the SCoP versus InterSePT, the comparison. What was the difference in the inclusion criteria for the two sets

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of patients?

DR. BULLER: The InterSePT study included patients that had a suicide attempt, or hospitalization to prevent a suicide attempt, during the past three years before entry into the study. They also included patients with a baseline suicidality that warranted entry into the study, and they added a third criterion, which was basically self-injurious behavior due to psychotic ideation that maybe command hallucinations. In addition, they used patients, both with schizophrenia that was about 60 percent, and schizoaffective disorder that was about 30, 40 percent.

So that high risk definition, and it was a high risk population, was based on a suicide attempt three years prior to the study, whereas, we used as the high risk definition a suicide attempt prior during the five years before entry into the study.

DR. GOODMAN: That's only a subset that met those criteria.

DR. BULLER: That was only a subset of about 7 percent in the SCoP study that met these criteria.

DR. MALONE: So what was the overall entry

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criteria for SCoP regarding suicidality? Was there a -- what was it?

DR. BULLER: The SCoP study did not recruit for suicidality. We just observed suicidality under normal conditions of use in the real world situation. So we did have these high risk patients. We did have patients with suicides in there, but we didn't specifically screen or recruit for them.

DR. MALONE: Okay.

DR. GOODMAN: Dr. Bilker?

DR. BILKER: I have a couple questions about the comparison of the hazard of suicide attempts, comparing risperidone and sertindole. The original analysis in the proposal was WRT plus 30 comparison, and what you presented was ORT plus 1.

So my first question was, can you clarify why the ORT plus 1 is the right analysis?

DR. PEDERSEN: The reason why the WRT plus 30 was the original analysis was that the original mortality analysis that was agreed with the European regulators was based on the WRT plus 30, and we, therefore, used that also for the suicide attempt

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reduction.

During the initial review, most appropriately, the FDA said to us that they thought it was correct and also in line with other suicide assessments on other drugs, that you only measure for the period when the person is on that drug and not while they get another extra drug or the periods afterwards, because a lot of different things may happen to a person in the 30 days that goes after the treatment. And that's why we put that in the analysis, in the presentation.

DR. BILKER: Okay, thank you.

The other question was about the p values from the different analyses. If you look at the WRT plus 30 or the ORT 1, look at your analysis or the FDA's analysis, none of them are significant. So I'm wondering -- I just want to hear more about your interpretation of the evidence provided by these analyses.

DR. PEDERSEN: Our way of looking at these studies is, first of all, that this is a consistency of point estimates that we are addressing here. If you as a primary endpoint would like to conduct a true suicide

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study, the estimate, at least for the time also that the InterSePT study was created and the previous discussions that we have seen, you would need studies around 20,000 patients, something like that, which is a very difficult thing to do in a broad population. And that's also why in the InterSePT study, you could say there's a way of enriching the population, both by selecting the patient but also including events that are not actually suicide attempts, in order for you to measure the behavior around that phenomenon.

So I fully understand the concern about the crossover of the 95 percent boundary here. The point is that whatever way you look at the data, not only within the SCoP but also within the other data we have, they consistently point in the same direction. And the p value in this respect could point to say, well, are we way off? That's something one can debate, and we're not saying that the exact benefit here is 20 percent or 30 percent, or anything like that. So we're not trying to link the benefit to a very rigorous percentage point here, but saying we see an overall trend that clearly supports the use of the compound.

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DR. GOODMAN: Dr. Laughren, and then Hendren and Day.

DR. LAUGHREN: I just want to comment on this issue of what is the best time frame for looking at suicidality. You seemed to imply that FDA thinks that looking at ORT plus 1 is the optimal period to look at. We didn't actually have that discussion, and I don't honestly know what the best time period is.

The reason, in our meta-analyses of antidepressant trials, for example, that we focused only on the double-blind phase, is that it was a

meta-analysis, and we were dealing with studies that were very different in terms of what happened after the nominal endpoint of the trial. In some studies, patients were continued on drugs, sometimes they were stopped cold turkey, sometimes they were tapered. So that's the reason that we didn't look at, say, plus 30.

In this trial -- I mean, this is one trial, where there is presumably somewhat more uniformity. And I think it's important to point out that your original time frame specified in the protocol was WRT plus 30, and anything beyond that is really a post-hoc

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analysis.

DR. GOODMAN: Dr. Temple?

DR. TEMPLE: Tom's last point is important. We are inclined to believe that you're supposed to live with the initial analysis. But there's a continuing debate in safety related studies about whether you should use real intent to treat or stop counting after the person's off the drug. I mean, if a drug is doing something bad, it's fairly obvious that if you stop the drug, the rest of the data ought to move closer. In other words, it's a way to obscure an effect. That's why in non-inferiority studies as a general matter, ICH documents. And we warn about using intent to treat because it gives you a bias toward the no, which is not what you want in a safety study or in a non-inferiority study.

So if someone had come to me and said we just want to do it in one day, I might have said, that seems all right because you don't want to lose the evidence of harm. But as Tom says, you dance with the girl you brought. So we are very nervous when the analyses start changing, but that doesn't mean you shouldn't

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look at them, but they make you nervous.

DR. GOODMAN: Dr. Hendren?

DR. HENDREN: I had two or three questions.

One on the SCoP trial, you had to recruit an awful lot of patients to get to 10,000. How did you recruit sites to participate in this trial?

DR. PEDERSEN: Well, it was done globally. There were more than 580 sites in that.

DR. HENDREN: Were they sites that you had previously used for sertindole trials that you knew and had an experience with, and then you could recruit them to keep bringing patients in?

DR. BULLER: The purpose of the study was to have a naturalistic setting, if you want, so we didn't go for academic centers that do the normal Phase II, Phase III trials. We wanted to have centers that are involved in the normal day-to-day care of patients with schizophrenia. So we are looking at hospitals, at private practices, at facilities that had both in and out patient care. Secondary, if you want, tertiary treatment centers, and we have Lundbeck presence in several countries in Europe, and we use the CRO to

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identify these kind of centers.
So what we have in that study is, really, a very wide variety of treatment settings, as it was mentioned, more than 500 different sites, in 38 countries. So we have a very large source of information from all kinds of treatment settings that you can imagine. But we didn't go to the academic centers that would do the normal Phase II, Phase III trials.
DR. GOODMAN: Dr. Day?
DR. HENDREN: If I could do a couple more.
Did you pay them for them to be in this trial, whether it was sertindole or risperidone that they were on? They got paid by you, your company in either treatment?
DR. BULLER: The investigators got reimbursed for the time spent on the study. In general, patients did not get paid, except in some instances where they were obliged to use public transport, so the public transport fees were reimbursed. Lundbeck provided the study medication for free.
DR. HENDREN: Either one of them.
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DR. BULLER: Both.
DR. HENDREN: And your exclusion criteria, you had drug naive patients, meaning that these people -- you excluded drug naive patients, so they had all been on something else before, and they were all now coming into a new trial, where they either had to stop whatever they were on before, or they failed on something before, knowing that they could be randomized to either sertindole or risperidone?
DR. PEDERSEN: That's a great description, yes.
DR. HENDREN: Why did you choose drug naivete as an exclusion criteria?
DR. PEDERSEN: First of all, because the labeling in several of the European countries was such that there was a requirement to have had previous treatment before you could be prescribed sertindole. That's the one part. The second thing is that sometimes drug naive patients have a different behavior, so to speak, at their first incidence than patients who have been on other medications first. So it was a simple way of making sure that the study did
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not have imbalances, where in one country you could only have one sort of patients, and in other countries, you could have other sort of patients, so we made it uniform.
DR. HENDREN: Can I have one last quick question?
Under comparison to QT prolongation on Slide 87, you mentioned in that slide that the dose was 20 milligrams of sertindole, but you didn't mention the dose, at least on the slide of the other comparators.

Were those doses the optimal dose or the dose that's most frequently used, or some way for those other medications?

DR. PRITCHETT: A variety of doses were used for most of the drugs in that study, and I believe that the slide, which comes from the manuscript, reported the highest dose used and the longest QT prolongation that was associated with highest dose.

Thank you.

DR. GOODMAN: Now, Drs. Day and Slattery.

DR. DAY: For Dr. Pedersen, a brief look at the risk plan. Ordinarily, this is left for the end of

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the meeting, and then there's no discussion for it, so I would like to ask just a couple of questions.

It is fleshed out quite a bit in the briefing documents, more than usual. And so, I was wondering, have you used some of the tools that you propose here in your European and other markets, and what has experience been?

So question number one, what is your experience with these risk tools elsewhere.

Number two, have you done any behavioral testing of comprehension of use of the different tools, such as the physician prescribing aid, et cetera.

And question 3, have you looked at potential effects on prescribing practices?

DR. PEDERSEN: To the first question, the labeling that we have in the countries obviously will be adhered -- we are attempting to make sure that that gets adhered to in the European countries also. The data, we have in terms to say how is that adherence and what are the consequences of that. We know that the safety data that we have reported now are based on that labeling. It's based on that sort of approach, for

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example, also in the SCoP study. The programs you can implement in a lot of countries are very different than the ones you can't implement in the United States. So we do not have a program in these countries, that is, as descript as the one that we have submitted to the FDA because you cannot do them the same way.

DR. DAY: Right. I understand how labeling constraints are different, different countries, but you had specific risk mitigation tools, and I was just wondering have you tried them elsewhere. The other additional tools beyond the labeling, say, on page 121 of your briefing document and elsewhere in that area. I just wondered if you have experience with them.

DR. PEDERSEN: We do not have experience with the same tools in the other countries, no.

DR. DAY: Thank you.

DR. SLATTERY: I had a question regarding the SCoP study design, particularly relating your comment of trying to make it a usual care kind of practice in a naturalistic sort of setting. But were there any minimum requirements of how often these patients needed

to be seen in follow-up? In particular, I'm wondering
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about how the suicide risks and suicidality was assessed, with any sort of frequency.
Was there any standardized measurement or guidelines for the clinicians about how this was assessed, and was there any other outside review of the risks other than the primary clinician?
DR. BULLER: Yes. Thank you for the question.
We have a slide that describes this procedure, so can I have the slide up, please?
If you look at the last line, the study assessments were initially done monthly on a four-weekly basis, and throughout the study, the patient had to see the site at least on a three-monthly schedule. And at these visits, initially we had a special form to record the history of suicide attempts. That was introduced after discussions with the FDA. And the investigator was informed at investigator meetings and by monitors to specifically ask for suicidal events, suicidal ideations. These were then reported in terms of the serious adverse event reporting system. So they were notified of these events within 24 hours, and then that information was
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further worked up by our safety department.
There was no outside overview at site of what happened, which is, I think, in line with normal clinical use. So there was no independent, separate review of the symptomatology at the site.
DR. SLATTERY: So there was a standardized assessment, I just wanted to clarify, of the suicidal risk. You mentioned going through -- was there a checklist, or an open-ended interview, or how was that assessed?
DR. BULLER: There was a checklist to assess the history of suicidal behavior. The assessment of suicidality was left to the site. There was no standardized instrument in line with the idea of having normal clinical practice. So every psychiatrist would elucidate that information the normal way they would normally interview a patient and assess a patient.
DR. GOODMAN: Okay. I was going to ask one last question, but I'm going to let Dr. Potter ask one, too.
DR. POTTER: Just very quickly, if we can go to Slide C-44. And I just wondered if looking at the
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distribution of the dosimetry for risperidone or sertindole in other countries, we know whether this use, which is in rather large numbers, is representative of the exact distribution you would see in prescription databases for, say, risperidone in Western Europe, the United States, or whatever, to get at this question of representality of how the patients were compared to other groups.
DR. BULLER: The dose distribution is

representative. We have another slide where we compare sertindole doses in Europe and Asia, and we can do that also for risperidone.

Slide up, please.

So this is the distribution in Europe on the left side of the slide and in Asia. It's basically the same presentation of data just for the two regions. And you see that in both regions, there's a preference for the lowest effective dose, 12 milligrams, and then the higher doses are used less frequently.

Slide up for risperidone, please.

You see a similar distribution; however, one has to say that in Asia, the risperidone dose range,

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the recommended dose range, starts already at 2 milligrams. So you see slightly lower doses in risperidone, but it is in line with what is reported from the markets.

DR. POTTER: Thank you.

DR. GOODMAN: Dr. Laughren, you had a comment?

DR. LAUGHREN: Yes. I'm sorry to come back to this, but if you could show Slide C-87 again. This is the slide comparing QTc changes for a number of different antipsychotics. I didn't notice this originally.

This is Bazett correction, which inflates the QTc for drugs that increase the heart rate. And so, it appears to suggest that sertindole falls sort of in the middle here, but I think if you look at drugs like risperidone and quetiapine, that have a pretty big effect on heart rate, that that's sort of an inflated score.

DR. MATZ: I'm Jorgen Matz, and I'm from the Lundbeck Safety and Pharmacovigilance Department.

You are quite correct that this is Bazett corrected, and it's taken from the published data. And

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also during the supervisor and advisory board meeting, there's also other data presented; and looking at the baseline corrected, different approach, or looking at a QTc interval. And you're correct that for some of these drugs, the QTc interval for some of them will be slightly lower. So, for instance, for taking ziprasidone, it will be about 20, as shown on this slide, but it will be like 16 milliseconds instead.

Does this answer your question?

DR. GOODMAN: Let me make sure I understand, Dr. Laughren.

Which values you think may be inflated here?

DR. LAUGHREN: The QTc value is inflated for a drug that increases the heart rate. And so, you're comparing a couple of drugs here that have a pretty big effect on increasing the heart rate with sertindole that I believe doesn't have much of an effect on heart rate.

Is that correct?

DR. MATZ: Sertindole does have an

alpha-adrenergic antagonistic effect, so there will be increases also in heart rate with sertindole, in particular in the titration period. When we look at our data and compare the effect on QTc Bazett or QTc Fridericia, our result is quite similar for those two corrections, almost identical, actually.

DR. LAUGHREN: But that's my point, that if these were Fridericia data, I think sertindole would appear to be a little bit more of an outlier in terms of QT, see?

DR. MATZ: Right.

DR. PRITCHETT: I have to confess that the -- I want to look at the figure from the manuscript at lunch. But I think you're correct that you could move it up a little, but I don't think you're going to move it up 10 or 20 milliseconds, you know. I mean, we're talking about a few milliseconds.

DR. LAUGHREN: You would move the others down.

DR. PRITCHETT: Yes. This is not going to change the overall impression that sertindole is somewhere in the range, bracketed by these other drugs.

DR. LAUGHREN: Well, I think it would, actually. We'll show some data in our presentation.

DR. PRITCHETT: Okay.

DR. GOODMAN: Okay. I'm going to actually go ahead and ask the last question because we're starting to fall a little bit behind and we want to get the FDA. This goes back to the question -- one of the themes here has been trying to interpret the data of the SCoP study, because although it's randomized, it's not double-blind, so it in some ways becomes harder to interpret.

So my question's really about expectation bias. Were either the patients or the clinicians aware of the hypothesis that sertindole might have more protective effects for suicidality than risperidone?

DR. PEDERSEN: In terms of the clinicians -- I mean, it was amended into the protocol as part of the endpoint there, but it was not something that was highlighted as a particular, and it's one of the features, one of the many features, that were assessed in the protocol.

DR. GOODMAN: But was it in the consent form?

DR. PEDERSEN: I don't -- no, it was not. It was not in the consent form.

DR. GRANGER: It wasn't even noted until 16 months after the first patient was enrolled as part of the assessed outcomes.

Is that correct?

DR. PEDERSEN: That's correct.

DR. GOODMAN: Dr. Malone, I'll give you a really quick chance to ask your question, then we need to have Dr. Kronstein come up.

Did you want to go ahead, still?

DR. MALONE: I'm just remembering from the ziprasidone meeting, there was a lot of talk about the metabolism of the drugs. So this drug is metabolized by the P450 system, and ziprasidone had another less-used metabolic pathway, which I think for this drug, for real life use, makes the use of an inhibitor -- the effect of the use of an inhibitor on the QT interval very important.

So in ziprasidone, they did do ketoconazole, and they showed it really didn't make a difference. But that data would be more important here because it is metabolized by the P450 system; so that for everyday use, patients are likely to get other drugs that affect the P450 system. And I don't know if you have any data

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on that. You said you didn't have the --

DR. GOODMAN: You heard that question?

DR. PEDERSEN: Yes, and I just wanted to assure myself. But the data that you actually saw before on Slide C-87, that's derived from the original clinical data. And part of these patients were also allowed to have concomitant medications, some of which included some of these compounds that would interfere with the cytochrome system as well.

We do have more specific data on this that we can discuss, but I don't know if it's the right moment to do that right here, but we can do that.

DR. GOODMAN: I think we should proceed with the FDA presentation at this point.

DR. KRONSTEIN: My name is Phillip Kronstein. I'm one of the medical officers at the FDA's Division of Psychiatry Products. I'll present some background information that you may have heard already, but it's important because it puts what follows into proper context.

Sertindole is a new molecular entity in the class of atypical antipsychotics. Like for other

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atypical antipsychotics, the mechanism of action appears to be mediated by the antagonism of dopamine and serotonergic receptors. The sponsor is seeking indications for, number one, the treatment of schizophrenia and, number two, the reduction in the risk of fatal and nonfatal suicide attempts in patients with schizophrenia. The proposed dose range is 12 to 20 milligrams once daily, with a recommended target dose of 16 milligrams.

A little bit of regulatory history first.

The original NDA for sertindole was submitted in 1995. At that time, concerns were raised about QT prolongation and the risk of sudden death. Sertindole was the subject of a 1996 meeting of the PDAC. The committee voted unanimously in favor of its efficacy, but the results were more mixed in terms of safety, with four in favor and two opposed. The sponsor withdrew the NDA from further consideration in early 1998, based on events in Europe.

What were these events?
Sertindole was authorized by the UK in May of 1996 and, subsequently, in other European member states. As you heard a little while ago, a potential safety signal regarding death rates during sertindole treatment was detected in the UK Medicines Control Agency's tracking database.
Due to sertindole's known effect on the QT interval, there was concern that the potential signal was a reflection of an increased risk of fatal arrhythmias. The European Committee for Medicinal Products for Human Use, also known as the CHMP, decided to suspend the marketing authorization for sertindole in the EU in June of 1999.
The sponsor conducted several retrospective, epidemiological studies to investigate the safety signal. Based on the results of these studies, the Europeans in 2001 recommended lifting the marketing suspension for sertindole. A condition for the reintroduction of sertindole in the EU was that the sponsor commit to accounting for all patients treated with sertindole for at least the first year after its reintroduction to the market by enrolling them in studies. The sponsor agreed to conduct the SCoP study, which you've heard about, with a large randomized, parallel group, active-controlled, open-label study, comparing the safety of sertindole and risperidone under normal conditions of use.
Following review of preliminary data from SCoP, which did not appear to show an increase in all-cause mortality for sertindole compared with risperidone, the CHMP in April 2005 recommended lifting the restrictions of marketing and launch activities. In September 2007, the Europeans agreed to terminate the SCoP study after the enrollment of nearly 10,000 patients. Meanwhile, at a pre-NDA meeting for resubmission in early 2006 -- this was several years after the beginning of the SCoP study -- the FDA expressed continuing concern about substantial QTc prolongation seen with sertindole and an apparent excess risk of cardiac deaths with this drug, and that was based on some preliminary results from the SCoP study.
At that time, the FDA suggested that sponsor do additional work to establish a benefit that could overcome this risk. For example, efficacy in patients shown to be refractory to standard antipsychotics or a reduction in suicidality. And as you heard earlier, they already had submitted an amendment to the protocol to start looking at suicidality.
A little bit of post-marketing history, of course being outside the U.S.
In addition to a case of torsades in the Phase II-III safety database and two cases in SCoP,

there were three spontaneous reports of likely or confirmed torsades; although, indeed, some of the cases were either associated with an overdose or complicated by certain concomitant indications that all remain of concern, as they're situations that can very well occur in the real world with clinical use. It is important to remember that it's very unusual to actually detect a case torsades -- usually a patient's just found dead -- so each documented case possibly represents several undetected cases.

In the period from 2006 to 2008, the sponsor's best estimate of exposure outside the U.S., as it's not approved here, is 13,000 patient years, the majority of which comes from non-European countries. The average market share of sertindole in the EU in 2008 -- and

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this is among other atypical antipsychotics -- was about .1 percent in volume and about .13 percent in sales.

I'm going to touch first on efficacy. You see three trials listed. M93-113 and 098 are the two pivotal studies. They are both eight week studies. As you can see with the highlighted numbers, the efficacy of sertindole 20 milligrams, the highest recommended dose, is about equivalent to haloperidol 16 milligrams, in one study about six points better and the other study about six points worse. And, of course, we're talking about a PANSS total score. The third study we consider a supportive study. It was 40 days. The reason we consider it supportive, it was positive in OC but not LOCF. We believe these studies established efficacy of sertindole in the acute treatment of schizophrenia.

The issue we've all been talking about is QTc prolongation. As alluded to earlier, this is the delta-delta, which is the difference between sertindole and placebo after baseline correction. Also, as touched upon, we're using Fridericia's correction

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because we believe that Bazett's overcorrects.

Looking at sertindole 20 milligrams, the maximum recommended dose, the delta-delta is almost 27 milliseconds. If you look at the 90 percent confidence interval, that goes up to 30 milliseconds.

We also looked at QTc outliers. The percentage of patients meeting outlier criteria for a QTc of greater than 500 milliseconds range from about 1.3, looking just at all doses, to about 1.9 percent at the 20-milligram per day dose. The Division does not consider these percentages reassuring. In other atypical antipsychotics with QTc prolongation, it rare to see any such outliers. For example, in clinical trials with ziprasidone, only .06 percent of patients had QTc intervals exceeding 500 milliseconds. Also of note, the percentage of patients meeting outlier criteria for a QTc prolongation of greater than 60 milliseconds from baseline was 10.5 percent for the

20-milligram per day dose group.

Now, coming to the SCoP study. Some of this you've heard before. This was a large open-label, parallel group, randomized study. It was a non-IND

designed to compare the safety of sertindole and risperidone under normal conditions of use in patients with a clinical diagnosis of schizophrenia. It was conducted in 593 centers and 38 countries. There were no centers in the U.S. Patients were randomized on an ongoing basis until the study cut-off date, which is decided by the European authorities, once enough exposure -- accumulated exposure had occurred. It was flexible dose with no set treatment period, and all concomitant medications were permitted, except, initially, other antipsychotics.

Just going to what I mean by non-IND study, meaning before the study, the endpoints, the design and the statistical analysis were not reviewed or approved by the FDA. This was done in conjunction with Europeans. They were discussed with us after the fact.

Just going over the study periods of importance again, the ones that I'm going to talk about most are the ORT and WRT. Again, the ORT period is the time, the period that the patient is only on either the randomized treatment, either sertindole or risperidone. The WRT period also includes the periods ORT plus the

period that someone might have been on an add-on antipsychotic period while they're still on the randomized treatment. Note that if someone never gets an add-on antipsychotic, ORT and WRT would be equal.

I've mentioned during the discussion that WRT, or whole randomized treatment, plus 30 days period, was the pre-specified period for the reporting and analysis of all events. These are the primary pre-specified endpoints for the study. The first primary endpoint was all-cause mortality. The second primary endpoint was cardiac events, including arrhythmias, requiring hospitalization. The sponsor did not perform an analysis of the second primary endpoint due to a limited number of events, and we agreed with this. So I will not be discussing the second endpoint any further.

Let me talk a little bit about the first primary endpoint, all-cause mortality.

The statistical analysis plan specified that if the confidence interval for the all-cause mortality ratio -- and that's the hazard ratio of sertindole to risperidone -- was entirely below the pre-specified

threshold of 1.5, the known hypothesis of excess mortality in sertindole treated patients would be rejected. In other words, one would conclude non-inferiority of sertindole to risperidone if sertindole was shown to be, at most, 50 percent worse than risperidone in the risk of all-cause mortality.

And again, this non-inferiority margin of 50 percent was based on agreement with the CHMP and not the FDA.

The secondary endpoints were cause-specific fatal events, in particular, cardiac and suicide. They also looked at suicide attempts, including fatal and nonfatal. And again, the analysis of suicide attempts, the second point, was added as part of the protocol amendment, approximately 16 months after the first patient visit.

Before going into the results, it's important to discuss a bit how events were classified.

The secondary endpoints, and those, again, being cause-specific fatal events as well as fatal and nonfatal suicide attempts, were classified in two separate ways. First, was using the Medical Dictionary for Regulatory Activities coding, also known as MedDRA

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coding, and the second way was through the Independent Safety Committee. I'm going to first discussed how MedDRA worked.

According to the protocol, individual investigators were to report serious adverse events and cardiac adverse events to the sponsor. The sponsor coded these events using MedDRA. Events were then classified based on their MedDRA definitions. The disadvantage to this approach is that investigators were not blinded to treatment. Also, there was no uniformity among the many investigators in how SAEs were reported, and instead it was based more on clinical practice.

Switching over to the ISC, the ISC was comprised of seven members with backgrounds in cardiology, epidemiology, pharmacovigilance, psychiatry, and statistics. Of note, three members were replaced over the course of the study reportedly due to scheduling conflicts. Using the SAE and cardiac AE reports from investigators, the sponsor prepared blinded case narratives for evaluation and categorization by the ISC. For the purposes of this

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study, the FDA considers the ISC classification of events to be more reliable.

So how did the ISC classify events?

The ISC met on a regular basis and at least every two months, depending on the number of cases reported. The ISC classified each of the blinded case narratives into one of the following categories. First, they decided whether the event was a death or another endpoint event. If it was a death, it was classified as cardiac, suicide or other, and if it was an endpoint event other than death, it was also classified as cardiac, suicide or other. If there was doubt as to the exact cause of death, the case was conservatively classified as putative cardiac by default. And after that, there also occurred some subclassification, that is of the cardiac deaths.

So as completion of the study, all cardiac

deaths, both the definitive and the putative cases, were reviewed again, just in case more information had become available that could change classification, and then subclassified into the following categories: documented cardiac arrhythmia causing death either

directly or indirectly; documented sudden unexpected death, a death that occurred within 24 hours of onset of reported symptoms and with no other obvious non-cardiac cause; and other possible cardiac deaths, a death related to a complication of a serious non-arrhythmic cardiac event. I've highlighted the second one as I'll be coming back to that later.

Results.

A total of almost 10,000 patients were randomized to receive sertindole or risperidone with one-on-one randomization. Patients were between the ages of 18 and 85 with a mean age of 38 years. A little more than half in each group were men. Total exposure to study drug in the WRT period was about 6,600 patient years for the sertindole group and 7,600 patient years for the risperidone group. The median number of days, patients who were exposed to study drug during the WRT period was 360 for the sertindole group and 476 for the risperidone group.

Looking at the first primary endpoint, all-cause mortality.

I've written five covariates here just to

remind myself to tell you that the sponsor used five covariates in their analysis, although there were only two specified in this statistical analysis plan. However, we've compared the two and found the results to be quite similar. You can see there were 64 sertindole deaths and 61 risperidone deaths. The point estimate is 1.117 with a confidence interval going up to 1.587.

So how does one interpret this?

The pre-specified, non-inferiority margin, 50 percent was exceeded. At best, one might be able to rule out that sertindole is approximately 60 percent worse than risperidone in the risk of all-cause mortality.

Some additional points about this first endpoint, the first primary endpoint. The sponsor's results differ somewhat from ours, as they are based on a 90 percent confidence interval. However, as a standard practice, the FDA has been utilizing the 95 percent confidence intervals, two-sided in both cases -- two-sided, I'm referring about the 95 -- in non-inferiority trials. Also, the pre-specified

non-inferiority margin of 50 percent was chosen in agreement with the CHMP and not the FDA, as it was an non-IND study. Whether or not this margin was appropriate to begin with is an open question.

So looking at some secondary results. First,

we'll look at cardiac deaths, both the MedDRA coding and the ISC coding. Again, keep in mind that the Division considers the ISC coding because it was on a blinded committee to be more reliable. For the ISC coding, there were 31 cardiac deaths in the sertindole group and 12 in the risperidone group. That makes for a significant point estimate of almost 3.

Next, talking about sudden cardiac death, which I alluded to earlier. Sudden cardiac death was not one of the pre-specified secondary endpoints, however, we consulted with our QT team and the Division of Cardiovascular and Renal Products to ask whether in light of the QT prolongation seen with sertindole use, we should focus on any other safety endpoints. They suggested that the most clinically relevant endpoint with regard to QTc, more so than all-cause mortality in which a sudden signal could get lost in a lot of noise

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or all cardiac deaths, would be sudden cardiac death, with any sudden, unexplained deaths being conservatively classified as cardiac.

As we had found out and talked about, the ISC had already subclassified definite and putative cardiac deaths into several categories. One of the categories, which closely matched the definition of sudden cardiac death, recommended by our QT team, was -- and this is what I highlighted earlier -- a death that occurred within 24 hours, onset of symptoms, and with no other obvious non-cardiac cause.

Here are the results for sudden cardiac deaths. I've written here "all patients" just to remind myself to tell you that there's a sensitivity analysis next that I'm now going to talk about, and that's actually quite similar.

There were 13 events in the sertindole group and 3 in the risperidone group. That makes for a significant hazard ratio of 5. Dr. Garnett in her presentation will touch just a little bit more about who these patients are.

So as part of an exploratory analysis, we

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removed the following patients from the sudden death analysis. First, those patients in the sertindole group who had risperidone added to their randomized treatment and then, vice versa, those in the risperidone group who had sertindole added to their randomized treatment because that was allowed by protocol. Of course, it makes sense to remove those patients because if someone's on both, one cannot attribute the event to one or the other. We also removed those in either group who had certain QT prolonging antipsychotics added to the randomized treatment. We could not remove other QT prolonging drugs because other concomitant medications were not collected in a systematic fashion.

This exploratory analysis did not change the number of cases; there were still 13 and 3, though it

did change the denominator slightly. But the results were very similar to the previous analysis.

There were two cases of torsades in the SCoP study, one confirmed and one possible in sertindole treated patients. They were none in risperidone treated patients. I can give you very brief blurbs about them, and I can give you more information later if you'd like it.

The case of confirmed torsades occurred in a 79-year-old woman with a history of hypertension and possible cardiac disease, but no known concomitant medications. Four days after that was recorded, she was found dead in bed. Just as a note, amiodarone was listed as a concomitant medication here, however, it was given after torsades, not before. The case of possible torsades, which occurred in a 43-year-old woman with a history of hypertension, was complicated by treatment with an unknown antibiotic and an unknown Chinese cough medicine a few days prior to the event, and she recovered completely.

Now, getting to the analysis of the suicide attempts, fatal and nonfatal.

The review team was of the opinion that neither the investigators nor the ISC's approach to the classification of suicide attempts was adequate. The investigator's classification, coded using MedDRA, was made in an unblinded an unsystematic manner. Although the ISC was blinded to treatment, reducing the risk of bias, the definition the ISC used for suicide attempt was too broad, including suicidal ideation and tendency.

We requested that all the ISC identified suicide attempts, again for fatal and nonfatal attempts, including ideation and tendency, be reclassified in the following manner.

We asked that all the case reports for the ISC identified suicide attempts during the WRT plus 30 days be gathered and forwarded to an outside, independent consultant with the proper expertise and training reclassification. And we asked the consultants code each of the case reports using the categories from the Columbia Classification Algorithm for Suicide Assessment, or the C-CASA. Just briefly, discussing the classification codes in C-CASA, the codes ranged from 0 to 7. The codes that we were interested in were codes 1, 2 and 3, corresponding with completed suicide, suicide attempt, and preparatory acts towards imminent suicidal behavior.

We then requested that the sponsor perform a Cox analysis of time to the first suicide attempt for sertindole versus risperidone, for all events coded 1, 2 or 3. Before that, though, we asked that the following patients be removed from the analysis. The first two you've seen already, basically, patients that

were both on sertindole and risperidone. And we also asked that those in either group who had clozapine added to their randomized treatment also be removed. And that's because clozapine has been demonstrated to reduce suicide attempts in patients with schizophrenia, in high risk patients. The sponsor forwarded a total of 159 blinded cases, previously assessed by the ISC as suicide attempts in the WRT plus 30 days period, to Dr. Kelly Posner at Columbia, who then reclassified them in a blinded fashion using the C-CASA.

Before presenting the results, it's important to explain why our results and the sponsor's analyses differ. Of the five covariates in the analysis, 212 patients were missing one covariate and 28 patients were missing another covariate. Among them were two patients who had suicide attempts and were in the sertindole group. Because these two patients were dropped from the sponsor's analysis, the sponsor's

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result underestimated the hazards in the sertindole group. The FDA statistical reviewers imputed the missing code rate values for all the patients excluded by the sponsor and then repeated the analysis. It's important to note that different imputations of the missing covariates yielded similar results.

So here are the results of the suicide attempts based on C-CASA reclassification. Looking at FDA analysis, there were 47 events in the sertindole group, 63 events in the risperidone group. The point estimate is .804 with a nonsignificant p value of .258.

Here's a graphical demonstration of the data I just presented. This is the cumulative probability of suicide attempts, and that's on the left on the vertical axis, and the horizontal axis, you see number of days. You see the two lines are quite close together, and, in fact, come completely together approximately around Day 750.

Here are the results of the suicide attempts based on the C-CASA reclassification and the ORT plus one day period. Although the WRT plus 30 day period was the pre-specified period for the analysis and

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reporting of events in the clinical study report, the sponsor presented this supplementary analysis based on the ORT plus one day period. I want to make a quick note these numbers are slightly different than you might have in the copy. The old numbers did not include two slides that were found later. These are updated numbers.

Looking at the FDA analysis, you see that there are 37 events in the sertindole group and 55 events in the risperidone group. The point estimate is .708 with a nonsignificant p value of .1054.

The sponsor presented two additional analyses, both of which the review team did not consider a reliable way to assess for a possible reduction in suicidality. The first looked at time to suicide

attempt for only the first year of treatment. This is an arbitrary cut-off, especially considering that sufficient numbers of patients remained in the study to allow for analysis, encompassing at least the first three years of treatment. And here you can see that at year 2 and event year 3, there's a substantial number of patients remaining, more than enough to do analysis.

The sponsor second additional analysis looked just at completed suicides, however, a wide variety of factors can determine whether or not someone dies in a suicide attempt, many of which are completely unrelated to the degree of suicidal intent.

So a summary of the C-CASA reclassification results. For the period WRT plus 30 days, again, the pre-specified period for analysis and reporting of all events, both the sponsor's and FDA's analysis revealed no significant difference in the time to first suicide attempt for sertindole versus risperidone. Here, you can see the sponsor's p value and our p value. The sponsor elected to repeat the analysis for the ORT plus one day period. The sponsor's analysis resulted in a borderline p value of .063. The FDA analysis for the ORT plus one day period also revealed no significant difference in the time to first suicide attempt for sertindole versus risperidone, with a p value barely consistent with the trend.

So looking at the overall picture, the FDA's concerns about the significant dose dependent, QTc prolongation with sertindole and the risk of sudden

death remain. In the SCoP study, there was a five times higher risk of sudden cardiac death, definitive and putative, in patients treated with sertindole versus risperidone. Analysis of the C-CASA reclassification data does not support a significant reduction in fatal and nonfatal suicide attempts in patients with schizophrenia treated with sertindole versus risperidone.

In light of these results, the question is whether there are any advantages with sertindole use over antipsychotics that are great enough to outweigh the risks in it. Thank you.

DR. GOODMAN: Thank you very much.

I think we should hold all our questions until all the FDA presenters have had a chance.

DR. GARNETT: Good morning. My name is Christine Garnett, and I am the scientific lead of the Interdisciplinary Review Team for QT Studies at the FDA, and I'm here to talk about the proarrhythmic risks for sertindole. And contributing authors to my presentation include Dr. Shari Targum and Dr. John Koerner from the Division of Cardiovascular and Renal

Products.

So my plan over the next 15 minutes is first to discuss the nonclinical, proarrhythmic potential for

sertindole. I will show you, using clinical trial data, that there is substantial QTc prolongation at the clinical doses for sertindole. I will describe the risk factors for QT prolongation that are specific to sertindole. And I will conclude my presentation by discussing the clinical events associated with the proarrhythmic effects of this product. And you'll see by the end of my presentation that the nonclinical and clinical data suggest that sertindole does have proarrhythmic effects.

Most drugs that prolong the QT interval do so by blocking the hERG channel current or I . And so
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even though the mechanism is not well established, we know that excessive QT prolongation can cause a fatal arrhythmia called torsades de pointes. Now, we also recognize that non-cardiovascular drugs also prolong the QT interval by blocking I and cause torsades. And
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on this slide, what I'm showing you are some non-cardiovascular that have been removed from the U.S.

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market because these drugs causes rare form of arrhythmia.

Now, sertindole, and its primary metabolite, dehydrosertindole, potently inhibit I . As shown in
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this table, the IC is in the nanomolar concentration
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range, and keeps the concentration for block I in
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contacts with the clinical exposures. And this means, with an IC of 12 nanomolars for sertindole, that I
50 KR
is blocked at clinical concentrations. Also shown in this table are other antipsychotic drugs that also inhibit I nanomolar concentrations. However, you can
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see that sertindole, haloperidol and thioridizine are the most potent inhibitors of I , whereas olanzapine is
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the least potent.

Now, the sponsor contends that sertindole has low proarrhythmic risks because sertindole also inhibits the late sodium channel current, and this would mitigate the effects of blocking I and,
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therefore, decrease the proarrhythmic effects of the QT prolongation. And I'd like to make several comments on that.

First of all, the blockade of the sodium

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channel current is shown here on the bottom right panel, where the Y axis is the activity of that sodium channel and the X axis is sertindole concentrations. And as you can see, sertindole inhibits the sodium current in both a concentration and rate dependent

manner. So if you focus at high rates, which is shown in the red curve, the IC_{50} for the blockade of the sodium current is about 51 nanomolars, and this is about four times higher than the IC_{50} for I_{KR} blockade. This is at high rates. If you go to slow rates, which is shown by the black curve, the IC_{50} is now 980 nanomolars, which provides an 80-fold margin at these slower rates. Therefore, the potency differences for the sodium channel blockade is accentuated at the slow heart rates where torsades is most likely to occur.

Now, the sponsor also asserts that their nonclinical studies show that sertindole has low proarrhythmic risks, however, sertindole is proarrhythmic in dogs with chronic AV block. Now, this is a sensitive model that captures the proarrhythmic effects of human torsadogens, such as terfenadine at doses similar to those of human doses. So in this

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model, sertindole is clearly positive. It induces torsades in 10 of 13 dogs at concentrations that are only five times higher than those seen in humans at the 20 milligrams per day dose.

Now, the concentrations in the dog at the dose that did not induce torsades was similar to the concentrations observed in humans, but this is not reassurance for safety. All this means is that there is no safety margin in this model that could be established for torsades. So our opinion of the nonclinical data is that there is proarrhythmic risk for sertindole.

In the remaining part of my presentation, I'll now focus on the clinical proarrhythmic risks.

Now, the international regulatory bodies have come together and have issued a guideline called the ICH E14 document, and this tells sponsors how to do a clinical evaluation of QT prolongation in the pro-risk evaluation of non-cardiovascular drugs. And in that document, it states that drugs that prolong the mean QT interval greater than 20 milliseconds has a substantial increased likelihood of being proarrhythmic, and

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sertindole falls into this type of compound, as shown in the bottom table, where at the highest clinical dose of 20 mgs per day, the mean change from baseline exceeds 20 milliseconds. And in the same time, for patient population, approximately 10 and a half percent of the patients had a change from baseline greater than 60 milliseconds.

Now, it's generally accepted that prolonging the absolute QT interval greater than 500 milliseconds confers increase proarrhythmic risk, and at the 20 milligram a day dose, 2 percent of the patients had absolute QTc values that exceeded 500 milliseconds.

Now, to put the magnitude of QT prolongation

relative to other antipsychotics, I have put together this table. Now, this comes from a different study that the sponsor has shown previously. Here, I'm showing the mean change from baseline -- this is Fridericia corrected -- for sertindole that was computed from the sponsor's data compared to the other antipsychotics in the published article. And these are at doses that are the highest clinical doses for these other antipsychotic drugs. And as you can see, as a

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class, these antipsychotic drugs do prolong the QT interval; however, sertindole and thioridizine have the greatest effects on the QT interval, where as risperidone and olanzapine have the least effects.

Now, sertindole also prolongs the QT interval in a concentration dependent manner. And what this plot is showing -- this is just a -- what I did was I took the data represented in the sponsor -- in Panel 69, the briefing document. I just re-plotted it. So the X axis is sertindole concentrations; the Y axis is QTc interval. And what I've done is instead of showing the individual datapoints, I grouped the individual datapoints by their concentrations. I put them in 10 equal bins, and then just plotted the QTcF, the mean and 90 percent confidence interval.

So this shows that the observed data ranges up past 300 nanograms per mil, but the mean of the quantiles stops around 150 nanograms per mil; that means most of the data from there is below 150 nanograms, but we do have observed data that exceeds 300 nanograms per mil.

Now, as you can see from the concentration QT

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relationship that as you increase sertindole concentrations, you get an increase in the QTc, but it is nonlinear. And once you've established this type of relationship, what you could do, then, is compute the QT interval at any concentration of interest. For example, for the 20 milligrams per day dose, which has a mean C_{max} of approximately 80 nanograms per mil, this gives an increase in the QT interval of 25 milliseconds, and this is consistent when we looked at the QT interval by the dose effect. Now, what's important about the fact that sertindole increases the QT in a concentration dependent manner is now we become concerned about any risk factor that increases a patient's exposure to sertindole.

So in this slide, I'm listing two types of risk factors. There are factors that increase sertindole concentrations, and then there's general factors that increase a patient's susceptibility to QT prolongation. And because the general factors are not specific to sertindole, I'm really not going to go into them. I'm only going to focus in on the factors that are specific to sertindole.

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So to understand these factors, you really need to understand a little bit about the metabolism of sertindole. Sertindole is primarily metabolized by the CYP2D6 isoenzyme system in the liver, and the genes and coding for this enzyme system is polymorphic. This means that there's a certain percentage of the population that are going to be poor metabolizers of 2D6. And the prevalences are about 7 percent in Caucasians, 5 percent in African Americans, up to 6 percent in Hispanics, and 1 percent of Asians. This means that these patients will not have the ability to metabolize sertindole. As a result, they will have a two to three-fold increase in sertindole concentrations.

Other factors that would increase exposure to sertindole would be concomitant medications that inhibit the metabolism. So if you take commonly prescribed antidepressants, such as paroxetine or fluoxetine, they will inhibit 2D6, and the patient will get a two to three-fold increase in sertindole concentrations.

Now, you can also inhibit the 3A4. Now, 3A4

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plays a minor role in the metabolism of sertindole. We don't know what happens when a potent inhibitor 3, 4, how would that result in increases in the sertindole concentrations, but the sponsor did do a drug interaction study with erythromycin. Erythromycin is a moderate inhibitor of 3A4, and it had modest increases in the concentrations, which is expected since this is not the predominant metabolic pathway. We're also concerned about any disease state that would change the liver function, such as cirrhosis or hepatitis. And with liver impairment, you get about a two-fold increase in sertindole concentrations. So once you've identified the risk factors, the increase for patients' exposure to sertindole, what you could do now is use the exposure response relationship to impute what would happen to the QTc interval.

So this is the same figure they showed earlier. And so, for the 20 milligram per day dose with a C_{max} of about 80 nanograms per mil, you get a 25 millisecond increase in the QT interval. If, however, a poor metabolizer of 2D6 were to receive the same dose, they would get three-fold increases in

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concentrations, which would translate into a 40 millisecond increase in QT. But this is not the worst case scenario. The worst case scenario would be if a poor metabolizer who's taking sertindole receives a drug that inhibits 3A4, because then we've shut down the metabolism capabilities for sertindole. And we don't know how this would affect the sertindole concentrations, but we know this would only exceed. It would cause the QT prolongation exceeding 40 milliseconds.

So increased clinical events associated with QT prolongation is a signal that the drug has proarrhythmic risks. And what we've seen in the SCoP study is there was two cases of torsades in the sertindole group. Now, two cases of torsades may seem like a low number, but I'd like to emphasize that clinical trials infrequently capture torsades, even through drugs who are known to have significant proarrhythmic effects. So the few cases of torsades should not be a reassurance of safety. More importantly, in the SCoP study, there was an imbalance of cardiac sudden death, 13 cases in the sertindole

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group versus three cases in the risperidone group.

This table just summarizes some of the key features of those 13 cases of sudden cardiac death, and I just want to summarize some of the key findings.

First of all, if you look at the age, the patients who experienced sudden cardiac death, they weren't of the older population. The median age is about 37, 38 years, which is consistent with the overall age in the sertindole cohort. Eight of the 13 cases occurred in female, so that's about 60 percent. It's a little bit higher than the percentage of females enrolled in SCoP, which is 45 percent.

These patients were not on the highest doses of sertindole. The median dose is 12 mgs per day, which is comparable to the median dose of the sertindole cohort. And interestingly, in the SCoP study, they collected routine ECGs, and at the last ECG collected before the event -- and this could occur days, months or weeks before that event -- you don't see prolongation greater than 500 milliseconds in most of the cases, except for the one that I've highlighted in yellow.

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So to summarize, I've shown you my presentation that sertindole potently inhibits I and KR induces torsades in dogs. I've shown you in the clinical studies, there is substantial QT prolongation with documented arrhythmia. There's a mean QT prolongation that exceeds 20 milliseconds for the highest clinical dose. There are documented cases of torsades, and there's an imbalance in sudden cardiac death. I've also described to you the risk factors for QT prolongation that are specific to sertindole, and these would include this uncontrolled pharmacokinetic variability to the CYP2D6 genetic polymorphism, concomitant use of inhibitors of CYP2D6 and 3A, as well as disease states that would impair liver function, such as cirrhosis and hepatitis.

So I would like to turn the podium over to my colleague, Dr. Willy, who will be talking about the risk management considerations for sertindole.

DR. WILLY: Good morning. I'm going to provide an overview of risk evaluation and mitigation

strategies, which are called REMS, and then I want to discuss some important risk management considerations.

A risk evaluation and mitigation strategy is a risk management plan that utilizes strategies that go beyond professional labeling to ensure that the drug's benefits outweigh the risks. REMS are designed to meet specific, serious risk mitigation goals, and the Food and Drug Administration Amendments Act, which is called FDAA, provides authority to require REMS.

When considering the need for REMS, the following criteria should be considered. First, does the project fill a significant unmet need. You want to think about the seriousness of the disease or the condition being treated, the expected drug benefit, and the availability of other effective treatments. You also want to consider the magnitude of the risk. You want to look at the seriousness of the known or suspected adverse events, the reversibility of the adverse event, and the extent of the clinical trial or other exposure data. And then you also want to look at whether data suggests there's ways to mitigate the risk. For example, will monitoring help, what's the duration of use of the product, is there an identifiable at-risk group, and will stakeholder education and communication assist?

A REMS can include a medication guide for patients, a communication plan for healthcare professionals, and elements to assure safe use. A medication guide can be required if the FDA determines one or more of the following. First, if patient labeling could help prevent serious adverse events; second, if the product has serious risks that could affect the patient's decision to use or continue to use a product; and lastly, if patient adherence to directions is crucial to the product's effectiveness.

A communication plan can be required if the FDA determines that such a plan for healthcare providers will support the implementation of a REMS. The plan may include letters to healthcare providers. It may include disseminating information through professional societies about the serious risks of the drug and any elements to assure safe use.

Elements to assure safe use might be required and can include any of the following: a prescriber training or certification; certification of dispensers; drug administration that's limited to certain healthcare settings; the documentation of safe use prior to dispensing; required monitoring of patients; and enrollment of patients in a registry. When thinking about elements to assure safe use, they need to be commensurate with specific serious risks in the labeling. They can't be unduly burdensome on patient access to a drug. And to minimize the burden on health settings, they must, to the extent practical, conform

with elements for other drugs with similar serious risks and need to be designed for compatibility with the established distribution, procurement, and dispensing systems for drugs.

In the case of sertindole, QT prolongation has been identified as a serious risk. It's known to be a potent blocker of the hERG channel current. The rate in the clinical trials is approximately 1.3 percent for patients experiencing an increased risk of QTc, from normal at baseline to a level of greater than 500 milliseconds. And we know from the previous talk, that factors can increase a concentration.

If we want to consider different options that

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might be used, a medication guide would be first. A medication guide might inform patients about QT prolongation risk and potential consequences. It might inform the patient about the symptoms they should look for and what to do. You could also educate patients about the avoidance of other drugs that might increase the risk for QT prolongation and the need, potentially, of ECG monitoring. A communication plan might be used -- it could be used at product launch and it could include a dear healthcare professional letter that would help get the message out about the QT prolongation risk and the differential risk with sertindole compared to other therapies.

Regarding elements to assure safe use, let me first say, generally, if FDA finds that a drug's benefit justifies risk, that risk is normally communicated through labeling and other communication strategies, and is managed by prescribers without elements to assure safe use. If we want to talk about elements to assure safe use for QT prolongation, we need to consider certain items. For example, is there a subgroup who should avoid the drug, is there a

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methodology to identify QT prolongation in a timely fashion, and is there a defined period of susceptibility?

In addition, there could be also challenges for the elements to assure safe use for sertindole, so any strategy would require patient compliance with taking the medication as prescribed and monitoring, and there could be some challenges with the complexity of obtaining appropriate monitoring because you might need different healthcare providers; for example, psychiatrist and an internist or cardiologist.

So in summary, it's important to consider the benefit of a drug and the magnitude of the risk before considering risk mitigation. A REM should not be used to approve a drug that has significant risks and limited benefit over available therapies. Thank you.

DR. GOODMAN: Okay. Thank you very much.

I believe that concludes the FDA's formal presentations.

Am I correct on that? Okay. Then we can

proceed with clarifying questions from the Committee members. I would like to start that off. You can

raise your hands, and Yvette will also identify you.

If I understand the presentation correctly, and when you looked at the SCoP study, you identified a hazard ratio of nearly 5 to 1 for sudden cardiac death in the comparison of sertindole versus risperidone. And certainly, at first blush, that seems like an alarming increase in relative risk. But it is a relative number, so the question I want to know is -- obviously, if you have a very, very low base rate, you have a large relative number, and it's not very meaningful. But what we're talking about is a drug that might be approved and a large number of individuals in the United States might be exposed to it.

What's the FDA's estimation of trying to translate that number, that increased hazard ratio of sudden cardiac death, into actual population? What would be the number of increased risk for sudden cardiac death, or what would be the number needed to treat -- some way of expressing that into real numbers rather than relative numbers, if you can extrapolate it.

DR. TEMPLE: I mean, if you assume that it's going to be the same as we're seeing in the study, you would say there was an excess of 10 sudden deaths -- this is the 13 to 3 analysis -- in about 5,000 people, or that's 1 in 500 over, you decide, either one or two years. Somebody else has to figure out the number needed to treat and number needed to harm. But 1 in 500 is the kind of number you're used to. That's, as mortal risks go, not trivial.

DR. GOODMAN: Well, we have a statistician on our group, so let's -- we're going to turn to Dr. Bilker for an answer here.

DR. BILKER: I just wanted to ask a question that related to that, which was, to put it context, can you compare this to other antipsychotics? How would this compare to, for instance, olanzapine or any of the other antipsychotics?

DR. GOODMAN: Or pick ziprasidone, where there has been some concern.

Can I turn that question back to the FDA first?

DR. TEMPLE: I mean, there are not a lot of

10,000 patient studies around, and the quality of data you have is different in a randomized trial from what it is in ordinary life. But you have a comparison with the control drug here.

DR. PINE: So you think that's all we should --

DR. GOODMAN: Microphone.

DR. PINE: So you would say -- to answer

Dr. Bilker's question, you would say that, as I've heard you say before, you would weigh the direct, head-to-head data far more than any other data to answer the question.

DR. TEMPLE: Well, as Mary sort of said, if you didn't think this had some particular usefulness or something, it'd be hard to think about saying yes, and we've already been through that. We approved clozapine with the known 1 and a half or so percent risk of agranulocytosis, at a time when we thought that had a roughly 10 percent mortality. It turns out the good monitoring reduced that considerably. So if you believe that, that's a risk of about 1 in 1,000; if something fatal, it turns out to be less than that.

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That was tolerated because they unequivocally showed they worked when other drugs failed, and in schizophrenia, that's considered a good thing.

We're not sure whether drugs like ziprasidone, which clearly has some increased QT -- we couldn't put a number -- or I couldn't put a number; maybe somebody can -- on what the risk there might be. So, you know, 1 in 500, if you believe that, and it also depends on whether you believe that more than the total mortality findings in the study, which are also germane. But that's a kind of specific risk that's at the high level of what drugs do in many diseases. I mean, you don't expect that from your antihistamine or something, but maybe in schizophrenia, you want to take a different view.

DR. GOODMAN: Dr. Pine, you have another question?

DR. PINE: Yes. Two clarification questions for Dr. Kronstein.

So one was, in your Slide 7, when you talked about the average market share of sertindole in the EU being very small, .1 percent, that kind of sent the

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message to me that there's not going to be much use for it, that that's what I took that to be.

Was that your intent?

DR. KRONSTEIN: I think more the intent was that when we're looking at the spontaneous cases, one has to take into account how much the drug is used.

DR. PINE: So that wasn't a statement about what you guys think about its potential. In other words, is there a need for it. That's one of the things that we're going to be thinking about. You didn't say this explicitly, and maybe you don't think this. So the low use in Europe doesn't say anything to you about whether there's a need for it.

DR. KRONSTEIN: I would -- I mean, I would leave that up to the Committee.

DR. GOODMAN: Dr. Temple?

DR. TEMPLE: Well, you'd also have to look at how it's labeled there, how scary it is.

DR. PINE: Yes, exactly.

DR. TEMPLE: We know, as this committee has pointed out, what the labeling says can encourage or discourage use. And maybe people are reserving it for special cases, which might reassure you or make you wonder whether there's really a population.

DR. PINE: Okay, that helps.

DR. GOODMAN: Dr. Pedersen?

DR. PINE: Oh, one other --

DR. GOODMAN: I'm sorry.

DR. PINE: About the CASA analysis data, I just wanted to make sure. The 1, 2 or 3 score that you used, that's the exact same primary cut point that you used in the black box analysis for both antidepressants?

(Dr. Laughren nods yes)

DR. PINE: Yes? Okay.

DR. GOODMAN: That would be only for behavior, not for ideation.

DR. PINE: No. I think it was the exact same 1, 2, 3 in a primary --

DR. LAUGHREN: That was the primary endpoint. Well, no. I take that back. We included four, ideation. I'm sorry. We did separate analyses on behavior. We looked separately at behavior, but our primary endpoint for the box warning is suicidality.

DR. PINE: Then why did you use different ones in the two --

DR. TEMPLE: Because there's way more events. You get a much more precise estimate.

DR. GOODMAN: It's probably also reliability of ideation in the context of that study.

DR. LAUGHREN: You have better assessments of behavior here. That's what it focused on.

DR. GOODMAN: Dr. Pedersen, go ahead, please.

DR. PEDERSEN: Just to clarify the comment about the exposure and the European scenario, the drug is currently under introduction. There are several countries yet where it has not been received. In Europe, you have to get a price before getting there. So I caution to say that this is a reflection of a need in any way. That's one part. The second thing is, the suicide data that we're discussing here have not been presented to any other agencies in the world.

DR. GOODMAN: Dr. Hendren?

DR. HENDREN: This is just a point of clarification or understanding the rules of the game. That's maybe not the right metaphor.

For the information that the FDA presented, was that new analysis, the new information that they -- was that information that the industry had an opportunity to review before their presentation this morning? You got to see everything they were going to present, but did they get to see everything that you were going to present?

DR. KRONSTEIN: That information came to us from industry.
DR. HENDREN: But you did a re-analysis, right, of their information?
DR. KRONSTEIN: The re-analysis of their information -- let me --
DR. GOODMAN: For example, when you looked at the suicidality, you had mentioned that you added in two cases that were eliminated. So I guess the question is, did industry have an opportunity to see your re-analysis?
DR. KRONSTEIN: We have an elimination side. There are two separate events that we're talking about here. One was the case of the ones that weren't -- you're talking about the two that weren't

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included in the analysis. Okay.
DR. GOODMAN: As I understand the question, you just want an example of making sure that there's an interaction --
DR. KRONSTEIN: So the two that were not included in the analysis, that was in the addendum to the NDA. That was shared with the sponsor.
DR. HENDREN: But you came to a different conclusion than the sponsor.
DR. GOODMAN: Please use your microphone.
DR. HENDREN: You came to a different conclusion than the sponsor did, right? Did they know that you had come to a different conclusion?
DR. KRONSTEIN: Yes. That was submitted as part of our NDA addendum, which was given to the sponsor.
DR. HENDREN: Thank you.
DR. GOODMAN: Dr. Bilker, did you still have a question?
DR. BILKER: Just one clarifying question.
The analyses of suicide attempts that were done, each of those analyses included a maximum of one

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per patient? Is that right, or were there multiple suicide attempts counted in there?
DR. PEDERSEN: Yes. For the SCoP study, there were only one event patient in contrast also to the InterSePT study, where the same patient could contribute to more events.
DR. BILKER: Thank you.
DR. GOODMAN: Dr. Harrington?
DR. HARRINGTON: I have two questions for Dr. Kronstein, and then a combined question for Kronstein and Garnett.
You had noted that the analysis on the secondary endpoint of suicide was added after the study was underway. I think Dr. Granger said 16 months. With all the files and documentation, was there any note as to why they added that? I mean, the assumption is that they saw the data accumulating, and they had treatment specific data because it was unblinded. But

is there any note in the file as to why that analysis was added?

DR. KRONSTEIN: Not that I saw. I know the discussions between the FDA regarding suicidality

occurred in January of 2006.

DR. LAUGHREN: We had suggested that it be added, I believe, didn't we?

DR. HARRINGTON: And did you suggest it based on knowledge of the ongoing treatment effect? Because the trial was unblinded.

DR. LAUGHREN: Well, it was in the context of that meeting in 2006. Maybe the sponsor can respond to that. I honestly don't recall how much data we actually had at that point. I think we mostly had the epidemiologic data. I don't know that we had data from SCoP. I don't think so.

DR. BULLER: Can I clarify this?

This amendment was basically in place in all the sites in November 2003. The FDA meeting was in June 2003. From the beginning on in the SCoP study, we collected information on serious adverse events, which included suicides and suicide attempts. What the amendment actually did was specify a combined endpoint of fatal and nonfatal suicide attempt as a secondary endpoint that was agreeable at the time to the FDA. With the amendment, we included a data sheet into the

case report form to collect suicide history.

Now, in terms of the numbers of patients that were entered by the time of that amendment, it's approximately 1,600 patients. It depends on whether you count the first of November or the last of November. And the exposure by that time is about 800 patient years. When we look at the number of events that occurred before or after -- and we're happy to present that data later on -- we see basically always a number in favor of sertindole. So we don't think that this amendment has changed anything in terms of the recording of the events.

DR. PEDERSEN: But it's correct that there was not a sharing. You did not know any data at that time; neither did we, actually, at that time from the study. It was still in its infancy.

DR. LAUGHREN: I think we were -- we were looking at the observational data for other --

DR. PEDERSEN: That's correct.

DR. LAUGHREN: -- studies, that basically suggested to us that that would be an important thing to look at, since you had --

DR. PEDERSEN: That's correct. We had the clinical trial database, the epidemiologic data, and the crossover data that indicated there was a reduced rate of suicidality at that meeting. We did not discuss the SCoP study other than the design of the study. And at that time point, you said that that

could be an interesting thing to consider as a way of balancing the perceived risk around the QT prolongation.

DR. HARRINGTON: We're playing at the margins here, and one of the questions that will be asked to us is the persuasiveness of the evidence, so the margins become important. The FDA had requested this reanalysis by the C-CASA group, but the study obviously wasn't designed -- the case report forms wasn't designed with that in mind.

Did the C-CASA investigator feel that the data were adequate to partition or to score those events into the particular categories? In other words, if they didn't have adequate information, what was the default? Did they give you a 1, 2, 3 or did they downgrade it to 4, 5?

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DR. KRONSTEIN: I don't have information on that. I know they classified all the cases, but I don't know.

DR. HARRINGTON: So they felt it was adequate.

DR. LAUGHREN: They have the same narratives.

And, Phillip, correct me if I'm wrong.

DR. KRONSTEIN: They have the same narratives that were given to the ISC.

DR. LAUGHREN: That the ISC had, and they did this blindly. And their usual approach is to have three different individuals basically rate those narratives, and it's two out of three.

DR. HARRINGTON: So then my final question, Dr. Kronstein -- and maybe this is more to Dr. Garnett, because you both suggested it. The first speaker this morning implied that clinicians can do a pretty good job of -- I think she used the phrase "personalized medicine," that we can in a sense pick out which patients may benefit from certain therapies, may be at risk.

Did I hear you right, Dr. Garnett, that there are some general factors here that you can pick out,

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but it's awfully difficult, even using regression modeling, et cetera, to determine which specific patients might be at risk for QT prolongation?

DR. GARNETT: Right, the factors that were specific to sertindole that we would be concerned about would be patients who are 2D6 poor metabolizers, and a way of knowing who they are would be through genetic testing, would be the best way of doing that. Without that -- I guess you could look at the concentration data. I think the sponsor has presented that in a briefing package, where you can look at the parent to metabolite ratios to get some sort of idea if they have poor metabolizing status, but that would be one uncontrolled type of risk factor.

DR. HARRINGTON: And did you guys use regression modeling to try to understand which patients might be at risk in this specific data set for either

QT prolongation or sudden death?
DR. GARNETT: Well, the sponsor in their briefing package -- and I don't remember what panel number; they probably know -- they did show the relationship for poor metabolizers as they identified

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as having this metabolite to parent ratio of less than .4. And what you see is that you don't see differences in the exposure response relationship; you just see these poor metabolizers have higher concentrations in sertindole. Now, what you don't see in there is the increases of concentration by dose. They just have all poor metabolizers and not various different dose levels because I couldn't stratify that by dose. But perhaps the sponsor has some more insight.
DR. PEDERSEN: If I can have this slide on, then I can at least indicate that's the data on poor and extensive metabolizers.
So there are both of these set of individuals in the database because at the time that the clinical data were collected and these blood samples were collected, we had no exclusion criteria, neither of the poor and extensive metabolizers or of the patient who had concomitant medication that might influence the enzymes. So this gives a picture of the various groupings, the poor and extensive metabolizers and the QT prolongation relative to the plasma concentration that had been measured in these individuals.

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DR. GOODMAN: Dr. Slattery and then Winokur.
Okay. Dr. Winokur, then.
DR. WINOKUR: So my question was actually a direct follow-up to what Dr. Harrington asked to Dr. Garnett.
I'm looking specifically at the table toward the end that you presented, which had the sudden cardiac death cases with sertindole, and I was trying to connect that. I just want to make sure I understand your view on this to the risk management idea that we then heard about in the next presentation. So a couple things I'm thinking through.
Number one, subjects enrolled in this study were considered appropriate candidates to be on sertindole based on information available that guides us at this point. And then you pointed out that looking at these 13 cases, a number of them are fairly young. In a number of cases, the last QTc value was actually --
I'm sorry? I'm just trying to continue.
Are there any other factors that you could identify? Do you have any thoughts about how a risk

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management program, from your perspective, would relate to what came out in these particular cases that you've looked at an analyzed?
DR. GARNETT: Just to comment on that QT interval that I put in the table, again, that is just

for last recorded QT interval prior to the event. If you look at the time frame, it differs between days, weeks to months, prior to that, and they are unremarkable. We don't know what happens at the time of event because we just don't have that information.

Shari, would you like to comment on how that could interpreted from this risk evaluation?

DR. TARGUM: I'm not sure I have much to add beyond what Dr. Garnett said. One of the pitfalls of a large simple trial is that we just don't have a lot of information. And in some instances, months passed between the last EKG and the terminal event.

DR. GOODMAN: Dr. Granger?

DR. GRANGER: For Dr. Kronstein, I recognize the challenges in the fatal suicide, but nonetheless, it seems to me as though that's a fairly hard and relevant outcome. And I think the sponsor's indicated

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that there were 10 deaths attributable to suicide.

Is that consistent with --

DR. KRONSTEIN: Which slide are you referring to?

DR. GRANGER: From the briefing document. I don't think you showed anything about suicide deaths. But I just think, again, in kind of balancing risk and benefit, reduction of -- so I kind of have assessed that there were 19 increased cardiac deaths, 10 sudden cardiac deaths, 16 last suicide attempts. And I think it was 10 last suicide deaths, according to the sponsor's information. I'm wondering if that's consistent with -- if you looked at that also.

DR. KRONSTEIN: Looking at -- and you're talking about just completed suicides, in other words.

DR. GRANGER: Correct.

DR. KRONSTEIN: Looking at the WRT period, it is 21 versus 13, 21 for risperidone, 13 for sertindole. That gives a p value of .71 with a hazard ratio of .83. Looking at the ORT plus one, risperidone, 19, sertindole, 9; hazard ratio of .501, the p value of .0876. And, again, keeping in mind pitfalls looking

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just at completed suicides.

DR. GRANGER: Okay, thanks.

And back to Bob's point about the best way to analyze with respect to the duration of follow-up for safety and outcomes. While certainly that may be the best approach, I also think that it is important for us to have the kind of preservation of the randomization in terms of making sure that the groups are balanced with respect to potential, unmeasured confounders. So for me, it's also relevant to know at least the total mortality in the entire trial period, the whole follow-up period, according to randomized treatment group as another sensitivity analysis.

Do we have that?

If you take all the patients, just looking at each randomized group, the total number of deaths in

the two randomized groups throughout the duration of follow-up.

DR. KRONSTEIN: You're talking about the whole follow-up period?

DR. GRANGER: Yes.

DR. KRONSTEIN: I haven't seen that data. I refer to the sponsor on that.

DR. PEDERSEN: Could we have the slide up?

These are the total number of deaths in the whole follow-up period, which includes patients who have gone off either the two treatments and have been followed on for whatever length of time until the date when we closed the study in January 2007. It's the total study. I mean, anything could have happened to these patients after they stopped the randomized treatment, and that's the exposure period you have there.

DR. GRANGER: Okay, thanks.

DR. PEDERSEN: Okay. Thank you.

DR. GOODMAN: Drs. Day, Potter and Malone.

DR. DAY: Question for Dr. Willy.

Can you comment on the presence of medication guides or other REMS tools for other drugs in the antipsychotic class?

DR. WILLY: In terms of for QT, med guides specific to QT prolongation?

DR. DAY: I was just meaning in general, what proportion have them and what are they for, especially relevant to the concerns of this drug.

DR. WILLY: Right. I can't give you the specifics on med guides for the class. I believe they may have med guides for other drugs, but I don't think -- there are none that's specific for QT.

DR. GOODMAN: Tom?

DR. LAUGHREN: Yes. There are only two antipsychotics that have med guides right now. Olanzapine, Zyprexa just got one recently, and that's focused largely on the metabolic issues, but also is a more general med guide. The only other one that has a med guide is Seroquel, quetiapine, and that's focused entirely on suicidality because it has some depression claims.

DR. DAY: And that's the topic of discussion tomorrow.

DR. LAUGHREN: Right. That certainly could be a topic of discussion for tomorrow.

DR. GOODMAN: Dr. Mathis, did you have a comment?

Okay. Dr. Potter?

DR. POTTER: Dr. Garnett, could you comment on whether or not with terfenadine were you able to produce the kind of curve you did in terms of QTc increase versus dose? Would you have seen the same shape curve, the same plateauing of that curve with

terfenadine, or is that known?
DR. GARNETT: I don't recall terfenadine per se.
DR. POTTER: I mean or any other drug where we have a known --
DR. GARNETT: You do see them, especially for the antiarrhythmics, where you're getting these large QT prolongations. If you push the dose high enough and get high enough exposure, you are going to start seeing this E type of shape.
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DR. POTTER: Right.
DR. GARNETT: And I think that can go back to the fact that this is inhibiting channels or enzymes, so you'll probably get to a threshold where you just can't inhibit anymore. But you have to be able to push the dose high enough to get higher exposures. Now, for non-cardiovascular drugs, a lot of times you just can't push the dose high because there will be some other

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dose limiting type of toxicity where you only see maybe a log linear or linear type of relationship.
DR. POTTER: What I was really trying to get at was does the shape of that curve in any way conform not on a hypothesis -- that's my question.
DR. GARNETT: Dr. John Koerner may be able to answer that question.
DR. KOERNER: I can't answer it with regards to the human QT data, but certainly in vivo and in vitro models with drugs that affect channels other than just hERG, if they have effects on inward as well as outward currents, and if there is some separation between the potencies in these particular currents, you can get various shape concentration response curves. It's certainly possible, and we've seen it with drugs like terfenadine, where there can be a biphasic dose response, concentration response in isolated tissues.
There's at least one study done with terfenadine in animals. It's somewhat different than what we're talking about here in the sense that it was an acute, intravenous infusion, and you can get a plateauing, in fact, a decrease in QT at high

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concentrations.
DR. POTTER: Thank you.
DR. GOODMAN: Dr. Malone?
DR. MALONE: I have two questions. I think they're for Dr. Garnett.
One is in the 13 deaths. I'm trying to estimate is there a period of maximal risk when you might have sudden death? I think a lot of clinicians might assume that most side effects occur earlier on, but what happened with these sudden deaths?
DR. GARNETT: I think Dr. Kronstein is going to be answering that question.
DR. KRONSTEIN: So here's a slide of time to sudden cardiac death in SCoP plotted. The Y axis is

time and days to sudden cardiac deaths. And you can see that on the right -- I don't know why I didn't make it on the -- on your right, you have risperidone; on your left, you have sertindole. And you can see as they cluster up, all the wait, almost 600 days. So there doesn't seem to be -- I mean, you can say maybe for 600 days, but that's a long period of risk. It's not a short time while you're titrating it, at least

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based on this.

DR. MALONE: The second question is there was a rare detection of torsades de pointes in the study.

Is there any way to estimate if you're picking up a rare event, how often that event may be occurring?

DR. GOODMAN: Dr. Temple?

DR. TEMPLE: Well, Christine pointed out that you don't necessarily detect torsades, you just find the body. It's worth remembering -- and I wish I could remember the exact name of the study. But in a controlled trial of d-sotalol, a pure, I guess, Type 3 antiarrhythmic, which is a well --

DR. PRITCHETT: SWORD.

DR. TEMPLE: SWORD, yes. Thank you. I couldn't remember it. Okay.

In the SWORD study, which showed increased mortality and terminated the development of that drug, there were enough deaths to show an increased mortality. They were surely, almost surely, due to torsades. There were only three cases of torsades in the whole study, and I believe two were in placebo and one was on drug.

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So you just don't necessarily see torsades even though that's what happened. Now, you do see some because torsades is more survivable, ventricular tachycardia than other ventricular tachycardias. So people do make it to the emergency room sometimes. And that's how we discovered terfenadine, because somebody made it to the emergency room, and Carl Peck and his colleagues figured it out. But you don't necessarily expect to, and even in SWORD you didn't see the torsades that was almost surely the cause of the deaths. So you can't expect that.

DR. GOODMAN: Dr. Laughren?

DR. LAUGHREN: Just a follow-up comment on the time to the event and the wide distribution in times. Certainly, all other things being equal, you would expect for something like this, that if it's going to happen, it happens right away. The problem is all other things aren't equal. Patients have other things. They might take another drug that blocks 2D6. They might have a low potassium for some reason because of vomiting or diarrhea, something like that, or they might inadvertently take twice the dose. There are

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other kinds of things that may change their instant circumstances that lead to that increased risk.

DR. GOODMAN: Dr. Winokur?
DR. TEMPLE: Can I add one thing?
It's worth thinking of what happens in people with congenital QT prolongation. They don't die at birth. They die at a higher rate than other people sort of all the way through their lives, whether that's because something goes on and lowers their potassium or who knows what. So it's not so clear what happens in this. It puts you at risk, but it doesn't kill you right away.
DR. WINOKUR: I apologize. I'm now a little out of sequence. I was trying to jump in after Dr. Potter's comment. I think his question about terfenadine to me is very important, and it reminds me of the discussion around the ziprasidone study. And we were shown some data in that meeting, where terfenadine by itself had an effect that was comparable to sertindole and also to ziprasidone. But when given along with its metabolic inhibitor, the change in QTc went from in the twenties to, as I recall, about 70 or

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80 milliseconds. So that brought up the issue of how important the potential drug interaction part of this is. And I think that's something that maybe we still need to hear some more about from the sponsor in terms of their view on that issue.
DR. GOODMAN: Somebody from the sponsor table want to respond? No.
All right.
Ms. Lawrence?
MS. LAWRENCE: Again, as a layperson -- and I guess this would go to Dr. Willy, with risk management. I haven't heard a lot of information with sertindole as far weight gain. Maybe there wasn't a significant amount. But I know with other antipsychotics, the side effects of these drugs can be so severe for the patient that to add another -- and I'm not debating the approval or anything. But has any consideration been given to this study, taking into consideration all the other side effects that can come before anything as severe as a QT?
We know that the illness provides risk of judgment for the patient, which then can lead to other

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parts of their lives that could put them at risk and developing a QT. My own son had this fatal situation this past summer. He was on Clozaril. And I know that all these drugs have risks and side effects. And I'm just wondering has anything been considered with this sertindole study as far as risk management?
DR. WILLY: At this point, I don't think we've had any discussion about the risk management, but the first part -- the first stage is trying to decide the risk benefits. And then once we decide that we think there's enough benefit, then we can move forward in terms of how we might want to manage or mitigate the risk.

MS. LAWRENCE: Thank you.
DR. GOODMAN: I think your question does raise another issue that we haven't talked about much today, which is the effects on metabolic syndrome. So I wonder if the FDA or the sponsor could make a few remarks on comparative risk of metabolic syndrome in sertindole versus other available atypicals.
DR. DAY: There's quite a bit about this in the briefing materials, including weight gain.

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DR. KRONSTEIN: This is the information that comes from the short-term placebo controlled trials. This is mean change from baseline for weight. You see that at the 20 milligram dose, you have 3.3 kilos. Keep in mind, we're talking about six eight-week trials. That's a significant amount of weight gain.
If you look at weight outliers, and those that are gained -- people that gained greater than 7 percent of baseline weight -- again, look under the 20 milligram dose, which is the highest recommended dose, you see 27.7 percent in the 20 milligram group versus 11 percent in the placebo group. It's a mean change in baseline for metabolic chemistries. It does appear that the fasting glucose goes up compared to placebo, though it's unclear about -- because you're pooling several studies, you can't quite see if it's dose dependent or not.
Looking at triglycerides, there seems to be a signal as well as a bit of a signal with total cholesterol, but looking -- it's better to look, though, at people who were outliers at endpoint, not at baseline. It's a more accurate way of looking at

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things.
There seems to be a signal with cholesterol, but it's a few percent versus placebo. In glucose, especially at 20 milligrams, it's definitely greater than two times placebo. And, again, this is a fasting glucose. That was specified in the studies.
Looking at triglycerides, greater than 200 milligrams/deciliter. It's not quite twice placebo. And looking at triglycerides, it's greater than 500 milligrams/deciliter. It's a small percentage, though, but it's obviously a significant increase in triglycerides. Again, these people are at endpoint, not at baseline.
One would need more control of long-term data to complete conclusions about this, but there definitely seems to be a signal there.
MS. LAWRENCE: Thank you.
DR. GOODMAN: Dr. Pedersen?
DR. PEDERSEN: There is some information in the sub-study from the SCoP. It's not a very extensive study in terms of there's about 120 patients in each of the two treatment arms. Not all of them follow to the

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very end, so there are some limitations to what you can

conclude from that. But that's at least up to one year exposure. And in that study, it does not appear to have a change in the metabolic parameters over that period of time. And in comparison to risperidone, it's at the same magnitude, both, with regard to weight gain and also with regard to -- slide on, yes.

These are the figures here. So you'll see the change. The BMI at the baseline and the last measurement have not changed over that period of time. The weight gain is modest. I think, obviously, when you see or hear the data from a short-term study with a fair number of kilograms added, you see what happens over time. And these are two different settings. One was more than 10 years old conducted in the United States in an in-house setting. So you can't immediately translate these proportions here. But we seem to be in the ballpark of where risperidone is in this respect.

DR. GOODMAN: Thank you.

Gail Griffith, and then we'll give the final word before lunch to Dr. Pine.

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MS. GRIFFITH: In Dr. Garnett's presentation, she talked about a two-fold increase in concentration with people who have hepatic impairments. And it occurred to me, just sort of on a macro level, that this is a population we're talking about that has a greater than normal -- greater than average risk of hepatic impairment due to drug and alcohol abuse over the years. So you have a lot of people, I think, who may come to treatment who may have liver dysfunctions that aren't going to be accounted for. If one in 500 people are at risk in a trial setting, it might be a much higher number if we took into account the hepatic risk.

It's not a question, but I was sort of stunned.

DR. GOODMAN: That's okay. I was looking for who --

MS. GRIFFITH: Well, I'm sorry.

DR. GOODMAN: They should answer it, yes.

MS. GRIFFITH: I noticed that they had lack of blood samples. I take it that no data captured any element of that risk in either the sponsor's analysis

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or FDA's.

DR. GARNETT: That's my understanding. In this SCoP study, they didn't collect blood concentrations, but I think the sponsor can answer that better.

DR. PEDERSEN: That's correct. We did not collect blood. But these patients would, obviously, also be part of the group of individuals that would be offered the treatment in the SCoP. The idea of the SCoP study was to make it as naturalistic in that sense.

MS. GRIFFITH: So you did not rule out people

with drug or alcohol histories?
DR. PEDERSEN: No.
DR. GOODMAN: Dr. Pine?
DR. PINE: Yes. Two specific questions for Dr. Kronstein. One is about excluding the patients on clozapine.
Did that have any effect on how many were there, and if you analyzed it either way, did it change anything?
Slide 40, page 20. Oh, I'm sorry. Slide 34,

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page 17.
I mean, my thinking here is that it seemed fairly straightforward to get rid of people on both medicines. That would seem the right thing to do. I could see it either way in terms of whether or not it would be right to include or take people out if they're on clozapine.
DR. KRONSTEIN: I have the total number removed from the analysis, but I don't have which of those were on clozapine, of all those three criteria.
DR. PINE: I see. How many total, just out of curiosity?
DR. KRONSTEIN: It took from -- sertindole from 47, it looked at the 46, and risperidone from 66 to 62. Actually, those numbers are one off, again, because I wrote that before that information.
DR. PINE: Four out of 60 in risperidone and how many out of --
DR. KRONSTEIN: About 4 out of 60 and about 1 out of 60 in the sertindole -- 1 out of 47. I'm sorry.
DR. PINE: All right. And that's any of --
DR. KRONSTEIN: Those are all three.

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DR. PINE: All right. So that was one.
The other one was Slide 40. I had a question about your middle bullet, which you said that looking at time to first suicide, for only the first year of treatment, you didn't like that because you thought it was arbitrary, which I would agree that that would be arbitrary. On the other hand, one could imagine that some kind of survival analysis in general might have more power than a categorical approach.
So could you say something about an analysis using all the data, not using any arbitrary cut point, if that revealed a between group difference in terms of time to first suicide attempt? Because we've all been saying that we're kind of skating on thin ice on both sides of statistical and clinical significance. So it would influence me if a more powerful analysis, done in a non-arbitrary, unbiased way, suggested that there was an advantage for the sertindole.
DR. LAUGHREN: The primary analysis did include all the patients, didn't it?
DR. PINE: But it looked at an event, yes/no classification. It didn't look at this --

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DR. LAUGHREN: Oh, it looked at time to first event, yes.
DR. PINE: And that found no difference in terms of time to first event? Is that right, if you used the primary determination?
DR. LAUGHREN: There was a numerical finding; it just didn't reach statistical significance.
DR. PINE: Okay. That's fine.
DR. GOODMAN: Yes. Go ahead.
DR. BULLER: Can I have the slide up?
Just to summarize what was said, this slide has been shown to you before. And this is for the various periods. So the primary period that is referred to would be the WRT plus 30 period. And we have presented the ORT plus one period, which is basically the monotherapy period. And the little white lines in there are the ones where the new FDA analysis is. So what you see on this slide is, basically, that however you slice the pie, it's always in favor -- at least the point estimate is always in favor of sertindole. And you see where the upper confidence limit touches the one or exceeds the one. That would

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be the ones that would not be statistically significant.
It is worthwhile, keeping in mind that this study was not powered for looking for suicidality, but it is a naturalistic study, and it shows you what happens in the real world. So you are not faced with a question, how do you translate the findings from a clinical study into a real world prospective? This is what the study actually shows.
DR. GOODMAN: Okay. Thanks, everyone.
We're going to break for lunch. We're going to reconvene sharply at 1:30 p.m. Please bring any of your valuables with you. Committee members, please remember that there should be no discussion of issues related to these hearings during lunch, amongst yourselves or with any member of the audience.
(Whereupon, a lunch recess was taken at 12:30 p.m.)

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DR. GOODMAN: Please bear with me as I read a statement to you. We're now beginning the open public hearing portion of the meeting.
Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's

presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include a sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have such financial relationships. If you

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choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the Agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair.

Thank you for your cooperation.

My understanding is that we have two public speakers who have signed up. I don't know -- well, I guess, number one, sometimes I have a slide with the names. I apologize; I don't.

Oh, there we go. Introducing Robert Bernstein, Executive Director, Bazelon Center for Mental Health Law. Welcome.

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DR. BERNSTEIN: Thank you very much.

Good afternoon. First of all, I have zero financial connections with anyone on earth, including everybody in this room and any pharmaceutical company. So let me assure you of that.

My name is Robert Bernstein. I'm a clinical psychologist and executive director of the Bazelon Center for Mental Health Law in Washington, D.C. Let me say at the outset that I'm very pleased to share the podium with the Vietnam Veterans of America. We honor the sacrifice and service of its members.

For almost four decades, the Bazelon Center has worked through the courts and in the halls of Congress to ensure that public schools, workplaces and housing are available to people with mental disabilities, enabling them to participate in community life. Through litigation partnerships with nearly 30 national law firms, we have conducted precedent-setting litigation, which has outlawed institutional abuse, won protections against arbitrary confinement, and established a right to treatment for inpatients of

state psychiatric hospitals.

Our work with Congress and in the courts, including the Supreme Court, created the right for people with disabilities to receive services in integrated community settings. Our advocacy has included numerous efforts to protect the rights of people diagnosed with schizophrenia. I'm here today not to comment on the safety or the efficacy of the medication before you. I'm here because the advisory committee process presents an opportunity to bring to people's attention the significant public health problem represented by serious mental illnesses like schizophrenia, and the importance of allowing individuals diagnosed with schizophrenia access to a broad array of treatments, particularly where there exists a potential benefit in reducing suicides and attempted suicides.

Schizophrenia is a psychiatric disorder that affects up to 1 percent of the world's population. It is characterized by severe but variable symptoms, including delusions, hallucinations, disorganized speech or behavior, blunted mood expression, profound apathy and social withdrawal. This array of factors,

in addition to the entrenched stigma attached to the diagnosis, too often leads to marginalized social status with attendant problems of unemployment, alcohol and drug abuse, and contact with law enforcement. Many people who have schizophrenia are incarcerated.

Not surprisingly, schizophrenia is associated with increased medical morbidity at a two to three-fold increase in mortality compared to the general population. About 50 percent of people diagnosed with schizophrenia will attempt suicide; from 5 to 10 percent will die from the attempt. Suicide attempts are, obviously, agonizing for the individual and family, but they're also costly to society. They commonly trigger cycles involving police and emergency personnel, assessment and treatment in hospital emergency rooms, and admission or readmission to psychiatric hospitals.

We at the Bazelon Center neither promote nor oppose the use of medication. We know that individuals who seek medication as a part of treatment often move through various therapies looking for either improved efficacy or in escape from troublesome side effects.

We also know that many find currently available medications unsatisfactory. We believe that each person should have an opportunity to make an informed decision from an array of choices in light of his or her specific needs in consultation with the doctor.

For this reason, we oppose many policies designed to restrict Medicaid drug benefits, including the short-sighted fail-first policy. Fail first requires an individual to endure a bad experience with

an older, less effective drug not of his or her doctor's choosing, before being allowed to access a newer more effective medication. The primary goal is cost containment, but we believe it comes at a high price, particularly to those most at risk. It is easy to see how such a policy might contribute to someone's deciding not to take prescribed medication, putting him or her at risk of coercive treatment.

So while we are not recommending any particular medication or treatment, we do believe that the consumers who seek medication should have a range of choices. Should the FDA determine that Serdolect is safe and effective, it would provide a new treatment

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option to address this debilitating and often fatal disease. Thank you.

DR. GOODMAN: Thank you very much.

Our next speaker is Dr. Tom Berger, Chairman of the PTSD and Substance Abuse Committee, Vietnam Veterans of America.

DR. BERGER: Thank you, Dr. Goodman and distinguished members of the Advisory Committee. Neither myself nor VVA is currently in receipt of any monies from the sponsor or any federal granting or contract agency other than the routine allocation of office space and associated resources in VA regional offices for direct services through our Veterans Benefits Program. This has been true for far longer than I'd like to remember.

It does pleasure me to follow Dr. Bernstein, and I will keep my remarks brief, to the point, since he's covered much of the information that I wanted to speak to. And, again, thank you for the opportunity to present VVA's statement regarding the use of sertindole for treatment of schizophrenia.

First and foremost, VVA believes that any

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antipsychotic prescribing must be closely associated with patient monitoring because there is a great deal of evidence that psychiatrists and public health settings, such as the VA and community health settings, often fail to monitor the side effects regularly in patients with schizophrenia. For example, in 2001, the VA provided care to more than 98,000 veterans with schizophrenia at a cost of $1.7 billion. This is before the start of the wars, ladies and gentlemen.

Veterans with schizophrenia occupy more hospital beds at any given time than veterans with any other illness. In addition, even when stabilized in the community, many veterans with chronic schizophrenia function poorly. Many are chronically or periodically unemployed. Some are isolated in the community, and the most severely ill may comprise at least 10 percent of homeless veterans receiving VA health care. Even those veterans who have been stabilized may have persistent psychotic symptoms that can interfere with their community adjustment.

As you heard my colleague just mention, schizophrenia is also associated with increased medical morbidity, which contributes to a significantly lower life expectancy. This has very important implications for our nation's veterans, particularly with recent reports of increasing numbers of suicides for both active duty personnel and particularly our veterans. This is the reason why VVA is present here today.

There's strong evidence, funded through the research, obviously, conducted by Lundbeck, that patients suffering from schizophrenia who are treated with sertindole have a significantly lower risk of suicide and suicide attempts than those being treated with risperidone, for example. This is an important benefit in the treatment of patients, particularly veterans, with schizophrenia.

VVA believes that this new pharmacological treatment with regular close monitoring of side effects by clinicians, coupled with evidence-based psychosocial treatment when appropriate, provides additional treatment options for persons with schizophrenia.

VVA again thanks you, Mr. Chairman, and the members of this committee for the opportunity to present our views on this important mental healthcare issue. Thank you.

DR. GOODMAN: Thank you, Dr. Berger.

I believe that concludes the open public hearing portion of the meeting. The agenda calls for a break, but I don't think we need one, not yet. So we will begin the panel discussion portion of the meeting. Although this portion is open to public observers, public attendees may not participate, except at the specific request of the panel.

Now, I wonder if we can get the slide with not the questions -- yes, the questions for which a vote is requested. We should get a glimpse of the questions for which a vote is requested, or required, to see where we're going, and then we'll turn back the slide to the questions for discussion and comment.

My understanding is that we do have some latitude here in, perhaps, adding questions for vote. I don't see any reason for us to have that discussion right now. I think we want to have a more detailed, in-depth discussion of the issues before we start changing the questions that are before us for voting.

Clarification. I have a clarification question for the FDA on the first question; has sertindole been shown to be effective for the treatment of schizophrenia?

Sometimes a distinction is made between efficacy and effectiveness. I'm assuming that that distinction isn't being made in this case.

Am I correct, Dr. Laughren?

DR. LAUGHREN: That's correct.

DR. GOODMAN: So in order to answer this question, we need only look at the efficacy data and make a decision whether it meets the predetermined standards in the absence of consideration of adverse events. It's a separate question from deciding about adverse events or recommending whether we think this drug should be on the market.

That was the only clarifying question I had.

The second question is, has sertindole been shown to be effective for the treatment of suicidal behavior in schizophrenia. The third is, has sertindole been shown to be acceptably safe for the treatment of schizophrenia. And I think here we're mostly speaking about risk of cardiovascular effects,

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particularly cardiovascular death, although one can also discuss other safety issues, such as metabolic syndrome.

Any questions before we go to the discussion leading up to these questions, among the panel members? Anything that either --

Tom, did you want to charge the committee any further or should we just proceed?

Dr. Temple?

DR. TEMPLE: Well, it's just worth noting, when we use the term "safe" we usually mean that the benefits outweigh the risks for some defined population with some defined method of use; something like that. That's what safe means. We know it causes harm.

DR. GOODMAN: Okay. Thank you.

Dr. Pine?

DR. PINE: And that is a yes/no question, right? You don't have degrees -- you're not asking about degrees of safeness; you're asking is it safe enough from that perspective, right?

DR. LAUGHREN: That's correct, a yes/no.

DR. GOODMAN: All right. If we could have the

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slide of the questions for discussion. There are three of them. They may not all appear on one slide. Here we go.

Before we tackle that first question, I thought it might be easier for us to discuss efficacy. As I just gave you, the preview of the first question is going to be about efficacy. So, obviously, if we don't think that the drug is effective or efficacious, it's moot to talk about whether we're satisfied with safety or whether it has certain advantages that it set it apart from other drugs already available on the market.

So I wonder if we first can have a discussion about effectiveness.

Is there a particular slide that maybe we should have up that shows the overall -- there are several studies that led up to --

You had reviewed it, Dr. Pedersen, earlier for us. There were a series of different studies.

Is there one slide in particular you think that would be helpful for us to have up there as a reference point?

DR. PEDERSEN: I think this may be the one that is most -- slide on. I think that the review also by the FDA was concurrent with our viewpoint, that there were two studies that were -- pivotal studies. There was one supportive study that both supported the efficacy of sertindole in dosages between 12 and 20 milligrams. And I think that is the most pertinent one to have up here.

I think that the data that Dr. Buller went through in terms of the Landmark study and the other study clearly showed the efficacy comparable to haloperidol. If that is a greater help to you, and the response rates also on that, we can certainly also pull that up.

DR. GOODMAN: And from my reading of the briefing documents and the FDA presentations, I don't think FDA had any questions about efficacy.

Is that correct?

DR. LAUGHREN: That's correct. The two studies that are of greatest interest to us are 113 and 98.

DR. GOODMAN: Okay.

Any comments from the panel on the issue of efficacy?

Dr. Malone?

DR. MALONE: So I guess, then, efficacy is really just the short-term efficacy that we're talking about.

DR. LAUGHREN: That's correct. We don't think that the sponsor has provided data from an adequate maintenance study to even address that question of maintenance. So this is acute treatment of schizophrenia.

DR. GOODMAN: Comments from the rest of the panel? Questions?

DR. HARRINGTON: So I'll play the naive cardiologist so that my psychiatry colleagues can weigh in. I mean, you'll, frankly, have to tell us, the non-psychiatrists on the Committee, as to whether or not in your arena this meets the standard of evidence for a therapeutic to be considered efficacious. And so some discussion from the psychiatry guys around the table would be hugely helpful to me.

DR. GOODMAN: I think that Dr. Pine has volunteered to start that.

DR. PINE: I'll just briefly put it in the context of the typical kinds of studies we discuss at this committee. We tend to see three kinds of studies, either studies where there's reasonably strong evidence of efficacy to the point where there's not much discussion that you need. There are studies where

there's really not very strong evidence of efficacy, where you could debate to the degree to which it's flat negative or maybe there's a hint of a signal and then something in between.

I think the evidence in terms of what we typically see from most treatments for this medication is clearly in the first category; that it's clearly relatively unequivocal evidence of clinical efficacy from the standpoint of the usual kinds of information that we see in front of this committee.

DR. GOODMAN: I don't disagree.

Other comments?

More affirmatively, I agree.

MS. LAWRENCE: Is this a yes or no answer to the first one, too?

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DR. GOODMAN: Sorry?

MS. LAWRENCE: Is it a yes or no answer to the first one, too?

DR. GOODMAN: For the first question, it's going to be yes or no, yes. That's my understanding, yes; if yes or no.

DR. LAUGHREN: It's yes or no for all the questions that you vote on.

DR. GOODMAN: But my experience, though, is that FDA is equally interested in our comments as our vote. But for the most part, the world will reduce it to our vote.

Dr. Winokur?

DR. WINOKUR: Well, just to put some additional words in, I mean, I feel that the general efficacy question I'm comfortable with, and we judge that by results of placebo controlled studies, where we have a couple of reasonable ones, comparison, to established comparators, which by itself wouldn't be enough. But in the context of placebo, is another line of evidence. The magnitude of the change in PANSS score, which is the main rating scale that we typically

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pay attention to, is typical to what we've generally seen in other drugs.

We didn't get as much data, but I think in the briefing document, we saw pretty strong data for positive symptoms and some suggestion for efficacy for negative symptoms. So from that perspective, by and large, it's looking like most of the drugs that we're accustomed to thinking they're established for general efficacy, would be my take.

DR. GOODMAN: The FDA, and also the sponsor, went over a little bit of the history of this drug vis a vis the approval process here. I forget the date. The last time it was before -- it was '96. I'm not even sure then that there was a question about efficacy; the question was about safety. And since then, there's been additional accumulated data. We need to have this discussion, but I think the psychiatrists on the panel can reassure the other

members that the evidence in favor of efficacy for schizophrenia is unequivocal.

So, then, let's move on to some of the harder questions.

The first one is, has the cardiovascular risk for sertindole been adequately characterized, and if so, does this risk pose an obstacle to the use of this drug in the treatment of schizophrenia.

Here, I think, although, certainly, the psychiatrist members can weigh in on it, we're particularly interested in hearing the opinion of the cardiologist members of the Committee.

DR. HARRINGTON: So I'll start off. Here I thought that the FDA did a very good job of presenting to us their view of the analysis, which I think is a fair, if not conservative, interpretation of the evidence. But I do think it's a fair interpretation of the evidence, is that the class of drugs clearly seems to be associated with prolongation of the QT interval.

You've heard in multiple discussions this morning as to how long that prolongation might be relative to other drugs that are widely used. The conclusion I've come to is that nice picture that we saw, putting into context with the other, is maybe not as clear as it was intended to be; that there are some challenges with that analysis as presented, and that,

perhaps, some of the FDA analyses are a more conservative interpretation, which suggests that there is substantial prolongation of the QT interval. And perhaps to me, most concerning, is this 1.9 percent outlier risk of people who have QT intervals beyond the 500 millisecond range.

So then you ask yourself, okay, is that just an EKG problem or is there something more to think about. And I think we have several pieces of evidence that are concerning, the first of which is that there is an association, as been noted by Dr. Garnett and others, between prolongation of the QT interval and risk for serious arrhythmic events. There is the challenging clinical studies about detecting arrhythmic events before they manifest themselves as a bad outcome, namely sudden cardiac death.

The third piece of evidence, which is concerning, is the observation within the large randomized trial -- comparing it with other drugs, and not with placebo, but with another QT active drug, albeit less so -- of somewhere the upper risk might be the FDA's five times risk; the lower might be a little

less than two. But I think it was Dr. Pine this morning that pointed out, however you look at the data, there does appear to be an increased risk of sudden cardiac death associated with use of the drug. Even all of that, it might be acceptable, based on what the trade off is.

I, Dr. Goodman, put it into sort of two categories, one of which is, does the good stuff outweigh that, and we should get to that discussion, and is the evidence surrounding the good stuff persuasive enough; and, number two, can you predict which group of patients might be at risk for the bad outcome. And I think a lot of us were pushing the FDA -- to a lesser extent, the sponsor.

But I think where a lot of us were pushing the FDA is, can you help us, can you predict who these patients are. And there are some general categories that people fall into, the liver impairments, the congestive heart failures, the poor metabolizers, et cetera. But I was left with a sense from the FDA analysis, and particularly looking at those 16 -- the 13 versus 3 sudden cardiac deaths, that it's awfully

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hard to predict, based on the way a clinician views the world, is you've got somebody sitting in front of you, and you're asking yourself, do I prescribe this drug or not; do I get enough information from their characteristics to make that assessment. And my interpretation of the evidence the FDA presented is that you don't have enough information.

So I, frankly, am uncomfortable about the cardiac risk. I think it's been well characterized. Has it been adequately characterized? Probably some work to do since there is a difference of opinion between the sponsor and the FDA as to how well that's been characterized. But I, frankly, think there is risk associated with use of the drug. We'll get to the benefit trade off. And I don't think, based on the data that I've seen, that a clinician could reliably predict who's going to be at risk. And I'm not sure that monitoring the QT interval is enough to cull out that group of people whom might be at risk.

DR. GOODMAN: Thank you very much.

Dr. Granger?

DR. GRANGER: Yes. I'll really agree with all

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those comments and a good summary by Bob. I mean, I'm impressed by the trial that was done, by a 10,000 patient trial. In a simple trial, I think it provided very important information and clarified these issues. I think it is too bad -- I understand the reasons, but I think it would be more informative to the U.S. community if that was done in a clinical practice environment that was more similar to ours. I don't know the details of psychiatric care in these other areas of the world, but I suspect that it would be even more relevant if it was done in Western -- in a U.S. environment, at least more of the patients enrolled there.

I also think it would be more informative if there had been more of a prospective collection of some of the cardiac data according to standardized definitions rather than SAE reporting and distilling of

narratives by events committees. I think we've learned that that's a relatively unreliable way to categorize, in a more systematic way, cardiac issues, probably any safety and clinical outcome issues.

But having said all that -- and I also tend to be somebody who believes more, actually, in all-cause mortality as being our best kind of aggregate measure of safety and efficacy. But I think this is a nice example where the FDA really did hit on the fact that for this particular issue, that a cause-specific mortality is much more informative about the key safety concerns with this drug, given the relatively lower incidence of those events. And as we've been talking about -- the one thing that's really statistically significant here is the increase in sudden cardiac death and in cardiac death. Even though the levels are low, I think when this would be applied in general practice to a broader population of patients where there might be less systematic exclusion of patients with cardiac disease, that it might be a much greater public health issue.

So I do think it's been well categorized, the cardiac risk, and that it's real and concerning. And as Bob points out, that might be able to be outweighed by a clear benefit, and we'll get back to that issue.

DR. GOODMAN: I believe the sponsor wants to respond.

Could you identify yourself, please?

DR. ANTZELEVITCH: Sure. I'm Charles Antzelevitch, director of the Masonic Medical Research Lab in Utica, New York, and a consultant to Lundbeck.

I'd like, if I may, to very briefly discuss our understanding of the mechanism arrhythmogenesis in long QT, particularly in acquired long QT -- slide up, please -- and our understanding of where sertindole fits within this scheme.

So our understanding of arrhythmogenesis and acquired long QT is that agents with Class 3 actions, or I KR inhibitory effects, amplify existing heterogeneities within the myocardium, principally in the form transmural dispersion of repolarization. And they do this by reducing net repolarizing current, usually secondary to a reduction in the current that we call I KR. And this leads to a prolongation of the actual potential, but because this occurs preferentially in a particular cell type within the ventricular wall, the M cells, it leads not only to a prolongation of the QT interval, but also to a dispersion of repolarization across the wall that can also be quantitated in the ECG as the interval between the peak and the end of the T wave. That reduction in net repolarizing current also leads to the development of early after

depolarizations, which give to the rise to extrasystoles that then capture this vulnerable window and precipitate torsades de pointes.

Now, in the case of a pure I blocker, we can KR expect to see the type of relationship that Dr. Garnett so beautifully showed us in her simulation of increasing actual potential duration in QT interval as a function of concentration of drug. But where we have other electrophysiologic effects, particularly inhibition of late sodium channel current, we can expect a different type of behavior, which I'd like to illustrate for you in the following slides.

DR. GOODMAN: I'm sorry. It's not completely clear to me how you're responding to the comments that were just made.

Could you kind of tell me where you're going with this?

DR. ANTZELEVITCH: I'd like to illustrate the fact that sertindole has properties that mitigate the

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I effect and that allow for, or do not allow for, the translation of a QT prolongation directly into the development of arrhythmias, so that we can have here a drug that can prolong the QT interval significantly but not necessarily result in arrhythmogenesis.

DR. GOODMAN: Dr. Harrington, please?

DR. HARRINGTON: So maybe I wasn't clear. I actually would agree with you. I think that's part of the problem, that if I could draw a straight line -- and I don't mean to have my back turned to you, but just speaking in the mic. If I could draw a straight line between drug, QT prolongation and death, it might be easy because we could cull out those people who had QT prolongation. I think what Dr. Garnett in particular left me with was this uneasiness around being able to draw that straight line.

So you may well be right, that the bad stuff isn't all found in the QT interval, but there's something else that leads to the drug being associated with an increased risk of cardiac death, and that's where I have my level of discomfort. You can come up with a mechanism that could make me feel a little

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better. I'm still faced with 13 versus 3.

DR. GRANGER: And we've also been talking about ranolazine as being a nice example of something that does have this about millisecond prolongation of the QT interval, and, in fact, it's antiarrhythmic. So I think we do agree that QT prolongation in and of itself is not what we're talking about, but when it's coupled with a plausible increased risk of torsades -- although there may be counter-arguments about how likely that is. But it's plausible, combined with the clinical data that we've seen, then it becomes more of an issue.

DR. ANTZELEVITCH: Well, one of the things

that we were very interested in is when we look at the patients who developed torsades de pointes -- and there are seven patients out of a 40,000 patient year history -- our confounding factors in each case, many of those confounding factors include the presence of concomitant antibiotics, hypokalemia, fluoxetine. These are all circumstances that can produce prolongation of the QT interval in torsades de pointes in their own right.

So one of the questions we asked at the basic science level is whether sertindole can amplify the effect of those agents. And if I may, I'd like to show just a couple of slides along those lines.

DR. GOODMAN: I'll give you about two minutes.

DR. ANTZELEVITCH: Okay.

So if I can have Slide M-58, then M-59 and M-60. First, M-62, please. Slide up. Thank you.

You've seen this slide before, but what you haven't heard is that sertindole is the most potent blocker of the late sodium channel current that has been identified to date. And it overlaps with the effect of the drug to block I_{Kr}, and this has important consequences.

Next slide, please? Thank you.

So in this experiment, what we introduce is a pure I_{Kr} blocker, E-4031, and then on top of that, we introduce sertindole at various concentrations within and beyond the therapeutic range. And what we see is that the I_{Kr} blocker prolongs the QT interval, increases TPTN, the transmural dispersion repolarization, but sertindole does not increase it further. In fact, it reduces the dispersion of repolarization -- next slide, please -- as you see on this slide.

So TPTN, the dispersion, is shown on the right side, and the drug actually produces a reversal of the effect of an I_{Kr} block.

M-60, please? Slide up.

In this example, you see that a pure I_{Kr} blocker, such as E-4031, produces the common triggers for the development of torsades. These are early after depolarization induced triggered activity, and sertindole, again, at therapeutic concentrations and beyond, suppresses the triggered responses, and showing that the inhibition of late sodium channel current, which I got the feeling from the FDA presentation was being dismissed as not relevant, is actually playing a major role in mitigating the effect of this drug.

If we can have now Panel 70 --

DR. GOODMAN: It's still not clear to me -- and maybe my cardiovascular colleagues can help

me -- how this changes our interpretation of this result, the signal for increased cardiovascular risk in the study. It's very interesting from a mechanistic

standpoint, but it doesn't seem to have bearing on the results that we've --

DR. ANTZELEVITCH: If you'll permit me one more slide.

DR. GOODMAN: Okay, you've got the one more slide.

DR. ANTZELEVITCH: Slide up, please.

This is the slide that you've seen before that deals with QTc as a function of sertindole concentration in poor metabolizers versus extensive metabolizers. You'll notice that the poor metabolizers have a shorter QTc than the extensive metabolizers. And the reason for that, we believe, is the presence of a more potent inhibition of the late sodium channel current in the poor metabolizers and the parent compound, because the dehydrosertindole, which is one of the main metabolites, actually shows far less potent inhibition of the late sodium channel current. And this is how we believe this impacts.

The other thing that you could see through this slide is that we have a fairly flat relationship, so that extrapolation of the type that we saw from

Dr. Garnett's presentation may not be entirely accurate because of the inhibition of the late sodium channel current. We do not achieve the QTc prolongation with increasing plasma concentration of sertindole that may be extrapolated from a pure I blocker presentation.

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DR. GOODMAN: Dr. Temple, Laughren and then Pine.

DR. TEMPLE: Christine may want to add to this.

We have conversations about QT prolongation and whether it's all related to I and whether there

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are sodium things that mitigate it. I have to say, those were conversations we had a lot of before we had the data. And what everybody here is saying is that may well be true. I mean, we don't really know, and we don't exactly who's at risk. But you have a study that showed what seems to be 13 versus 3. You can argue about whether that's exactly the right number, and it does seem to me that that's what you're confronted with even if, in fact, the drug does mitigate itself at very high doses or something like that.

The conversation now, really, I think -- Tom

can tell me whether he agrees -- is about what the data suggest. And that's ont to disagree with this at all. We have these conversations all the time, and have for a long time, and there's great debate about it. And I'm not suggesting there's an answer either.

DR. GOODMAN: Dr. Laughren. And then, Dr. Pedersen, I'll give you a chance.

DR. LAUGHREN: Well, I just wanted to make sure that Christine had a chance to respond.

DR. GARNETT: Sure. One thing I'd like to clarify in the slide that I showed, where I showed the relationship between QT prolongation and sertindole concentrations, first of all, that wasn't a simulated figure; that was the sponsor's figure that they have right here. Actually, it's not the metabolizer slide; it's the other one. I just used sponsor data. And when I was using that relationship to show QT prolongation, it was based on observed data. This is not simulated data or model-extracted data. I was just reading from the observed data line. So as you increase the concentration, using the observed data, you get an increase in prolongation.

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I also don't agree with the comments just said that patients that are poor CYP2D6 metabolizers have a shortened QT. If you stratify -- separated the patients who are poor metabolizers with extensive metabolizers in that slide, you could see the poor metabolizers do have increased concentrations, and then subsequently have an increase in QT. You don't see poor metabolizers in that figure shifting in the relationship relative to the extensive metabolizers. They're at the same relationship; they're just at the higher end. From my perspective when I look at that, they have the same exposure-response relationship; they just have higher concentrations.

So what I was showing earlier was not based on any type of model extrapolation; it was based on just looking at the observed data.

DR. GOODMAN: Thank you for the clarification. Dr. Pedersen, and then Dr. Pine.

DR. PEDERSEN: Yes. The point I would like to make is the data -- if we take this into the data we actually observed in the SCoP study that has been adjudicated as 3 versus 13, first, if you go into the

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slide that was presented also by the FDA -- I believe it was their Slide 20 in your books -- you will see that the adjudication process actually -- since this was a safety committee and they were particularly concerned about protecting patients that were at risk for cardiovascular scenarios, then any -- you see at the bottom, that any case that they were unsure of, they would then allocate those to a potential cardiovascular grouping.

In fact, when you have a committee of this kind and they get the signed form, they obviously get no information about what drug the patient is on, but just they get information also related to what, for example, QT is D measurements they have had. Then they are not entirely blinded because that's part of the information they get. So they're concerned about the

safety.
If we take -- slide on -- the different other classifications that are made and you put it in the context of the absolute risk that we're talking about here, which is the slide of the second line, and has the ICS subclassification, which is 3 and 13, these are

the actual risks we're talking about that Dr. Granger also at some stage asked about what is the real -- what is the magnitude here, when you have the differences between the risk in the two groups per 100 patient years.
So we're talking about risk of this nature here. If you take any case -- if you go through that -- that anyone has considered having a potential, sudden, unexpected death, then you get the 23 and 17. And those two figures with the absolute risk rates of 0.12 is not statistically significant. So while I obviously understand that when you see these data, I think it's important to also understand the nature and the limitations of making this sort of conclusion, based on the reports that are coming in here. Thank you.
DR. GOODMAN: Dr. Pine?
DR. PINE: So my question's actually right along these same lines.
So it does look related to what Dr. Temple was saying, as interpreting the results of the SCoP study is really clear and gives an independent set of data.

One of the complications, obviously, as we've been talking about it, is that data can be looked at from many different ways, as a function of time frame, outcome, definition, et cetera, and the findings are not totally clear across those.
So I wondered if we might hear from the two biostatisticians in terms of leaving aside some of the particulars and some of the questions where you really need particular expertise in cardiology or psychopharmacology.
When you look at the story told from both ends, and when you acknowledge how important the outcome data are from the SCoP study, what is your take on the message, from a statistical standpoint, that the data are saying?
DR. GOODMAN: With respect to cardiovascular --
DR. PINE: Cardiovascular outcomes, just cardiovascular outcomes.
DR. BILKER: I'm seeing it the way Dr. Harrington is. There's an increased risk.
DR. KELSEY: I would agree.

DR. GOODMAN: Could you elaborate a little bit more, though? Because, again, Dr. Pedersen just made the case that when you separate it out, although the numbers are of concern, that it's not statistically

significant, if I'm not mistaken, right, once you break it out from the all-cause mortality.

DR. BILKER: When you start doing that, you're starting to do subgroup analyses, and I'm not sure that they planned or powered for that, in particular.

Am I right?

DR. PEDERSEN: The other calculation was also a subgroup analysis.

DR. BILKER: Right.

DR. PEDERSEN: So, I mean, it has the same level of uncertainty around it. I think the point of concern here is that a committee that was asked to do something particular to protect safety for a particular concern during a study is sort of transformed into an outcome measurement here, even when we have not -- we have a process that is, in some ways, leading you into that conclusion, if at all possible. And if you go through these case record forms and say what are the

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absolute criteria that was actually put on there, with no information within 24 hours, and ask different people to classify them, then you get to the different classifications and the numbers that I showed you in the bottom.

So I think that gives the uncertainty around what is it we're truly talking about. And I would assume that the p value calculation that we produce is no less appropriate than the one that was produced around the 3 to 13.

DR. BILKER: Right. So there's an issue of subgroup analyses and the criteria were changed.

DR. PEDERSEN: No, the criteria that has been used here, that's the subjectivity that is associated with making for cause analysis. These people all have had -- the people on the safety committee are obviously not the same people in some of the others, but they're all safety experts in respective ways. And that's the sort of biases you have with available information and the adjudication you make when you start making adjudication based on these reports.

DR. GOODMAN: Yes, but the bias should be the

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same in both groups.

DR. PEDERSEN: Except for the --

DR. GOODMAN: Yes, the randomization.

DR. PEDERSEN: Except for the fact that there is information concerning the ECGs that is being made that makes these committees unblinded de facto to the safety because they obviously require the information they need to have, and there's a lot more ECGs taken in patients on sertindole.

DR. GOODMAN: You make the same argument around the suicidality, and I don't think you'd want to.

Dr. Temple and Dr. Harrington?

DR. TEMPLE: Actually, I wanted to follow up on something that Wayne had raised before.

Another way to look at the discussion that's going on now is to say, well, maybe the 13 versus 3 is persuasive for the sudden death matter, but there is another thing to look at, which is overall mortality. However, you think that was influenced. And even whether you're convinced that there's a suicidality or suicidal effect at all, how do you put those together

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when you're thinking about risks?

So maybe -- you could be convinced by the 13 versus 3, a subset analysis of course, but a pretty plausible one from the way the way -- to have done it.

How does that fit with the rest of it?

DR. PINE: Can I ask -- because I do think that's a statistical question. Specifically, how do you explain that there is no difference in the all-cause mortality?

DR. GOODMAN: Then we're going to go to Dr. Potter because he's been so patient.

Okay. Dr. Bilker?

DR. BILKER: Let me make sure I understand the question. You're asking why is there no difference in the all-cause mortality when there is a difference in the suicide rate?

DR. TEMPLE: It's more how do you put the two facts together. I mean, whether you can have an explanation for all this, I don't know. I think we probably have to be smarter than we all are to do that. But as an observation, there were more total deaths, so it's a, you'd think, more reliable number. But there

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it sits sort of even, even in the face of what some people have said is fairly convincing finding on the sudden death.

So how do you put those beliefs together? I thought that was a little bit what the previous discussion was sort of getting at.

DR. PEDERSEN: If you look at the numbers that were in the two-year observation period and also in the one-year observation period, where you have the most number of events, I think the certainty around what we're discussing here is based both on the denominator, but it's certainly also in terms of how many events do we have at a particular time you're dealing with. And if you get into the time periods of one and two years, in particular, the two-year period that we have shown you, that is the period where you have both a very high number of patients and also a high number of events as part of the observation, and there there's actually not an increase in overall mortality; its actually less than that.

At the pre-specified interim analysis, there was the decision point for the EMEA to close the study

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at the hundreds event. There was also not an over (ph.) reporting of mortality in the sertindole group. So it's a matter of what happens -- if you look

at different time points -- and you have to recall when you look at the confidence interval; that they looked at these data at a pre-specified interim time point and said we have enough information now. So if you closed the study before the pre-specified number of events, they should have given the overall confidence because they could see that the added-on time period, with the way these rates had fluctuated over time, would not change.

So we're dealing with an uncertainty around the point of equivalence here.

DR. BILKER: One other point to keep in mind is that the total exposure time on sertindole was actually less than the total exposure time on risperidone, which would actually favor sertindole.

DR. PEDERSEN: But that's also why one of the shorter periods could be useful. If you look at the period, one and two years, actually it's helpful in that respect.

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DR. GOODMAN: Dr. Potter? Let me just let Dr. Potter speak.

DR. POTTER: Again, I was wondering if the FDA or any of us could help put the meaning of these numbers in perspective. I mean, following up on what Dr. Temple was saying, in a very simple minded way, I was thinking, well, gosh, if you have more deaths from sudden death, sudden cardiac death, but the overall's the same, then that means you are protecting from total deaths. If you just look at total deaths, then you might argue that sertindole really is doing something in favor of total deaths in another space. So is it a wash or something like that in the end. But that's just a very high-level thought.

What I was really trying to get at is the interpretation of the numbers in terms of the context of the question, does this apply to what we might expect in the United States or something else like that.

Has the FDA or anyone put together cumulative data sets across all of our experience with antipsychotic trials? I mean, obviously, I know we've

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done this in the suicidality space to try to get a feeling of what the data says.

Has this exercise been undertaken in terms of what we believe are signals about sudden deaths in trials in schizophrenic patients across classes of drugs? Do we have that background data?

DR. LAUGHREN: We have not done that in any systematic way. I mean, you saw some data presented earlier by the sponsor, looking at mortality rates across NDAs. We haven't taken it beyond that.

DR. HARRINGTON: But you did provide us a paper from the New England Journal, which, albeit observational data, did suggest that there was a consistency of the message here that in the New England

Journal analysis, there was an increased risk of cardiac death.

DR. GRANGER: Two-fold.

DR. HARRINGTON: Yes, about two-fold, which is certainly -- I think Chris pointed out that while you might be less certain about the sudden cardiac death, perhaps take the cardiac death as the broader category, and now we go from an odds ratio of 4 point something

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to an odds ratio of 2.8. And if we just used the MedDRA coding of cardiac death, which still in that odds ratio of 2, the New England Journal article gives us an odds ratio of around 2 for an increased risk with the atypical antipsychotics.

Now, I actually agree with the sponsor that we're dealing with a lot of uncertainty here, and that's why my comment was -- and by no means would sit here and tell you I am sure that this drug has X percent increased risk of cardiac death. I just don't think we've seen the data. And that's why I left my comment, Dr. Goodman, that I don't think it's been adequately categorized. I do think there's a fair bit of uncertainty. And then, the question to us who are trying to answer a public health question is, are we comfortable with the level of uncertainty we're being presented with.

So that transitions to Bob's comment, which is -- and I had raised it, and said either the drug has some other trade off to make you willing to accept the bad stuff or you can predict who's going to have the bad stuff. So let's take Bob's comment that there is a

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trade off.

Well, in the total mortality that the FDA gives us, the odds ratio is 1.12, broad confidence interval. And that's where I had said this morning, I'd hope we'd get to the discussion, that you guys would tell us what is an acceptable level of the boundary here. If we use the 1.5, it doesn't make it in this. If we use some other analyses, the 90 percent confidence interval, it barely makes it.

So what is the psychiatry community willing to trade off here? Are you guys willing to trade off a 40 percent increased risk of death for what you perceive with this drug? Are you willing to trade off as much as a 60 percent increased risk of death? To me, that's what the essence of Bob's question is getting at, because I agree. I mean, if cardiac death is up -- and total is roughly the same, so, obviously, there's some other things that are balancing that, but now the uncertainty is broad.

DR. GRANGER: I'll just reinforce that.

So for cardiac death, 31 versus 12, p value .002, but still includes pretty wide confidence

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intervals -- we generally say 43 events for something that causes a modest -- that likely has a modest, maybe

even substantial increased risk, still is relatively small number of events to make a definitive statement. But I think what we agree is that it's a real -- that this data shows a clear statistically significant, clinically meaningful increased risk of uncertain magnitude in terms of cardiac risks. So that's what -- I think that's what we're dealing with from a cardiac standpoint.

DR. GOODMAN: Ms. Lawrence?

MS. LAWRENCE: I'd go back to my same question. As a family member, if there is this risk, how are we going to determine who is a candidate for this risk and is that going to cost the healthcare system a lot more -- I mean, how are we really going to be able to find out who has this risk, even though I know it's not a hundred percent that you can determine that. But to set somebody up who already has a very devastating illness, and then to know that they have this risk, I don't know, quality of life I think has to be considered here. It's pretty devastating. So I'd

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go back to how will we determine who's at risk.

DR. GOODMAN: Dr. Temple?

DR. TEMPLE: That was two question you asked. I just want to be sure everybody knows this. One is, can you predict who's at risk for the cardiovascular event, very good question, been discussed; and can you identify a population that might benefit enough in some way to make it worth that risk. Those are two separate questions that the Committee has to deal with. I just want to be sure they're separate.

DR. GOODMAN: Gail Griffith?

MS. GRIFFITH: Could I suggest also there's a third? How do we monitor in the course of treatment? So it's really a three-part issue.

DR. GOODMAN: The sponsor had a comment, and you've been standing there.

DR. PRITCHETT: I'm Ed Pritchett. I feel compelled to answer a question that Chris Granger asked this morning because he and I are colleagues. And I don't think you got a clear answer of how long were these patients followed in the so-called intention to treat mode. And the answer is, everybody who was

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randomized was followed until January of 2007 for mortality. So those figures you saw this morning, which was 1.1, like all the others, was, in fact, everybody, except for the 12 pages lost at follow-up, followed from the time they were randomized, no matter what therapy they were on, until January of 2007.

So up to that point, the intention to treat principle was pretty well preserved and pretty well balanced. So you now have that answer.

By the way, what you make out of this subgroup, different outcome analyses, when total mortality appears to be the same, is great issue; charming discussion.

I'd just like to comment about Ms. Lawrence's question about identifying patients. If you looked at the patients who had torsades de pointes and arrhythmia identified during the study, where they actually carry a diagnosis of TDP, they were in many ways a lot like patients that we see with TDP. The two who are fatal were both women and they were both elderly. In fact, all five of them were women, and two of them -- of the three nonfatals, two of those were hypokalemic and

appeared to have other forms of heart disease. And one of them was taking ajmaline, which is a quinidine like drug used in Europe. So it's the concomitant medication.

So one way to protect people is to identify not some dramatic new thing that's completely different, but it appears that torsades in some ways sort of fits what we know about torsades with other drugs.

Thank you for letting me say this.

DR. GOODMAN: Thank you very much.

Psychiatrists and this panel has grappled with similar issues before, with other antipsychotics. And I was interested in hearing comments from members of this panel, some of whom may have actually participated in some of those discussions of ziprasidone, to put this sertindole in context, to make sure that we're being consistent in what we're expecting and what our level of comfort is.

So maybe Dr. Winokur, and then Dr. Malone.

DR. WINOKUR: So coming back to the first part of our first question, has the cardiovascular risk for

sertindole been adequately characterized? And a way in which I'm not still not clear -- and I think we've brought this up before, and this relates directly to the ziprasidone study. I'm unclear, but I'm concerned about the issue of effects of other medications, particularly ones that are metabolic inhibitors. And I'm going to express the opinion that in psychiatry, currently, at least in the U.S., we're a polypharmacy profession. And one of the consultants gave the example of one of the sudden death cases. It was on another medication. It happened to be fluoxetine.

Now, that's a drug that I'm not particularly inclined to think about as being an arrhythmia risk per se, but, certainly, it's a potent inhibitor of the metabolic pathway for sertindole. So I'm not clear yet that we have an adequate characterization of how this drug in more general practice, where patients are predictably going to be on many other drugs, a number of which would inhibit its metabolism, which would then affect -- we've heard the plasma level and potentially the effects on QTc. That to me is still something that we haven't had adequately clarified for ourselves. And

that was very important in the ziprasidone discussion,

a drug that had a relatively comparable QTc effect, but was not significantly affected by drugs that were put in to see if they would inhibit metabolism.

DR. GOODMAN: So you're saying that the quality of the data you had available to you when you conferred about ziprasidone was superior to what you have here at hand?

DR. WINOKUR: Exactly, because that additional analysis gave us some guidance.

DR. GOODMAN: I'm not sure Dr. Temple completely agrees.

DR. TEMPLE: Well, we thought we had a pretty nice study, but what influenced us I would say even more was that it wasn't that different from other drugs; it was 14 or 15. That's not like 25, which is a level that makes you quite nervous. And also, we were at least somewhat reassured -- who knows, maybe falsely -- by the fact that it seemed to plateau, and that, as someone pointed out -- Christine pointed out; somebody pointed out -- anyway, there was hardly anybody over 500, which is another thing that makes you

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nervous.

So those things were reassuring there, although it still got labeled as think about other drugs first.

DR. GOODMAN: Dr. Malone?

DR. MALONE: I was going to say some of the same things. The other thing, though, is that there was a different metabolic path for ziprasidone that doesn't exist here; and that if you were given -- there was no competitor for that other pathway, which was a key pathway. Here, we're using a metabolic pathway that there are many competitors that could influence the levels.

I don't recall that there were any sudden deaths associated with ziprasidone at that meeting, which one of the key issues here is sudden death. I don't think there was sudden death with ziprasidone.

DR. GOODMAN: Sponsor has a comment.

DR. RAVN: If I could just -- Lasse Ravn. I am from the Safety Department.

Discussing ziprasidone, there is a very nice briefing book in relation to the advisory committee in

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2000. And they actually have a line listing of all of the deaths occurring in the clinical trials. There were 28 of them, and there was a little narrative attached to each of these cases. And five of these cases are patients found dead. Three of them are cardiac arrests. One is a collapse in association with exercise, one is a suspected cardiac arrest, and one is an unknown cause. And I'm quoting what they state as the cause of death.

So they have 40 percent of their cases, which is classified not as sudden or unexpected death, but death where we don't know what patients die from. And

I guess to take this to a more clinical level, it's exactly what we're dealing with here because these patients, they kind of tend to live and to die alone, or isolated as we've heard. So what we are dealing with, I think, at least to some extent, is not the cause of the death but the amount of information we have available when it comes to these people. In comparison, we think that we have approximately 30 percent, not 40 as with the ziprasidone. We think we have approximately 30 percent of our deaths where we don't know with certainty what the patients died from.

DR. GOODMAN: I'd like to return to this discussion question, so that we can quibble about the first part of it, whether the study was adequate or not. I think there probably could be suggestions generated how to do a more definitive, better data, better study. But we have to deal with what we have at hand, and there is a signal there. In fact, I think some people expressed that it could be worse than what's represented.

But in any case, dealing with the data at hand -- the next question is, does the risk pose an obstacle to the use of the drug? Let's take that as a relative question. Let's return to the issue of could there be some way of mitigating that risk by monitoring or screening, some of which was already done in the study that we heard about, and for both groups as I understand it now, and eliminating individuals with prolonged QT at baseline. And despite that, there was emergence of SAEs, cardiovascular SAEs, including sudden cardiac death.

So I'd like to hear first from the cardiologist members. I think I've already heard this, but I'd like to hear again whether there are measures that could be taken to identify -- to reduce the risk posed by this medication, for cardiovascular endpoints.

DR. GRANGER: I think Bob had commented on this, but I'm a bit discouraged that the data that we have seen provides a path to have a high level of certainty that one could substantially mitigate the risk. I think one could partially mitigate it by doing, as you pointed out, what was done in the trial by periodic monitoring of QT interval; although we saw only one of the deaths, albeit EKGs, that may have proceeded by a considerable period of time, had a QTc greater than 500 milliseconds. So that suggests that wouldn't be at least a highly reliable way to prevent problems. Certainly preventing people from using additional medications that might worsen the QT problem might be helpful. Pharmacogenetics might be helpful, but how practical are those in the way we're actually using drugs these days?

I mean, I was amazed to see that there's this, whatever it was, $15 billion worth of atypical

antipsychotics sold last year just in the top four. I mean, the drugs are obviously very widely used. Now, that I think could be controlled substantially, but I think it might be naive to think that the drugs wouldn't be used -- that this drug wouldn't be used more broadly than what we might kind of map out as the optimal way to use it.

So I think the answer is yes, there could be some protection, but it would be modest.

DR. HARRINGTON: Yes. I think that there's probably some -- and many people have indicated this -- general principles that prescribers could be counseled on, and then patients could be educated on, regarding concomitant drug use. Someone had brought up the hepatic impairment issue, patients in congestive heart value; like the trial, cull out those people from the beginning who have a long QT interval.

So there are some things I think you could do, Dr. Goodman, but I'm left with these cases where people are found dead, et cetera, young people. Now, we don't have a lot of information as to their other comorbid issues in addition to the schizophrenia, but you are

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left with this general sense from the FDA presentation that, yes, there are some general principles, but I don't think we could make this risk go away, is my interpretation of the data I've seen so far. And, certainly, the New England Journal paper that was provided to us from the FDA suggests that there is a risk out there with widespread use of this class of drugs.

DR. GOODMAN: Dr. Pine?

DR. PINE: To come back to the second part of your comment or your question, Dr. Goodman, about putting it in context and thinking about relatives, and maybe to make some issues that might not be familiar to the non-psychiatrist a little more familiar.

Also, to come back to an issue that Dr. Temple raised, I do think the case of clozapine is informative. So clozapine's a medication where -- not to be overly precise, but I think there was a comparable concern about a serious adverse effect. My sense of it -- and, again, this is going back 15 years, so it's hard to remember exactly how precise. I would think that there was more definitive concern about a

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very serious event, although the overall rate, as Dr. Temple mentioned, might have been lower than the overall rate here. And that was a circumstance where the field kind of went into it with open eyes, saying this is a serious risk, but that did not stop it.

I do think -- to raise the issue explicitly that you started your comment with -- it is good to put the issues that we're talking about right now against that broader context. I think everybody would agree that there's clearly reason to be concerned. How concerned in terms of confidence, in terms of

magnitude, nobody's going to be able to figure it out, but that doesn't mean that we can't move forward on the one hand. On the other hand, it means like what happened with clozapine; we need to weigh both the seriousness of the outcome, its prevalence, and is there a mitigating need.

DR. GOODMAN: That's a perfect segue into the second question.

So is there some advantage that sertindole offers that offsets some of the apparent increased cardiovascular risks? And we've been asked to focus on

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whether it has protective effects against suicidality.

There's several slides. Maybe we could put up the slide that compares the results to the InterSePT study. That might have been the sponsor's slide.

DR. PEDERSEN: C-111. Yes, thank you. Slide on.

DR. GOODMAN: If you take this at first blush, if you just look at face value, it looks like they do as well as the InterSePT study, which, in part, led to approval of clozapine to have indication for suicidality. So I thought we might want to spend a little bit of time dissecting this and seeing are these studies, or these data, comparable, and can we make the inference that they're similar results.

Dr. Malone?

DR. MALONE: I think it's always hard to look at these kind of things without a head-to-head study. But one of the things that came out today is that the populations for each of the studies were very different, which then makes it almost impossible, I think, to comment on this data. It looks like the patients in the InterSePT were more severely at risk

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for suicidality, and you had an improvement, and that the population for sertindole was more of a general population without a specific increased risk.

DR. GOODMAN: It's certainly my understanding that the InterSePT study was specifically designed to evaluate suicidality, and that consideration occurred later in the course of the study presented by the sponsor.

Is there any, then, advantage of looking at the subgroup in the sponsor's study that identified as having a higher risk of suicidality?

Dr. Tamminga, you had a comment?

DR. TAMMINGA: I do.

I wanted to just point out another aspect of the SCoP study that was different than the InterSePT study. And that is, the SCoP study inadvertently ran into the observation of a decrease in suicide attempts, and the outcome measures in the SCoP study was a decrease in suicide itself and in suicide attempts. And suicide ideation was really not taken into the final analysis.

So how I look at the benefit side of this

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sertindole data, the SCoP study uses, first of all, a naturalistic group of patients, and, second of all, uses a harder outcome measure, although the two studies are very, very different.

The SCoP study is a study that's not going to be done very often in schizophrenia because it's a 10,000 patient study, and suicide is such a rare event that we have to look at the consistency of data that we see not only in the SCoP study but in the other studies that have been done with sertindole to indicate, from my point of view, a reduction in the suicide risk.

DR. GOODMAN: Any other comments from the Committee on this slide?

DR. GRANGER: I mean, part of the issue here, again, gets around the confidence, doesn't it, the strength of evidence. I think the best FDA analysis of this was -- for suicide attempts using WRT plus 30 was the 46 versus 62, and it was not even approaching statistical significance.

DR. GOODMAN: Can we have that slide? Do you have the number?

DR. GRANGER: Let's see. It was 37 I think.

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DR. PEDERSEN: These are the figures. The white figures are the FDA figures in here.

DR. GRANGER: So, yes. I think that does it. So it's the lower -- the primary analysis, presumably, really would be the WRT plus 30 and the FDA analysis there.

The point estimates are all on the left-hand side. There probably is a reduction in suicide, but the challenge is that the confidence is just not there to be more conclusive about that. I think that's part of our challenge. My sense is that we have a greater degree of confidence that there's a true cardiac risk than that there is a reduction in suicide.

DR. GOODMAN: Dr. Pine?

DR. PINE: I'm not sure -- and I'd be interested in the FDA's take on this. I'm not sure that I would at least agree with the way you put it right there, on the one hand. On the other hand, I think you look at data, trying to prove a benefit, that you may or not believe, differently than you look at data about a potentially fatal adverse event. So even if the evidence is equal -- and I think you

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characterized it right, that if it's different, it's not that different. I think the FDA would probably weigh data leaning towards a fatal side effect quite heavily, and probably more heavily than --

DR. GOODMAN: The completed suicide is fatal, too.

DR. PINE: Yes, but this is not completed suicide; this is suicide attempts. But maybe they can comment on that.

DR. LAUGHREN: I think it's generally true

that the standard of evidence for efficacy is higher than the standard for safety. On the other hand, for, in effect, on something like suicide, as we did with clozapine, as I pointed out, we had one robust study, but we also had observational data that we relied on to push us over the edge on that issue. To some extent, it is a weight of evidence argument, even there, with something -- and that would be a very different standard that we might use in a more routine claim, like anxiety or depression. So it's not so straightforward. But I think in general what you're saying is true, is that the standard is higher for an

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efficacy claim than it is for making a judgment about a risk.

DR. GOODMAN: I think in your question -- you don't specifically ask this, but we can ask a parallel question as to the first one.

What do we think about the adequacy of this evaluation for a protective effect in suicide? And a cardiologist is going to answer that.

DR. HARRINGTON: Well, this is, to me, as Dr. Pine had said, not dissimilar from the cardiac death question. And what I look at here when I look at the data is that there's just uncertainty everywhere. And the confidence intervals on the overall mortality are broad. The confidence intervals around cardiac death are broad. The confidence intervals around suicide attempts are broad. I'd like to believe -- I mean, there's a nice story here, that there's a lower risk of something really bad happening to these patients being mitigated, but it's counterbalanced by something else.

What I'm left with, Dr. Goodman, is that, from a public health perspective, what's our obligation?

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Giving approval to things with p values of .06, .09, yet, it all lines up, it looks pretty good, I've got a good feeling about this one, seems to me to be treacherous grounds. It's different than practicing medicine. I mean, we're not being asked to practice medicine here; we're being asked to opine on broad public health issues that, frankly, could also set precedence down the road. Well, you know, .06 was okay last time; is .07 okay this time? That's my level of uncomfort.

DR. GOODMAN: Before you do, Dr. Pine, let me try to answer my own question about the adequacy. I don't think this is an entirely adequate study for evaluating protection against suicide. Some of those drawbacks have already been pointed out in contrast to the clozapine study. This was not from the get-go designed as a study for evaluating suicidality. Only a subgroup of the patients were pre-defined -- or were defined, actually not even pre-defined, but were defined as being at higher risk.

So you would want to have a study where the

intention from the beginning was to evaluate changes in
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suicidality. You might use a different measure. You would collect those data prospectively. You would be very careful to randomize both groups of people with similar histories. You probably would, although it's controversial, include some information about ideation as well as behaviors, and then strive to make that data as reliable as possible.

So if we're going to set a high bar for establishing efficacy, either in this study or going forward, I would prefer to see a study that addressed some of the limitations I just identified.

Now, Dr. Pine or Dr. Hendren.

Dr. Temple?

DR. TEMPLE: A couple of points. You could do a study in people with very high risk of suicide, but you could do a more general study in a population that has the risk of suicide that's lower. I don't think we have a particular preference for those, except that you can do a much smaller study in the former group. We need to check my recollection, but my understanding is they became interested in suicide, suicidality, fairly early in this study before they would have been
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contaminated. So it's reasonably prospective.

The other thing, though, that I think you're saying is, it's going to be very hard to say it meets the usual test for effectiveness, be less than .05, persuasive on the primary analysis. But I guess I would throw back to everybody -- and that would very much affect us, if they wanted a claim for presenting suicidality. We'd be very nervous about changing the ground and stuff like that. That doesn't mean you can't think about those data. I just want to put that out. We're not very good in explaining how to think about data that don't meet the standard, but we do it for safety all the time because we have to. It's irresponsible to insist on a p value.

In this case, for example, and the whole case of QT, we label drugs for QT abnormalities long before we have any evidence that it actually kills you because we have an expectation; we think it's gonna. And it would take rather more to exonerate a drug. That would be a real challenge. That would be very hard to do, and you don't think they did that here because you think there's an excess of sudden death. So they
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didn't do that. But you can think about all these things and the total mortality, too, even if we wouldn't be ready to say give a claim for this, which is a different standard in law and elsewhere.

DR. GOODMAN: Dr. Pine?

DR. PINE: So I wanted to come back to the point that Dr. Harrington was raising, in that there is a lot of unknown. And I think relative to all the data that we've seen, the one thing that is fairly clearly

known from the data is that the medicine is reasonably effective for schizophrenia.

So I guess the question that I would have is, if we accept that the data for suicidal attempts or any other suicide measure are equivocal -- and like you said, we can just think about them -- but then we also accept the observation that many patients with schizophrenia will not respond to one antipsychotic or two antipsychotics. And we don't really, as a field, have a good idea about why that is, or why one medication works in one group of patients but another medication doesn't.

Does it count that this is a relatively unique

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antipsychotic that has been shown to work where there is a long history of use? Does that count in terms of evidence of benefit to go against this concern about risk, in the way you guys think about it, or do you need us only to say it needs to either show benefit in something related to suicide or not?

I don't know if my question is clear.

DR. GOODMAN: You don't have to answer it. That's okay, Dr. Temple. You can think about it, though.

DR. TEMPLE: I do want to mention one thing. I'm sorry to talk so much.

Where we've been extremely worried about something, as we were for clozapine, and there are other examples of this, extremely worried, we have often, but I will not say always, said there is a way to do that study. You take people who fail on the previous therapy, and you randomize them back to the supposedly failed therapy and the new therapy, and show a difference. And that's more or less what was done for clozapine. It's a very high burden. I mean, everyone assumes that someone who failed on a previous

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therapy wouldn't respond to that therapy if you gave it to them again. That's completely wrong. They often do. We have many examples of that.

Now, having said that, we have sometimes felt that the availability of an alternative is sort of a good thing where a failure is common. My personal view is I like the first way I described it, but it's hard to get everybody to do that.

DR. GOODMAN: So, Dr. Temple, if there had been no concern about sertindole's effects on cardiovascular risks, would we be having this meeting?

DR. TEMPLE: No, we would have approved it long time ago.

DR. GOODMAN: But by default, you're saying that -- I think that's answering your question, Dr. Pine.

DR. PINE: Yes, that answered my question.

DR. GOODMAN: That even if we can't define it exactly with a serious disorder like schizophrenia, where you can't identify in a particular case who's

going to respond to the right medication, it's good to have an array of treatments available to you.

DR. TEMPLE: Yes. I'm merely reminding people -- I mean, this comes up with nonsteroidal, anti-inflammatory drugs all the time. Everyone assumes that you need a lot of drugs because some people respond to one and some people respond to the other.

Merck did a study to try to document that. They took people who failed on Celebrex, and they did the right study. They randomized back to Celebrex and Vioxx, I'm sure expecting that Vioxx would beat Celebrex cold because they had already failed on the Celebrex. There was absolutely no difference between the treatments.

We have older experiences going back a long way. The only way to really prove that it works in non-responders is to do the test I described, but that doesn't mean people can't make other judgments about what constitutes reasonable data. I'm not saying they must do that, but there are different levels.

DR. GOODMAN: Dr. Hendren, and then Dr. Malone.

DR. HENDREN: I guess as I just went through this whole process this morning in listening to the

logic of how each step went along, the first one is to say is this medication effective. We would say, okay, it's effective. But then we'd say, well, is it more effective than what we have right now? And there wasn't convincing evidence, except maybe for suicide. So it seemed that when the industry presented their slides, at least they say said it was more effective in some of these areas, or as I reviewed the data that we got, maybe it was more effective in some of the lipid measures or others. But then when it got reanalyzed, it didn't seem like it really broke out in a convincing way.

So then there was suicide, and if you listen to the analysis done by MedDRA of a kind of flawed efficacy study in the sense saying, here is an open-label convenience study almost, where they recruited a number of people that were following along with the medication. And if you analyze the data based on their scoring it on some dictionary definition that they happened to choose and identify then it was effective, but if you score it based on the C-CASA kind of more rigid way of classifying things, it didn't

prove to be effective. So then you go to the next question of saying, well, then is it safe, is there a risk, is it worth doing just number one? It's effective. Maybe it's a good alternative, but when you go to safe, you say, no, it doesn't seem to be convincing that it's safe.

I guess, as I asked the question this morning, I was surprised that the people from industry knew that

the FDA was going to come in and, to some extent, blow their study apart, and not present more convincing evidence that would say, listen, this really is safe; or, listen, this really does make a difference for suicide. Because I thought -- and maybe this isn't the right way to talk in this meeting, but it was slam-dunk. I mean, those guys came in and presented data that said, no, it doesn't work on suicide and it's not safe; end of story almost. I mean, what do you do after that? And so I haven't heard the rest of the story that makes you say, what's the next answer that says this is why they're not right or we need to reconsider it.

DR. GOODMAN: Dr. Tamminga, you had something

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to say?

DR. TAMMINGA: Yes. I would like the opportunity to just share a few observations and, perhaps, say why -- nobody would say the FDA is not right, but other factors that someone should take into consideration.

Suicide and attempted suicide are rare outcome factors, so that these are not entirely clear in all the studies that have been done, but there's a consistency to the data. And if you put up the slide that's right here, there's a consistency to the data even before the SCoP study that would suggest that there's some low suicide rate in sertindole in previous epidemiological studies.

Coupling this with the data showing a trend in a low suicide rate with the SCoP study, for me as a clinician, understanding the importance of suicide, -- so I can emphasize, if the Committee would let me for a minute, the importance of suicide and the prevalence of suicide in schizophrenia. I showed you the data when I started; that in the very latest Finnish birth cohort study, half of the people who died

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before they were 39 years old, died of suicide. The rate of suicide is 10 percent in schizophrenia populations. And suicide is a very significant factor and risk factor to a clinician.

So what I know as a fact about schizophrenia is that suicide is very important; that there's a trend across a number of different studies, including the SCoP study -- there are trends towards lower suicide rates with the use of sertindole. And I can tell you, there really isn't anything else. I mean, we compare this all the time to clozapine, but clozapine is a very, very difficult drug to use for many reasons. Although it is indicated for use in suicidality, there are so many difficulties with the drug that it, in my experience, gets used rarely for that indication.

So I'm looking at the sertindole data and see that there's a trend over a number of different studies, wouldn't get an approval for the treatment of suicide in schizophrenia, but would nonetheless

persuade a clinician that it would be something to try, and a very serious side effect, that's important in the illness. So that would be my answer.

DR. GOODMAN: Thank you.

Could we have the questions back up, the first two questions back up?

Dr. Hendren, you want to respond or no?

DR. HENDREN: I sure appreciate how it important it is to think of something that can help with suicide. I think that was convincing, and I think the tests, the things that people in the audience have said -- it's just that if I was in practice, I wouldn't be -- if I were seeing someone in practice, I am in practice, and I though that there was a risk of suicide, I'd be a little terrified to be trying this sertindole. I'd be thinking, whoa, you know, I don't even know how I can monitor well, how to keep them from dying from the prolonged QT interval. I don't feel like I've gotten a handle on that yet, or a way to somehow really characterize it very well. And as I listened to the FDA presentation this morning, I was thinking, boy, thank God these guys are thinking about that because what if a number of patients did die, and how would you feel -- I don't know. I'm getting carried away.

But it's so complex, and you want so badly to find something to help with suicide. And if there's a way that, perhaps, it's because of the side effect profile, less akathisia, less EPS, maybe that makes it less uncomfortable for people, maybe they could do better. That would be good. But it would be nice if somebody could make that link to at least say, now I understand how this might work, how this might make a difference.

DR. GOODMAN: Dr. Pine?

DR. PINE: So I actually think both of the comments that Dr. Hendren just made are very helpful and very clarifying. I just want to reflect on both of them.

So the first one, is it a slam-dunk? I would say -- and you guys in the FDA can correct me if I'm getting this wrong. If it were a slam-dunk either way, we would not be talking about it. So it's not a slam-dunk that this is a great medication, but it's also not a slam-dunk that it's ridiculous for us to talk about it. And I think it's a really tough call.

I agree with what you said that the FDA did a great job, but I think everybody would agree that it's a very tough call on both sides; number one.

Number two. I also think it is helpful, your last comment, to think, would there be a situation where there would be a need for a medicine like this. And, again, we get into hypotheticals. But, you know, one could imagine that situation. I don't think

anybody, or at least myself, would think of this anywhere near a first line, based on everything that we've said. And I don't know if that's what you're looking to hear.

On the other hand, I think this issue of -- exactly the way Dr. Temple laid it out. This is a very serious condition. Many patients don't respond. We don't know why. We can't predict who. We need to be very careful before take things off the table.

DR. GOODMAN: Could the person at the sponsor's mic identify herself?

DR. JONES: Yes. I'm Dr. Judith Jones. I'm consultant to Lundbeck and a pharmacoepidemiologist. I wanted to make a very brief statement about benefit and risk and the numbers involved.

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If we posit, in fact, of the 3 million or so schizophrenics in the U.S., 1.5 million are at risk for suicide, but not necessarily in one year but at some point in their life, and certainly, 10 percent of those will be successful in that, I think we have to -- we can't do a calculation, risk-benefit calculation. I just want to create the numbers.

I would not argue at all about the strength or lack thereof of the data to show lack of suicidality. I think that's something you have to decide. But then you have the risk. And keep in mind, there's two factors about the risk. One is it is on an order of magnitude or less, lower -- and I'm not arguing that there is evidence of risk, but it's low.

Now, we discussed the Ray study in the New England Journal of Medicine, which shows that, in fact, across the board, antipsychotics have an increased risk, cardiovascular risk. And in this study, depending on which analysis you use, you have a similar level of risk. The difficulty in the data set that FDA has selected is that the ISC, the Independent Safety Committee, was totally biased because those patients

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who had ECGs were patients taking sertindole. The patients who did not have ECGs were not taking sertindole. And in my opinion, the judgments -- and you saw the instructions in the FDA slide -- tended to bias the committee.

So I can't entirely trust that data, and I think the multiple analyses are probably more reliable, which puts us back in the same area that all the other antipsychotics are. So it's just a few comments for consideration.

DR. GOODMAN: Thank you.

Dr. Harrington?

DR. HARRINGTON: Dr. Jones, could I just have you clarify, again, in reading the Ray paper, that that was a two-fold increased risk of sudden cardiac death compared with people taking nothing. This was a several-fold increased cardiac risk compared taking inactive therapies. So if you could comment on that.

Then the second is that Dr. Pritchett and others made the point this morning that the estimate and the confidence intervals around the QT prolongation sort of overlap with the others. And so I'm wondering

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how you think that -- if that statement's true, then how do the investigators pick out, looking at the EKG, which patients are on which treatment? It seems that those two statements are contradictory.

DR. JONES: Well, I don't know the number of the slide in the FDA slide set, but, in fact, the instructions -- it's Slide 20 in the FDA set. The instructions to the adjudicators were to consider it a cardiac risk if you're uncertain. That's number one. Number two is that the adjudicators certainly knew about the characteristics, known characteristics of the drug. And, obviously, sertindole is already labeled to be possibly cardiotoxic. So I'm just positing that there is a bias in there.

The second thing --

DR. HARRINGTON: Did the sponsor test them? We've done that in studies, where we actually test our people to see if they have knowledge of the treatment. You know, this is common in beta-blocking studies, can they tell who was on it. And almost uniformally, they can't. But I'm wondering if you formally tested that.

DR. BULLER: No, we have not done any formal

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testing.

DR. GRANGER: And just to reiterate. Certainly, the investigators would have had more information about treatment assignment as an open-label trial, of course, than the adjudication committee. I think that was the FDA's point, that albeit not perfect, it clearly would be less apt to be biased, again, given Bob's comment about the overlap of QT prolongation. And even that, I mean, their job was to classify -- primarily to classify according to time of death, whether it was a sudden cardiac death or not, I wouldn't -- being on a lot of these adjudication committees, I find it implausible that that would be a major confounding effect.

DR. GOODMAN: Dr. Laughren, I may need your help in working through the logic here of the next question.

Was it your intention that we engage in a discussion of this question ahead of a vote or after a vote? We could do an "as if" scenario.

DR. LAUGHREN: The idea was to have this discussion before you vote.

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DR. GOODMAN: We have to assume that -- making a hypothetical that we end up concluding it's a drug with sufficient benefits despite its risk, in order to weigh in on it.

DR. LAUGHREN: But it speaks partly to the issue of whether or not -- that the drug could be used

in a real clinical setting.
DR. GOODMAN: Dr. Day?
I'm willing to do that. I just want to make it clear that we would be making an assumption --
DR. LAUGHREN: Right, of course.
DR. GOODMAN: -- and for the purposes of discussion.
DR. DAY: I would like to say how much I appreciate this opportunity to discuss that first. I've been on many different advisory committees for FDA, and, generally, what happens, the logic goes through is it safe enough, is it effective enough, and then what kind of risk mitigation strategies would you have. And what happens is there's never time for that at the end of the day.
So at this point, I would like to ask our

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cardiology colleagues about the following.
Because of the cardiac risks, is there a way to, say, have something like a medication guide that explains something about arrhythmias or something that a patient could recognize or that a caregiver could recognize to get them to the hospital before it's going to be too late?
Am I being clear enough on this? Are there symptoms, signs and symptoms, that patients could be told about so they could be watching for them and get medical attention before they become too extreme? Because if the answer is no, then there's other things that would happen here logically.
DR. GRANGER: I think the answer is no, that, generally, the first symptom might be either cardiac death or something more serious. I mean, certainly there may be torsades, episodes that can be treatable.
UNIDENTIFIED SPEAKER: Like eternal damnation.
DR. GRANGER: Yes, exactly. Maybe not more serious.
But maybe your follow-up is what else can be done, and there have been, I think, reasonably

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successful examples, and maybe clozapine is one of them. But, certainly, defetilide -- we really take defetilide prescribing seriously with certification programs and careful review of concomitant medications that may prolong QT intervals. So I think that kind of program can be fairly successful.
DR. DAY: And related to that, for the psychiatry colleagues, we know that in other classes of drugs, like the SSRIs, they got approved and then they got widely prescribed by people outside of psychiatry. Now, it's presumed that if someone is schizophrenic, they're going to be seeing a psychiatrist, we would certainly hope, and it wouldn't be as widely prescribed.
Can anybody inform us about prescribing practices within this class of drugs, the antipsychotics? Who's doing it?

DR. GOODMAN: Dr. Malone?
DR. MALONE: I think it was interesting, the talk from the VA. I think a lot of the prescribing is done in public clinics, and the monitoring isn't always that good in those clinics. I think the second thing

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you want to remember about telling patients anything is that this group of patients has a lot of cognitive impairment, so I don't know, really, how you can tell them complex things.
DR. DAY: And that's why I also include or their caregivers.
DR. MALONE: If they have them, but many of these patients do live alone.
DR. GOODMAN: Dr. Temple?
DR. TEMPLE: We come and we talk about risk mitigation. The concept of med guides, and, presumably, also information for physicians, certainly includes that, and maybe avoiding certain concomitant therapies are all part of that. But part of the job is to make sure people understand the risks of the drug they're about to take. So one of the three reasons for having a med guide -- the third one we can ignore for the moment. One of them is to explain how to avoid risks, but the first one that's listed is to explain to them what the risks are, so they can make an informed decision about whether they want to be on this drug or not. So it's worth remembering that. That's not

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specifically -- that's not strictly speaking mitigating the risks, but it's part of risk mitigation strategies, letting people know.
DR. GOODMAN: Dr. Day, would you add anything on this issue of what could be done to mitigate risks, from your experience and your body of research?
DR. DAY: There's a whole wide range. These risk plans, where they were previously called risk maps, and now REMS, and whatever they'll be the next time, goes from labeling all the way to registries and physician attestations and patient attestations that they've studied and understand and so on. I think the first step off of labeling gets into the medication guide area, being able to inform people more. These tools for physicians are useful as well.
I actually conducted some comprehension studies of medication guides and whether people really understand them and know what to do. And the results are they understand the benefits really well, and they understand the risks a little bit or not at all, or sometimes okay. And it depends upon the medication guide and so on. But if they have trouble

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understanding it, I don't think the answer is don't tell them.
DR. GOODMAN: We haven't taken a break in a while. I was wondering if we should take a break now, come back and just have a little bit more discussion,

brief discussion, give an opportunity for the sponsor and the FDA to have some closing remarks, and then go to a vote.

A 10-minute break.

(Whereupon, a recess was taken at 3:21 p.m.)

DR. GOODMAN: Okay. We're ready to resume. So we've been asked to vote on three questions. I've gone over those already with you. There will be more discussion. Let me read the instructions, though, about the voting, unless I forget it later.

We'll be using the new electronic voting system for this meeting. Each voting member has three voting buttons on your microphone; yes, no, abstain. Once we begin the vote, please press the button that corresponds to your vote. You will have approximately 20 seconds to vote. After every one has completed their vote, the vote will be locked in. The vote will

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then be displayed on the screen. I will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record as the reason why they voted as they did. As I understand it, that reason can be very brief.

I've been told that when you press this in, you may not be clear that you're actually -- your vote is registered. Whatever your last press, will count as your vote. So make sure your last vote is the one you are trying to endorse.

I'd like to turn to discussion of the first question, which is, has sertindole been shown to be effective for the treatment of schizophrenia?

Is there any need for further discussion among the Committee members?

Any remarks from FDA or the sponsor on this issue? And you're welcomed to think ahead to the next questions, too, if you'd like to make some concluding remarks.

DR. PEDERSEN: Should we make them now?

DR. GOODMAN: Yes, please.

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DR. PEDERSEN: We believe the SCoP study has shown the same overall mortality in a very large study with point estimates that are fluctuating around 1, which start with the upper confidence intervals. We haven't discussed the lower ones, and sometimes we are debating what are the risks here and what are the benefits. But the primary endpoint of the study in terms of the overall mortality, we have seen that.

The second question here has been related to suicide. We have consistent data from the clinical, preclinical, and also consistent measurements within the studies that indicate a problem that has wide significance with these patients. We have in a difficult setting, which it is, to measure. We have shown strong data, albeit not with p values that are consistent for every measurement, but with point

estimates that clearly indicate that this drug does something when it's compared to another active agent that benefits these patients. And this effect is particularly important to see that this is preserved in a group of patients that we can identify beforehand, those that despite other treatment have had suicide

attempts and then are in a study, that constitutes 7 percent of the patients, but they account for 40 percent of all the suicide attempts. And in that group, the effect was maintained.

The study has a strength in the sense that it is naturalistic. That means that it is not difficult to translate the observation in terms of overall outcome of mortality or effects on the hard endpoint like suicide attempt the way it's been classified by CASA, or even suicide as such where it also translates into the community where it's going to be used. It's not taken from a very elite special setting with a lot of safety around it. So this is the -- we would say it is the everyday setting of it.

We do, however, recognize that there is an uncertainty around what is a rare but significant event in terms of the QT prolongation and the risk that it may have to translate into sudden death. With the numbers we look at here, the absolute risk that we're talking about here is around probably 0.1 in some of these calculations if you accept the adverse event reporting as a basis of that decision. That turns into

a number needed to treat around -- or a number needed to harm, around seven, 800 or something like that.

If one needs to consider what could we do to mitigate that risk, I would point to the fact that we as a company have experience in the United States with managing REMS. We have currently two REMS programs ongoing of a different nature, and we are in the process of negotiating a REMS program for a third product also with the FDA. So there's clearly something we are willing to do and we have experience in doing in terms of how to best make sure that what we see as the benefit in terms of the antipsychotic properties of the product itself and also the potential to particularly help patients with a known history of suicide, that that becomes available for patients in the United States.

DR. GOODMAN: Thank you very much, Dr. Pedersen.

Dr. Hendren, yes, go ahead.

DR. HENDREN: I was just wondering if -- you apparently have indications a lot of places around the world, and now, once again, in Europe. You have some

way of people turning in and monitoring whether there are sudden deaths associated just in general, don't you? Not part of yours studies but just being aware of people noting --

DR. PEDERSEN: We have a regular reporting of safety that we're committed to and that we're doing. And through that program, we would capture event frequencies that would be reported to the authorities. As you also could see from the exposure levels that we're dealing with, it's fairly new also because the introduction of the product in Europe is fairly recent. So we don't have data from that that could give us anything that resembles the strength of what we have already.

DR. GOODMAN: I'd like to turn to a vote on Question Number 1, unless there's a need for further discussion from the Committee members, or comments from the FDA.

Go ahead.

DR. LAUGHREN: Actually, let me clarify not Question 1 or 2. I think those are clear enough. But Question 3, I just want to make sure the Committee

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understands what we have in mind with that question.

Basically, what we're asking is whether or not the Committee thinks that there are circumstances where this drug could be used in an acceptable manner in the community. Is there a population? Is there a way to use it? Is there a way to inform clinicians and inform patients, and manage the risk in some way that its use would be acceptable?

I know that's a little bit complicated, but that's really what we have in mind here. Is it possible to use this drug in a way -- despite the risks that we think are inherent with the use of this product, is there a way that it could be used in an acceptable manner?

DR. GOODMAN: Now, you're referring to Question Number 3, right?

DR. LAUGHREN: I'm referring to Question Number 3, but I'm just worried that you're going to get this --

DR. GOODMAN: The way you are posing it now, it's not been shown, but could it be found acceptably safe.

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DR. LAUGHREN: Could you use it in a manner that would somehow manage that risk in an acceptable way? In other words, is there a setting, is there a population, is there a way that clinicians could be instructed to use this in a way that you would find acceptable?

DR. GOODMAN: I think it's a fourth question, but let me defer to the other members of the Committee.

DR. PINE: He's -- not redefined it. That's how I understood the third question, but it's helpful to hear it stated that way. That really is the third question.

DR. GOODMAN: If that's the case, we would need to reword it I think, Dr. Laughren.

DR. LAUGHREN: And that's fine.

DR. GOODMAN: That's why I said that the Committee certainly has the right to reword these questions in a way that they make sense to you.
Dr. Harrington?
DR. HARRINGTON: Could we propose it as a fourth question, with the third question being, has it been shown to be acceptably safe for the broad
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treatment of schizophrenia, and then maybe a fourth question that cones in on your element, which is might it be acceptable safe in certain populations for certain indications, et cetera.
That's just a suggestion, Mr. Chairman.
DR. GOODMAN: Yes, I like that. That would be my preference, is to add a fourth question. We need to wordsmith that, though.
DR. GRANGER: And to be clear, though, we're talking about based on the available data.
DR. GOODMAN: Yes.
Would the FDA give it a try? Would you like to pose the fourth question for us, and then we can --
DR. PINE: I wrote down what he said.
DR. GOODMAN: Okay. You want to read it back?
DR. PINE: Despite the risk, is there a way that this medication could be used in an acceptable manner? Is there a setting where the risk could be managed? That's what he said.
DR. GOODMAN: Dr. Day, you're an expert on managing --
DR. DAY: I wasn't going to wordsmith, but I
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was going to say that I appreciate FDA giving us a sense of what they intend, but, in fact, what is written is what we would be voting on and what the press and the public would pick up. So I'm strongly in favor of either leaving number 3 the way it is and adding number 4 at your pleasure, or rewriting number 3 because the words are what they are on the page, and they have some interpretation.
DR. GOODMAN: Well, I guess we could vote on it. But my preference would be to leave 3 as it is and add a fourth one, and then those votes will count for all four questions.
Dr. Temple?
DR. TEMPLE: In some ways, number 3 is the up or down, yes or no question. And up or down, yes or no always refers to the drug as it will be used, labeled, risk modified and so on. So there's some case, I think, for rewriting 3 to make it clear that what you're asking, is it okay for everybody because why would we ever ask that -- is there a population and a set of circumstances in which you think this drug is safe for use. You can do it either way; obviously,
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it's your call. But, to me, that's what that question always meant, even if it didn't say that.
DR. DAY: And to me, I've always felt

constrained by that broad question, which you have to answer yes or no first and then go further. If you say yes, then is there a subpopulation and so on. So I'm glad this is at least up for discussion today.

DR. GOODMAN: Dr. Malone? Looking for inspiration here.

DR. MALONE: I don't have any inspiration.

Would the circumstances include that it might be a first or a second --

DR. TEMPLE: Absolutely.

DR. MALONE: I have a question. Once you say in some circumstance, it might be hard to think of what drugs in some circumstance wouldn't be safe to use. It's kind of an open-ended some circumstance.

DR. TEMPLE: When we approve a drug, it's always for a specific population with specific labeling, with specific contraindications, and sometimes with a system for making sure those things happen, that people get the labeling they're supposed

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to get, that only certain physicians get it, a wide variety of things which Mary could tell you more about if you wanted to know.

What this was trying to point out -- I guess what I would hope this would point out is, everybody knows this isn't just going to be dropped over the wall. I mean, there's this sudden death problem to deal with and all that. So it's sort of obvious that it would be for -- if it's for anybody, it would be for a defined population. And that's what 3 always meant. I know that's what Tom meant. And he was just trying to say that you might want to know that for sure, and have it reflected so that you answer the question that's really of interest to us, which is can you define population, labeling, warnings, and all that stuff, that would make this drug acceptably safe despite this little problem it has.

DR. GOODMAN: As I read it over -- I'll go with the will of the Committee -- my preference would be to retain number 3. So number 1 is efficacy; number 2 is, is there an advantage for suicide behavior; number 3, is there a cardiovascular risk,

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basically, or not. And then the fourth is, could we envision a situation --

DR. TEMPLE: That's not what it says.

DR. PINE: That's not what 3 says.

DR. GOODMAN: But in our discussions, most of our concerns have been about the cardiovascular risk.

MS. GRIFFITH: Maybe we should change it to reflect cardiovascular risk in number 3, if that's what we really are driving at.

DR. HARRINGTON: See, I took it to -- I agree with the comments, Dr. Goodman. For me, acceptably safe means that you have enough certainty that some good outweighs the some bad. And the some good here might be this effect -- maybe a neutral effect on total

mortality, maybe an uncertain effect on total mortality. But then I'm starting to then balance that against cardiovascular risk. So, I agree. I think if we just say cardiovascular risk, it narrows it down too much.

DR. TEMPLE: But if you read it the way Bob just described it, then you're reading it the way Tom wanted you to, and you may not need to change anything.

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So, I don't know. Do you think this discussion introduces number 3 as it is, satisfactorily?

DR. LAUGHREN: The problem is, unless you change the question to reflect that -- we understand here in this room what we're talking about when the Committee votes on this, but, as it's been pointed out, others may not. When the rest of the world sees this, they'll just see the language as it is. That's the problem.

DR. GOODMAN: Okay. My preference would be to add a fourth question.

DR. DAY: And what would you put in that question? Can you phrase it?

DR. GOODMAN: The problem I'm having is it's a hypothetical. These are not the words I would choose, but we're -- could we identify a subgroup?

DR. TEMPLE: I mean, I think this is now based on available data. What the question would be is, can you see a population, labeling, blah, blah, blah, that could be granted on the basis of available data, that would make the drug approvable as safe.

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That's what the question is. It's not hypothetical after a lot of other data; it's now. And that's what we need to know because we've got to make a decision, so we need your opinion on that.

DR. LAUGHREN: We can give some examples. I'm not suggesting that these are the way to label this product. But, for example, ziprasidone is out there now, despite the fact that it has a QT signal. It doesn't have a QT signal or the cardiovascular risk signal that this drug has, but it has a signal that led us to basically make it not a last resort drug, but the labeling says, think about other drugs before you prescribe this drug because of the QT effect. And that's in the absence of any data suggesting that it has any advantages at all over other drugs in term of efficacy.

Clozapine is another example of a drug that has a very special way that it's put out there. It's basically a registry, and a very strong label that -- and that's, again, a different situation because there you have actual data showing that it has benefit in a population of patients who are refractory

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to other drugs.

So what we're asking you to do here is to

think about all the data you have for this drug, and decide what you would like labeling to look at and other aspects of the distribution and delivery of this product that would make its use acceptable, if you think there is. Given what you have in hand -- I mean, you know, you have to deal with what we have.

DR. GOODMAN: If we reworded 3 as, has sertindole been shown to be acceptably safe for the treatment of schizophrenia under specified conditions, or certain conditions? That would narrow --

DR. TEMPLE: And we'd ask you what you thought those conditions should be.

DR. LAUGHREN: And that's the problem. Maybe you should have that discussion first.

DR. DAY: That's what I was going to suggest, so we're moving towards the questions.

But before we do, could we just have some general discussion about what sort of things the Committee would like to see if this drug were to be approved in terms of REMS type things or not, from the

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label to the registry?

DR. GOODMAN: I agree. My problem is on the cardiovascular side. I think I've heard repeatedly from our cardiologist colleagues that there's no way, with any assurance, of estimating who is at greatest risk or being sure that one could monitor for that risk and intervene before there was a -- but, absolutely. Let's have the discussion.

Ms. Lawrence, and then Dr. Pine.

MS. LAWRENCE: Well, my comment, with the Clozaril, there's a blood test. It's not easy and not everybody's compliant, but there is a blood test to check. With this, as we've all kind of been hearing, there may not be any specific testing to do. There's a compliancy even with the blood test for Clozaril and there could be a compliance with these type of tests or procedures that people would have to go through. I don't know.

DR. GOODMAN: Dr. Pine?

DR. PINE: So I think the question is -- and it relates to what Dr. Malone said a little while ago -- can one imagine a situation. And I would agree

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with what you said --

DR. GOODMAN: We're not allowed to imagine.

DR. PINE: No, but that's really the question that they're asking; can one imagine the situation if we accept the fact that we're not going to be able to predict who is ultimately at risk definitively, cardiovascularly, where there would be a use for this medication. And so, just thinking about that for myself, the issue is, as laid out by Dr. Malone, there are some medications where you clearly would say absolutely not; there's not a situation where I would ever imagine using this medication.

Here it would be, is there a group of patients

that fails two, three, four different antipsychotics, either because the patient or their family do not want to take one of the other ones or because of some other issue, that they've tried every other medication, or they don't want to have weekly blood monitoring for clozapine. Is that a reasonable thing to imagine happening? I mean, that's really the issue as I see it.

DR. GOODMAN: Dr. Malone? Dr. Laughren, and

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then Dr. Malone. Sorry.

DR. LAUGHREN: As clinicians, think of how you could imagine yourselves using this product if it were available. If you had access to it, how would you want to use it?

DR. PINE: I can speak for myself that there are many patients with schizophrenia that we see, where they do not respond to any medication, and for whatever reason, they cannot take Clozaril. And that is a -- I wouldn't say it's an incredibly frequent circumstance, but it's a clinically significant, meaningful, problematic circumstance. We don't have enough good treatments.

DR. GOODMAN: We're about to show a proposed question, but, Dr. Malone, go ahead.

DR. MALONE: Even though it might be true that you can't predict who's going to have sudden death, there might be things you would suggest for monitoring. For instance, a large percent has a QTc that rises over 60 milliseconds. So baseline EKGs would have some place, and perhaps regular monitoring of EKGs would have some place, even if they weren't totally

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definitive. And then there would be certain conditions that the cardiologists have described, like congestive heart failure. I don't know all these cardiac conditions; that you would want to be extremely cautious about using this drug. So even though you can't totally predict, you could mitigate some.

DR. GRANGER: And I think, in fact, the sponsor has some wording on that in the documents, on attempting to avoid the high risk population, with the caveats that we have gone over.

DR. GOODMAN: Here's a suggestion. Let's suppose that, as a committee, we vote no to number 3, in which case, despite the risk identified by number 3, or safety issues you have, do you believe there's a way for the medication to be used in an acceptably safe manner in some group of patients.

Would that satisfy what you're looking for?

DR. LAUGHREN: I think that begins to get at it, yes.

DR. TEMPLE: How would it be if you added to number 3, "for the broad treatment" or something like that, "of schizophrenia"?

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DR. GOODMAN: I like that. I like that. That

further distinguishes the two.
Can you put that in? For the broad treatment of schizophrenia.
Dr. Malone?
DR. MALONE: This might just be words, but for some group of patients -- it might be more than just for some group of patients, but including certain monitoring --
DR. GOODMAN: With certain patients under certain conditions. But I'm not sure -- all right.
DR. TEMPLE: I mean, you can presume we'll invoke any intelligent monitoring that we or the company can think of. You can presume that I think. You have to decide whether, with that, you still think there's a population, but you don't need to do the details of that monitoring I don't think.
DR. GOODMAN: Again, a question of internal logic, and we're going to put this back up.
Dr. Laughren?
DR. LAUGHREN: Actually, the way you have it written, it says, "in an acceptably safe manner." So

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that speaks to the issue of what kind of monitoring you might have, and then it goes on to say "in some group of patients." So it deals with both of those I think.
MS. LAWRENCE: Do we not say what the risk is?
DR. GOODMAN: We can discuss it, but I think we all know what it is.
MS. LAWRENCE: In the question? I don't know.
DR. GOODMAN: The question, I think internal logic. If as a committee, let's suppose on number 3, we vote note, then we would go on to 4. If we vote yes as a majority, then we wouldn't go on. Let me put this more simply. We'd only go on to 4 if there's a majority no vote for number 3.
DR. LAUGHREN: Right. But somewhere in the record, we would like some reflection of your thoughts about what it means to be an acceptably safe manner and what it means to focus on some group of patients.
DR. GOODMAN: Okay.
DR. TEMPLE: And we're not that worried about you not getting to number 4.
DR. GOODMAN: Dr. Harrington?
DR. HARRINGTON: And it may be worthwhile or

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informative for FDA that if people vote no for 3, they have the opportunity to answer 4, because that might help the FDA as they think through some of the issues.
DR. GOODMAN: We would then have to reword -- we take out "despite the risk". So we could just model 4 after 3, with the first three broad and the other one in the subgroup. That would be they way of getting at --
DR. TEMPLE: You don't need "despite the risk".
DR. GOODMAN: So we get "despite the risk". So the model -- it'd be exactly the same as 3 except in

a subgroup of patients.
DR. PINE: I personally -- again, getting back to this issue of we know the context, other people are not going to know the context. I like that it says "despite the risk" in there because it acknowledges that this is an unusually risky circumstance.
DR. GOODMAN: Okay. I actually agree with Dr. Pine.
Any other comments? Dr. Hendren?
DR. HENDREN: Yes. I wonder on number 4, if

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you feel like you don't know the answer, if you could then vote abstain. Because I feel somewhat confused at this point about whether it really helps with suicide or doesn't help with suicide. And I feel confused about whether it has an acceptable EKG profile --
DR. GOODMAN: I think abstain would be a satisfactory answer. I understand.
Dr. Potter?
DR. POTTER: This actually relates to Question 2 in the way it's worded, to get to Dr. Hendren's comments.
You're saying shown to be effective. I think for many people on the panel -- and maybe the FDA can help us here -- the standard of efficacy in a well controlled study, we sort of all understand, clearly -- as they made clear, this is a very large study. It is an open, simple, large trial. So I'm just curious is the effectiveness standard here well understood by everyone because we have heard about point estimates sort of looking a little different one way, and we've heard much more formal ideas about what effectiveness might mean.

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So I have a suspicion there's maybe a range of understanding about what we mean by that statement "shown to be effective." Maybe I'm the only one.
DR. PINE: Well, is it specifically the same standard that you usually use or is there a different standard?
DR. LAUGHREN: Making a judgment about efficacy is always a judgment. I mean, there's not an absolute rule. As I said, in a case like this, you may be -- since it's so difficult to gather the data for an event as rare as suicide or even suicide attempts, and you have to resort to much larger databases sometimes to do that, I think that the standard -- not that it's not high, but you may accept different levels of evidence.
So I don't know that -- I still think that the words are the right words.
DR. POTTER: But my point was, if people had in their mind that the standard was a specific p value under certain things, you're saying not necessarily if I hear you correctly.
DR. TEMPLE: Let me make a suggestion. Treat

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2 as if it's the usual effectiveness question, maybe relying on one study or something like that. And say, have they made it unequivocally, but.

But in number 4, in thinking about whether there's a group, you consider the good lean, even if it didn't quite make it. You consider the equivalence of mortality in the trial. And you weight all that stuff in thinking about whether there's something that can be done. But leave the effectiveness as an effectiveness standard.

DR. GOODMAN: Unless there are strenuous objections, I'd like to leave the wording as shown. All right.

We're going to proceed with the voting process with number 1. So re-reading part of the instructions.

Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the flashing button firmly. After you've made your selection, the light will continue to flash. If you are unsure of your vote, please press the corresponding button again, but not more than twice, is my

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recommendation. We don't want you to be that unsure. Remember, your last vote is the one that's going to be registered.

Okay. So who opens up the voting? Let's proceed with voting.

You all opened up that up for us now? It's not flashing. Mine isn't flashing.

(Pause)

DR. GOODMAN: There's no life on my unit here. We're attempting to vote the answer to Question Number 1. So let me re-read it in the meantime.

Has sertindole been shown to be effective for the treatment of schizophrenia? Yes, no, abstain.

DR. DAY: Do we have to press the attend button first? Because now, that's the only one that's flashing.

(Pause)

DR. GOODMAN: I'm going to read the results for Question Number 1. 13 yes, zero no, zero abstentions.

I think we know what everybody voted, but do we still need to have everybody give a reason?

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State into the record with each person's name. I think I still need to go through this.

Dr. Bilker, yes.

DR. WAPLES: They need to go around the table.

DR. HENDREN: I voted yes. I believe that the trials that we reviewed adequately supported that sertindole has been shown effective for the treatment of schizophrenia.

DR. SLATTERY: Marcia Slattery --

DR. GOODMAN: Dr. Slattery, you said you just voted, right? Yes.

DR. SLATTERY: That's okay.
DR. GOODMAN: I'm trying to turn off my other microphone.
Dr. Day?
DR. DAY: My mic was off. Yes, the weight of the evidence.
DR. GOODMAN: Dr. Bilker?
DR. BILKER: Warren Bilker. I voted yes. I believe the evidence is clear that it shows --
DR. GOODMAN: Their microphones are not working.

DR. GRANGER: Chris Granger, yes. I believe the trials demonstrate its effectiveness.
DR. GOODMAN: Wayne Goodman, yes. The study results are clear, unequivocal.
DR. PINE: Daniel Pine, yes.
MS. GRIFFITH: Gail Griffith, yes.
DR. KELSEY: Sherry Kelsey, yes. The data and the discussions.
DR. HARRINGTON: Robert Harrington, yes.
DR. WINOKUR: Andy Winokur, yes.
MS. LAWRENCE: Margy Lawrence, yes.
DR. MALONE: Richard Malone, yes.
DR. GOODMAN: Yvette, could you show the slide for Question Number 2?
Any need for further discussion on number 2? Okay. Then go ahead and cast your vote.
My light's not flashing. How about other people?
DR. HENDREN: We can vote yes, no or I don't know?
DR. GOODMAN: Or abstain, yes.
Okay. Lights are flashing, cast your vote for

number 2.
(Pause)
DR. GOODMAN: Okay. The results are as follows: 1 yes, 12 no, zero abstain.
We need to go around the room and give your name and your vote, and a reason.
DR. HENDREN: My name is Bob Hendren. I voted no, it had not been shown to be effective. I guess in that way, if the question has to do has it been shown to be effective, I would say no, but I didn't know that it was shown to be ineffective.
DR. SLATTERY: Marcia Slattery. I voted no, largely because, as we discussed, the study was not designed to assess this question, and, therefore, was not adequately assessed.
DR. DAY: Ruth Day, no, because of the measures looked at, confidence, measures not all green.
DR. BILKER: Warren Bilker, no. There is some evidence but I don't think it's efficient to make the claim.
DR. GRANGER: Chris Granger, no. And likewise, I think the evidence was not of sufficient

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strength to declare that it has been shown to be effective for treating suicidal behavior.

DR. GOODMAN: Wayne Goodman, no. The study did not prove that it was beneficial.

DR. PINE: Daniel Pine, no, based on the discussion between Dr. Potter and Dr. Temple and the standard that is regularly applied for efficacy study. The data clearly don't meet that standard.

MS. GRIFFITH: Gail Griffith, no. I agree with Danny Pine. I also thought in terms of what an ad might look like if you had a direct consumer ad that suggested this drug might in fact help prevent suicidality.

DR. KELSEY: Sherry Kelsey, no, based on the evidence presented.

DR. HARRINGTON: Robert Harrington. I voted no. I do want to applaud the sponsor for trying to answer a question like this in a big trial, but I felt that the strength of evidence was not sufficient to say that it was definitely effective.

DR. WINOKUR: Andy Winokur. I voted no. I think we saw a signal that is quite suggestive in an

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extremely important area, but I don't think the design or the evidence was strong enough to vote, in a regulatory sense, in favor.

MS. LAWRENCE: Margy Lawrence. I voted yes because I felt that there was some attempt to show some efficacy on this issue.

DR. MALONE: Richard Malone. I voted no. I don't think it really met the usual standard for efficacy.

DR. GOODMAN: Okay. Thank you, everyone.

Let's turn to Question Number 3.

Has sertindole been shown to be acceptably safe for the broad treatment of schizophrenia? And you've heard the discussion.

If not, let's reset the machine and cast our votes. Mine is flashing.

(Pause)

DR. GOODMAN: Okay. I've got the results for Question Number 3: 1 yes, 12 noes, zero abstentions.

Let's start with Dr. Malone, if you could read into the record your vote and your reason.

DR. MALONE: This is Richard Malone, and I

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voted no. I think it has some safety concerns, and it doesn't have any clear efficacy advantage, and there are other medicines currently available. So I think it was, as a general treatment, not acceptable.

MS. LAWRENCE: Margy Lawrence, and much to probably everybody's surprise, I voted yes because of Question Number 4 that's coming up, so at least we would have some limitations.

DR. WINOKUR: Andy Winokur. I voted no. I think we had some significant safety concerns that I

couldn't feel comfortable overlooking at this point.
DR. HARRINGTON: Robert Harrington. I voted no for reasons that have been previously stated. I felt that the safety data, while not definitive, were suggestive enough to warrant a no vote.
DR. KELSEY: Sherry Kelsey. I voted no because of the safety concerns.
MS. GRIFFITH: Gail Griffith. I too voted no because of the safety concerns.
DR. PINE: Daniel Pine. I voted no for all the reasons that have already been stated.
DR. GOODMAN: Wayne Goodman. I voted no for

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those reasons.
DR. GRANGER: Chris Granger. I also voted no for those reasons.
DR. BILKER: Warren Bilker. I voted no for the same reasons, safety concerns.
DR. DAY: Ruth Day, same, and inability to determine in advance who's at risk.
DR. SLATTERY: Marcia Slattery. I voted no for the similar safety reasons.
DR. HENDREN: Bob Hendren, and I voted no for similar safety reasons.
DR. GOODMAN: Okay. Let's turn to the fourth and final question.
We turn to it because the Committee as a whole voted no to number 3.
Number 4. Despite the risk, do you believe there is a way for the medication to be used in an acceptably safe manner in some group of patients?
(Pause)
DR. GOODMAN: The results on number 4: 8 yes, 2 no, 3 abstentions. And let's start with Dr. Hendren.
DR. HENDREN: Bob Hendren. I abstained. I

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didn't feel there was enough information to say whether there was an acceptably safe group to use this medication.
DR. SLATTERY: Marcia Slattery. I also abstained for Dr. Hendren's reasons, but also, in addition, to know what we would be monitoring.
DR. DAY: Ruth Day. I abstained for the same reasons, and could potentially be convinced the other way if there was a group that was identified. Of course, the FDA can review this and decide whether there would be some REMS that could be put in place to then make this more acceptable.
DR. BILKER: Warren Bilker. I voted yes, thinking that this could be used as a second line treatment, not as a first line.
DR. GRANGER: Chris Granger. I voted no. With the totality of the evidence, in my opinion, showing a signal of cardiovascular risk in the context of other standard treatment. And without convincing evidence of a counterbalancing benefit, although suggestive, not strong enough to warrant subjecting a

potential large body of patients to that cardiovascular
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risk, but recognizing that this is difficult. And I think it's with some uncertainty that I make that vote. And I also applaud the sponsor for doing the big trial. But, again, I just feel that the evidence is unconvincing of enough of a counterbalancing benefit against what I think of as a fairly convincing risk.

DR. GOODMAN: Wayne Goodman. I voted yes. I was torn between yes and abstention. Certainly, I understand why those people abstained. The evidence is not clear. I remain hopeful that a subgroup of patients could be identified with the appropriate predictors. And I'm cognizant of the need for having available an array of different treatments for this devastating condition.

DR. PINE: Daniel Pine. I voted yes. I would say that this was one of the more difficult votes, and it, as other people have said, is a very difficult decision to make in light of a lot of equivocal evidence. Probably the biggest reason for me, related to what Dr. Goodman just said, is the refractory nature of the condition, and the seriousness of it, and the need for many more new treatments.
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MS. GRIFFITH: I would echo what Dr. Pine and Dr. Goodman said. I would hope that this would be a treatment of last resort, but --

DR. GOODMAN: What was your vote?

MS. GRIFFITH: I voted yes.

DR. GOODMAN: Okay.

MS. GRIFFITH: Sorry, Wayne. Yes.

DR. KELSEY: Sherry Kelsey. I voted yes. I think the CV risk is real, but I think that's counterbalanced by the need for additional treatments, the positive effects on schizophrenia symptoms and the good signal for the suicide issue.

DR. HARRINGTON: Robert Harrington. I voted yes. I shared Dr. Pine's angst over voting yes. It would be a cautious yes. This is where I took Dr. Temple's comments into deliberation, that now I consider the totality of the evidence as opposed to a specific piece of evidence. And the fact that there is this trend toward reduction in suicide against an active comparator as opposed to against placebo, offered me some comfort that things went in the right direction.
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I do believe that this would be somewhere down the therapeutic choice chain, but I remain concerned that there is a real safety risk here that patients and their caregivers would have to be very adequately informed about when they made that decision. So very care and caution applied to the labeling discussions.

DR. WINOKUR: Andy Winokur. I voted yes. Again, a difficult call. This is an area of tremendous need in our field, both from the treatment refractory

and the tremendous importance of suicide. And, again, as other people have commented, I think the signal is something to keep in mind, even if it's not, in my view, quite at the level of regulatory approval.

I'm hoping that the FDA, in collaboration with the sponsor, who sounds quite eager to work out a sound monitoring plan, can figure out an appropriate way to monitor and choose from the safety point of view.

MS. LAWRENCE: I'm Margy Lawrence. I voted no because I just don't see any possibility of monitoring the situation, even looking down the road at healthcare costs, compliancy. I just don't think it's going to be possible to monitor it.

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DR. MALONE: I'm Richard Malone, and I voted yes, mainly so that there would be other treatments available for treatment refractories, schizophrenics, and considering that there could be a monitoring system that could be used, at least to reduce the risk of problems with this drug.

DR. GOODMAN: Unless you have additional business for us, Dr. Laughren, I think our job is done for today.

DR. LAUGHREN: I think it is, and I thank the Committee for your hard work. This is a very tough issue that we dealt with today, and we'll see you tomorrow.

DR. GOODMAN: We're adjourned.

(Whereupon, at 4:27 p.m., the meeting was concluded.)