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U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Psychopharmacologic Drugs Advisory Committee

Date: April 8, 2009
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Location: Hilton Washington/Silver Spring
8727 Colesville Road
Silver Spring, Maryland

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DR. GOODMAN: Good morning. I'd like to remind everyone present to please silence your cell phones, Blackberries, I-phones and other devices, if you've not already done so.

I would like to identify the FDA press contact, Ms. Sandy Walsh. If you're here, please stand and identify yourself.

There she is.

We'll start with a round of introductions of the Committee. I'm Wayne Goodman, and I'm at the National Institute of Mental Health. And maybe we can start with Dr. Potter and go around the rest of the table.

DR. POTTER: I'm Dr. Bill Potter from Merck Research Labs, and I'm the industry nonvoting representative.

DR. MALONE: I'm Richard Malone, Professor of Psychiatry at Drexel University, College of Medicine.

MS. LAWRENCE: I'm Margy Lawrence, patient representative, affiliated with National Alliance of Mental Illness here in Montgomery County, Maryland.

DR. HARRINGTON: My name is Bob Harrington.

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I'm a Professor of Medicine and a cardiologist at Duke University.

DR. KELSEY: I'm Sherry Kelsey, a statistician and Professor of Epidemiology at the University of Pittsburgh.

MS. GRIFFITH: My name is Gail Griffith. I'm the consumer rep to this committee and I'm a writer and activist on mental health issues.

DR. PINE: Daniel Pine, child and adolescent psychiatrist, NIMH Intramural Research Program.

DR. WAPLES: Yvette Waples, the DFO for today's meeting.
DR. GREENWAY: I'm Frank Greenway. I'm an endocrinologist and I run the clinical trials area at the Pennington Center, which is a research campus at Louisiana State University.
DR. NEATON: I'm Jim Neaton, a biostatistician at the University of Minnesota.
DR. ROBINSON: I'm Delbert Robinson. I'm a psychiatrist, and I'm at the Feinstein Institute for Medical Research and the Zucker Hillside Hospital in New York.

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DR. MATHIS: Mitchell Mathis, Deputy Director, Division of Psychiatry Products, FDA.
DR. LAUGHREN: I'm Tom Laughren, Director of Division of Psychiatry Products at FDA.
DR. TEMPLE: Bob Temple, Director of the Office of Drug Evaluation 1 at FDA.
DR. JENKINS: John Jenkins. I'm the Director of the Office of New Drugs at FDA.
DR. GOODMAN: Okay. I will now read a brief statement for the record and for the benefit of the audience and all the participants 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 is that today's meeting 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,

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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 welcome to today's meeting.
I'll next turn the microphone over to Yvette Waples, who will read the conflict of interest statement.
DR. WAPLES: Good morning, again.
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 of supplemental new drug application 22-047, S-010, S-011, and S-012, Seroquel XR, quetiapine maleate, proposed for the treatment of major depressive disorder, and supplemental new drug application 22-047, S-014 and S-015, Seroquel XR, quetiapine, proposed for the treatment of generalized anxiety disorder.

The Seroquel XR drug product is sponsored by AstraZeneca Pharmaceuticals, LP. Particular safety issues for discussion today are regarding exposing a greatly expanded population to a drug with known metabolic side effects and possible risk of tardive dyskinesia. This is a particular matters meeting on which specific matters related to Seroquel 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.

With regards to FDA's guest speaker, the Agency has determined that the information to be provided by this speaker is essential. The following interests are being made public to allow the audience

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to objectively evaluate any presentation and/or comments made by the speaker.

Dr. Wayne Ray is an employee of Vanderbilt University School of Medicine, Department of Preventive Medicine. Dr. Ray has acknowledged that he received a research contract from Pfizer, Incorporated, which ended in 2007. In addition, Dr. Ray received consultant fees from plaintiffs and insurance company attorneys regarding unrelated products to this meeting. As a guest speaker, Dr. Ray will not participate in committee deliberations, nor will he vote.

We would like to remind members and temporary 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 participants to advise the Committee of any financial relationships that they may have with any firm at issue. Thank you.

DR. GOODMAN: Okay. Thanks you, Yvette.

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I would like to now 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.

Now, it's time to proceed with our first presentation from the FDA, which will be by Dr. Tom Laughren.

DR. LAUGHREN: Good morning. I'd first like to welcome everyone to the meeting today. Our topic for today is several new drug applications for the drug Seroquel XR, for the treatment of major depressive disorder and generalized anxiety disorder. Now, as you know, Seroquel XR is an atypical antipsychotic agent that is currently approved for schizophrenia, both for acute and maintenance treatment in schizophrenia, and also for bipolar disorder, including the acute treatment of both depression and mania and for maintenance treatment in bipolar disorder. Now, it seems clear that expanding the claims for this product

into generalized anxiety disorder populations and major depression would likely, greatly expand the use of this

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product.

Now, we've provided you with our FDA review documents, and we've also provided you with the sponsor's background package for these claims. I can tell you that the Division has concluded, based on our review of the data, that the sponsor has submitted sufficient data to support the conclusion that Seroquel XR is effective for both the acute and maintenance treatment of both major depression and generalized anxiety disorder, and that the overall safety profile for this drug appears to be roughly similar to what we've observed for this drug in the other conditions for which it's approved. In other words, the profile looks about the same in major depression and generalized anxiety disorder as it does in schizophrenia and bipolar.

The concern, and really the issue for this meeting that we want you to focus on, is what are the implications of approving this product for these additional claims, and what are the public health consequences of doing that. And in particular, we'd like you to focus on the metabolic risks that are

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fairly clearly laid out for this drug, the possibility of tardive dyskinesia, and a new concern that was raised again recently by a paper published by Wayne Ray in the New England Journal of Medicine, focusing on possible risks of sudden cardiac death, not with this drug in particular, but all the atypical antipsychotic drugs. And we've provided you with that paper and the accompanying editorial in your background packet, and so, we'd like to have some discussion of that as well.

Now, the formal presentations at the meeting today will, first of all, include a summary of the safety and the efficacy data for these new claims by the sponsor. The sponsor will also address the broader questions of the potential longer-term risks of expanding the use of Seroquel XR into this broader population.

Now, since we feel that the sponsor has done an adequate job of summarizing both the efficacy and the safety data for this product, we are not going to have separate FDA presentations on those issues. We will, however, have presentations on the issue of sudden cardiac death. We have invited Wayne Ray to

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talk this morning to present the results of his study, and then Marc Stone from FDA has some comments as well on this issue that he will present.

The Division has not yet reached a final conclusion on these applications, and so we seek your advice before we do that. After you've heard all of the findings and the arguments, we will ask you, first of all, to discuss and comment on several general

questions pertinent to the risks and benefits of Seroquel XR. And those issues are, first of all, what are the public health consequences of expanding the use of Seroquel XR into a much larger psychiatric population with MMD and GAD; and secondly, in particular, the less well-defined concerns about these longer term metabolic risks, the potential risk for tardive dyskinesia, and a concern for an increased risk of sudden cardiac death, be considered in this risk benefit discussion.

Finally, we will ask you to vote on two questions. I suppose, really, it's four questions. But, first of all, has Seroquel XR been shown to be effective for the treatment, first of all, of major

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depressive disorder and then of generalized anxiety disorder. So I suppose, in a sense, those are two separate questions. And then separately, has Seroquel XR been shown to be acceptably safe for the treatment, first of all, of major depressive disorder and then generalized anxiety disorder. And inherent in that second question is considering all of these longer-term risks that would be part of such an approval.

As was true yesterday, you should feel free to modify these questions if you feel that they're not worded correctly, and you feel that you can make important changes. And, of course, you're free to discuss other related issues and even pose other questions that you might vote on. So I'll stop there. Thank you.

DR. GOODMAN: Thank you very much, Tom.

We would now like to proceed with the sponsor presentations, and it will be a series of presentations.

Invite you up to the microphone.

DR. SCOTT: Good morning members of the Committee. My name is Mark Scott, and I head up

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development for quetiapine in the United States. AstraZeneca is pleased to be here today to review the development programs for quetiapine XR in the treatment of major depressive disorder and generalized anxiety disorder. We will be referring to these as MDD and GAD throughout today's presentation.

Last year, AstraZeneca submitted supplemental new drug applications for quetiapine XR and MDD and GAD. For MDD, approval was sought for acute and maintenance treatment as a monotherapy and as adjunctive therapy in patients where current antidepressant use provided an incomplete response. For GAD, approval was sought as acute and maintenance treatment as a monotherapy.

AstraZeneca received complete response letters from FDA for both applications. FDA was clear, and Dr. Laughren just mentioned, that efficacy had been established in both applications. However, potential metabolic risks and potential risks for tardive

dyskinesia, and sudden cardiac death needed to be discussed. A risk for sudden cardiac death among patients treated with antipsychotic was highlighted in

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a paper by Ray in the New England Journal of Medicine earlier this year. FDA also highlighted that a benefit-risk assessment was necessary, as many additional therapies are used in these patient populations.

This is our agenda today. Now, it's changed a little bit, so I'll kind of walk you through. I'll give you some background on the use of quetiapine XR in the approved indications and the rationale for development in major depressive disorder and generalized anxiety disorder. Dr. Hans Eriksson will discuss the efficacy and safety seen in MDD and GAD. Dr. Ihor Rak will now talk to the issues of tardive dyskinesia, metabolic risks, and sudden cardiac death. Dr. Howard Hutchinson, our chief medical officer, will provide our benefit-risk assessment as well as outline our risk management plan. And Dr. Alan Gelenberg from the University of Wisconsin will speak to clinical use. And I'll come back and take questions from the Committee.

I'll now provide a brief history of the development of quetiapine and the safety profile in the

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approved indications.

This slide contains the approvals for quetiapine in the United States. As you can see, quetiapine has been extensively studied and gained approval in schizophrenia as well as in manic and depressive episodes associated with bipolar disorder at multiple doses and in two formulations. Quetiapine XR, the extended release formulation, was developed to allow once daily dosing and faster titration in both schizophrenia and bipolar mania. In relation to these approved indications, those sought for MDD and GAD are at lower doses in a range of 50 to 300 milligrams per day.

Quetiapine is approved in schizophrenia and bipolar disorder in numerous countries. Quetiapine has been extensively investigated, with over 26,000 participants participating in clinical trials sponsored by AstraZeneca. Specific studies have been conducted in pediatric populations in schizophrenia and bipolar disorder as well as in elderly populations with MDD, GAD and elderly dementia. Information from all of these studies form the database for extensive safety

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evaluations, and we estimate that more than 22 million people have received quetiapine since its introduction.

With the current use of quetiapine, the safety profile has been well characterized in clinical studies and through pharmacovigilance. There are two box warnings. The first is present for all antipsychotic and provides a warning for increased mortality among

elderly patients with dementia related psychoses. The second is for increased risk of suicidal thinking and behavior, and this warning is present for all antidepressants.

A number of warnings and precautions have been identified with quetiapine use. The warnings are associated with potential risk for tardive dyskinesia and metabolic variables of weight, glucose and lipids will be discussed further by Dr. Rak. And the common adverse events listed on this slide are also commonly seen in both MDD and GAD.

Before moving to development programs for major depressive disorder and generalized anxiety disorder, I will briefly speak to the nature of both.

Major depressive disorder and generalized

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anxiety disorder are highly prevalent and highly disabling psychiatric disorders that are each associated with increased mortality due to suicide. Some patients, despite multiple attempts at treatment, continue to remain symptomatic. For these two disorders, treatment guidelines exist and recommend that SSRIs or SNRIs as the first line of pharmacologic treatment. After that, physicians utilize many options, either alone or in combination, and when available approved treatments fail to help patients, physicians may resort to treatments with no demonstrated efficacy or poorly characterized safety profiles. Dr. Gelenberg will speak to these points in far more detail later in the presentation.

I'll now walk you through the rationale for development of quetiapine XR in MDD and GAD from a mechanistic and clinical perspective.

Quetiapine XR in a dose range of 50 to 300 milligrams a day engages well established targets for depressive and anxiolytic treatment. This pharmacologic profile involves dopamine and serotonin receptors and norepinephrine reuptake inhibition. The

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American Psychiatric Association guidance on changing antidepressant therapy are that when two medications from the same class have been tried and are ineffective, an antidepressant from a different class should be tried. Appreciation for quetiapine's distinct mode of action and clinical profile provides a rationale as to why it represents an important addition to the currently available treatments for MDD and GAD, and thereby will increase the individual patient's chances of finding an effective treatment.

Now, for the development of Quetiapine XR in MDD and GAD, we saw in the clinical trials in schizophrenia, as well as in manic and depressive episodes associated with bipolar disorder, reductions in both depressive and anxiety symptoms, and this provided the clinical basis for development. But these clinical findings, coupled with the prevalence, seriousness and the need for additional options, led to

the development of programs today.

At the end of the Phase II meeting with FDA, AstraZeneca proposed to add a description of disease severity to the approved indications to reflect the

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need for safe and appropriate use. As will be shown, the development programs recruited patients with at least moderate symptoms, and the FDA agreed to the program but not to the inclusion of severity into the labeling. Separate applications were made in 2008.

The indications proposed are predicated on the agreed development program in both disorders. We're not looking for use of quetiapine for all patients with major depressive disorder or generalized anxiety disorder. Our intent is to offer another option within the treatment cascade. Our program studied patients with at least moderate symptoms, and our goal is to provide a safe and effective option for patients where first-line therapies may not be appropriate.

Now, Dr. Hans Eriksson, our medical science director, will review the safety and efficacy seen in MDD and GAD. Thank you.

DR. ERIKSSON: Thank you, Dr. Scott.

Good morning. My name is Hans Eriksson, and I'm the global medical lead for Seroquel at AstraZeneca. I've been involved with this project for the last five years, and today I will discuss the

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efficacy and general safety profile in major depressive disorder and generalized anxiety disorder. I will provide an overview of the clinical development programs for MDD and GAD, and look specifically at patient characteristics, key study endpoints, and key efficacy data. Then I will address general safety data in the short-term and longer-term studies.

At first, however, I would like to point out that the dose range that was evaluated in these development programs was 50 to 300 milligrams, and this is lower than the doses used in indications of schizophrenia and bipolar disorder, where doses up to 800 milligrams were used. And the decision to use this dose range was based on the findings in the development programs for depression and bipolar disorder and other studies in depression and anxiety. So we, therefore, used 300 milligrams as the highest dose and explored doses down to 50 milligrams.

There were eight studies in the MDD program. Four of these studies were short-term monotherapy studies with a duration of six to eight weeks. Two of these studies, Studies 1 and 2, were traditional fixed

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dose studies, and the other two, Studies 3 and 4, had a design where patients who had not responded adequately after two weeks treatment with an antidepressant had their doses -- sorry, who had not responded adequately after two weeks treatment had their doses doubled in the blinded fashion.

Study 5, which was a longer-term, randomized withdrawal study, was designed to address maintenance of efficacy. Study 6 and 7 were adjunct studies in the acute setting where quetiapine XR was given to patients who had failed to respond adequately to an antidepressant. Study 14 was conducted in an elderly population, about 65 years of age, where the same dose range of 50 to 300 milligrams was explored.

The patients had major depressive disorder, or MDD, diagnosed according to DSM-IV, and the main severity rating scales that they used here were the Hamilton Rating Scale for Depression, which I will call HAM-D, and the Montgomery Asberg Depression Rating Scale, which I will refer to as MADRS. Both these scales have been extensively used in MDD studies during the last several decades. HAM-D was used for inclusion

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and MADRS was used to rate severity. Patients had to have a HAM-D score of at least 22, or in some studies 20, in order to be included. A score of 20 to 22 is considered to reflect moderately severe depression.

The mean rating at inclusion for the acute Studies 1 to 4 was about 26 for HAM-D and about 31 for MADRS. This represents moderate to severe depression. The mean age of enrollment was 43 years; 85 percent of these patients had been depressed before. On average, they had had nine depressive episodes prior to this one, and 1 out of 6 of these patients had previously attempted suicide. So it's very clear that these patients needed a qualified intervention for moderate to severe depression.

The primary endpoint in the acute studies was a change from baseline in the MADRS total score. In the longer-term maintenance study, the primary endpoint was the time to recurrence of depressive symptoms. Key secondary endpoints included response defined as at least with 50 percent improvement in MADRS score relative to baseline and remission defined as a MADRS score of 8 or less. And response and remission reflect

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the proportions of patients where clinically meaningful improvement is being seen.

When discussing efficacy, it is very important to remember, just as mentioned earlier today, that the FDA has recognized that efficacy has been established in MDD as well as in GAD. So today I will focus on the key findings, and I'll start with the primary efficacy endpoint in the short-term studies in MDD.

Each treatment arm in each trial is here represented by a point estimate for the mean difference versus placebo, shown as a dot, together with the associated 95 percent confidence interval. Differences to the left of the vertical zero line favor quetiapine and differences to the right of the reference line would favor placebo.

All studies, except one, showed a statistically significant defect of quetiapine XR on

the primary efficacy variable. In Study 1, each of the three doses, 50, 150 and 300 milligrams, showed a statistically significant effect in improvement in MADRS score compared to placebo. For Study 2, both the 150 and 300 milligram doses of quetiapine XR were

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significantly better than placebo as was the already approved antidepressant duloxetine.

Study 3 was a modified fixed dose study where patients who had not responded adequately to 150 milligrams quetiapine XR had their dose increased to 300 milligrams after two weeks of treatment. And also in this study, quetiapine XR was significantly better than placebo.

Study 4 was a failed study. Neither quetiapine nor the approved antidepressant, escitalopram, reached statistical significance when compared to placebo.

In Studies 6 and 7, quetiapine XR was given to patients who had failed to respond adequately to another antidepressant; 300 milligrams quetiapine XR were significantly better than placebo in both these studies and 150 milligrams was significantly better in one study.

Finally, in the study in elderly patients, flexible dose treatment with quetiapine XR was significantly better than placebo.

So overall, this slide shows us that in six or

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seven short-term studies in the MDD program, quetiapine XR, given at doses of 50 to 300 milligrams, provided consistent efficacy versus placebo, including adjunctive treatment and in elderly patients.

This slide from Study 1 shows MADRS scores over time. Here, all the quetiapine doses, 50 milligrams, 150 milligrams and 300 milligrams, were studied. We can see that at Day 4, all three treatment arms were statistically significantly better than placebo, and this separation continued throughout the study. Additionally, there was no evidence of a dose response in this fixed-dose study.

There were effects on secondary parameters that supported the findings in the primary variable. Separation from placebo within the first week of treatment was consistently seen for all the six positive short-term studies in MDD. Significant effects on response were seen for quetiapine XR in the fixed-dose monotherapy, modified fixed dose, adjunct and elderly studies. Significant effects on remission were seen for quetiapine XR in the fixed-dose monotherapy, adjunct and elderly studies. Remission,

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as you remember, was defined as having a MADRS score of 8 or less, and these patients can be considered to be practically free of depressive symptoms.

This slide shows the general design of the two longer-term studies, Studies 5 and 12, and we will

refer to these studies several times during today's presentation.

In Study 5, patients with MDD were treated with quetiapine XR open label with flexible doses from 50 to 300 milligrams until clinical stabilization occurred. Dose adjustments were made by the investigator according to clinical judgment. Now, from 4 to 8 weeks, depending on clinical status, stable patients continued in the open-label stabilization phase with flexible dosing during 12 to 18 weeks. So the total duration of quetiapine XR treatment prior to randomization, therefore, ranged from 16 to 26 weeks.

Patients who maintained their improvement were then randomized to either continuing on quetiapine XR or switching to placebo for a period of up to 52 weeks. Drug was administered in a blinded fashion with flexible dosing. This allowed the investigator to use

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any of the doses, 50, 150 or 300 milligrams. The key efficacy endpoint was time to relapse, defined as a depressive event, and the definition of a depressive event encompassed rating scale criteria or other clinical important criteria like initiation of antidepressant treatment.

So to continue with Study 5, here are the data presented on the Kaplan-Meier curve. Patients who were coming from the open-label phase were randomized to continue on quetiapine XR or switching to placebo. The quetiapine XR patients, represented by the blue line in this graph, were at the lower risk of depressive relapse compared to the switch to placebo. The hazard ratio was 0.34.

We can also see that at the point of entry into the randomized withdrawal phase, 21 percent of the patients were on 50 milligrams, 46 percent were on 150 milligrams, and 32 percent were on 300 milligrams. And this reflects the treating clinician's choice of dose during the open-label period. The reduction in the risk of relapse was statistically significant for each dose, demonstrated by the hazard ratios and the

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p values, and the highest risk reduction was seen for the highest dose. So efficacy was demonstrated in maintenance treatment, and efficacy was also demonstrated for each dose, from 50 milligrams to 300 milligrams.

So to summarize the MDD findings, at lose doses, 50 to 300 milligrams. Quetiapine XR is an efficacious antidepressant consistently reducing levels of depressive symptoms, as monotherapy, as adjunctive therapy in patients with inadequate response, and in elderly patients. Symptom improvement was seen within the first week. Efficacy was also seen in terms of higher response and remission rates compared to placebo. The risk of relapse during maintenance therapy was reduced. Importantly, 7 out of 8 studies were positive. This compares favorably with other

recent development programs for MDD, where often about half of the studies have been failed or negative.

Now, we'll turn to the GAD clinical development program. It had a design very similar to that of the MDD program. This program included five studies, three acute monotherapy, fixed-dose studies,

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one longer-term maintenance study, and one acute monotherapy study in the elderly population. The three acute monotherapy studies were eight week studies. Two of them included active comparators approved for GAD. The longer-term maintenance study, Study 12, had a design similar to Study 5 in MDD. And the elderly study, Study 15, explored the dose range from 50 to 300 milligrams, with flexible dosing of quetiapine XR.

So patients should fulfill the DSM-14 TR criteria for generalized anxiety disorder, GAD. The Hamilton Rating Scale for anxiety, the HAM-A, was used to assess severity. For inclusion, HAM-A had to be 20 or higher. The MADRS score could not be above 16 because you want to avoid including patients who had significant depressive symptoms. Mean HAM-A at the inclusion was 25.5 and mean age at enrollment was 41 years. The duration of anxiety symptoms was about 13 years, and about 4 percent of these patients had previously attempted suicide.

The primary endpoint in the GAD studies, the acute GAD studies, was the change from baseline in HAM-A total score. In the longer-term maintenance

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study, the primary endpoint was time to recurrence of anxiety symptoms. Response was defined as at least 50 percent improvement in HAM-A score relative to baseline, and remission was here defined as a HAM-A total score of 7 or lower.

Here are the results for the primary efficacy endpoint in the short-term studies in GAD. The three fixed-dose, short-term studies, 9 to 11, were all positive with statistically significant improvements in anxiety scores for two of the quetiapine XR dose arms in each study. We can see that in Study 9, 300 milligram generalized quetiapine XR did not reach statistical significance. In the elderly study, a statistical significant improvement in anxiety scores was seen for quetiapine XR compared to placebo. So across the short-term GAD studies, quetiapine XR showed a consistent pattern of efficacy versus placebo, including in elderly patients.

There were effects on several secondary parameters that supported the findings of the primary variable. Separation from placebo within the first week of treatment was consistently seen for all four

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short-term studies in GAD. Significant effects on response were seen in the fixed-dose studies and in the elderly study. And significant effects on remission were seen in the fixed-dose studies and in the elderly

study.
Here are the results from the longer-term study in GAD, Study 12. Patients coming from the open-label phase and being stabilized on quetiapine XR entered the randomized phase at the time point zero. Patients who were randomized to continue on quetiapine XR, represented by the blue line, were at the lower risk of an anxiety relapse compared to those switched to placebo. The hazard ratio was 0.19.
We can also here see that at the point of entry into the randomized withdrawal phase, 26 percent of the patients were on 50 milligrams, 49 percent were on 150 milligrams, and 25 percent were on 300 milligrams. We can also see that for the randomized phase, each dose was associated with a significant reduction in the risk of relapse, indicated by hazard ratios and p values. Therefore, efficacy was demonstrated in maintenance treatment and efficacy was

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demonstrated for each dose separately, from 50 milligrams to 300 milligrams.
So to summarize the GAD findings, at low doses, 50 to 300 milligrams per day, quetiapine XR is an efficacious, anxiolytic agent that consistently reduces the level of anxiety symptoms as monotherapy and in elderly patients. Symptom improvement was seen within the first week. Efficacy was also seen in terms of higher response and remission rates compared to placebo. Quetiapine XR reduces the risk of recurrence of an anxiety event during maintenance therapy. And importantly, 5 out of 5 studies in GAD were positive.
So to look at both MDD and GAD, today we have demonstrated that in moderately to severely ill patients with MDD or GAD, quetiapine, which is a drug that has a distinct pharmacological profile, consistently showed efficacy in the dose range of 50 to 300 milligrams in acute treatment in adults and acute treatment in elderly patients, and in longer-term maintenance treatment. Efficacy was also demonstrated in MDD when quetiapine was given adjunctively to patients who had failed to respond adequately to an

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antidepressant alone. Efficacy was consistently seen within the first week of treatment in MDD and GAD. And summarizing overall efficacy, 12 out of 13 studies were positive, indicating robust clinical efficacy.
I will now briefly discuss general safety data from the MDD and GAD program, and then my colleague, Dr. Ihor Rak, will continue with a focus on specific safety topics. I'd like to point out that for the analysis of safety, we have pooled the data from the MDD and GAD studies in agreement with the Agency.
This table shows the seven short-term monotherapy studies in non-elderly adults, including 2,718 MDD and GAD patients. It displays adverse event incidences for, starting from the left, placebo, and then all quetiapine XR patients, then quetiapine XR

patients per dose. And to the right in this slide are the corresponding data for the active comparators. Adverse events occurring in more than 10 percent of the patients in any dose group and within a parent dose response for quetiapine XR are highlighted in orange. These adverse events, dry mouth, somnolence, sedation, dizziness, have normally been seen to be among the most

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frequently reported in previous studies with this compound in other indications.

So now I will continue to discuss adverse events in the short-term monotherapy studies in non-elderly patients. For serious adverse events, SAEs, we are looking at incidences of 2 percent or lower for the active treatments and placebo. For adverse events leading to death, there was one patient in the 150 milligram quetiapine group, a homicide. For withdrawals due to adverse events, there was an increased with dose for quetiapine XR. The most common adverse events leading to withdrawal for quetiapine XR was sedation and somnolence.

For all the active treatment arms, withdrawals due to adverse events ranged from 8 percent to 21 percent. And the incidence of adverse events observed in these short-term monotherapy studies was generally similar to what was seen in the adjunct therapy studies and in the studies in elderly patients. And the adverse event profile was generally similar irrespective of age, race and gender.

The adverse event profile during the

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open-label phase of the longer term studies were similar to what we just reviewed, with dry mouth, somnolence, sedation and dizziness being the most frequently reported adverse events. For the randomized phase of the longer term studies, the adverse event profile tended to be similar to placebo with weight increase, the only commonly observed adverse event that stood out as occurring more frequently among quetiapine XR treated patients.

So to summarize the general safety profile of quetiapine XR in MDD and GAD, the most common adverse events were sedation, somnolence, dizziness and dry mouth. Weight gain was reported more frequently for quetiapine than for placebo during longer-term treatment. And the general safety findings, based on adverse events in the short-term and longer-term studies in MDD and GAD are consistent with the known safety profile of this drug seen in indications using higher doses.

I will now turn the podium over to Dr. Ihor Rak.

DR. RAK: Thank you, Dr. Eriksson.

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Good morning, everyone. My name is Ihor Rak, and I'm Clinical Vice President of Neuroscience at AstraZeneca. I'm very pleased to address the important

longer-term safety topics. These data will form the basis for an appropriate and meaningful risk management plan to help informed MDD/GAD patients and informed prescribers achieve the benefits of quetiapine treatment. We will review the longer-term safety data of quetiapine from all approved indications, as well as longer-term safety data from the MDD and GAD clinical studies, specifically addressing tardive dyskinesia, metabolic and cardiovascular assessments, and sudden cardiac death.

The quetiapine clinical studies database was analyzed using five safety pools to characterize the potential risks as described in the briefing document. Today's presentation focuses on the following three key safety pools. Pool A includes over 26,000 patients from all studies, all indications. This is an all-inclusive data set, however, Pool A is best used to provide descriptive analysis of the data and to identify potential, rare adverse events. The number of

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patients who were treated with quetiapine for at least 12 months were 1,329; at least 18 months, 645; and for at least 24 months, 394.

Pool B includes all short-term placebo controlled studies; 8,853 patients were treated with quetiapine. Data are short term but allow a statistical comparison to placebo.

Pool C includes all indications, all randomized withdrawal longer-term studies in over 2,000 patients, with a mean time on randomized treatment of 26 weeks. The number of patients who were treated with quetiapine for at least nine months were 493, and for at least 12 months, 205. It should be noted that all patients in this pool, Pool C, even those randomized to placebo, received quetiapine prior to randomization.

By looking at these three key safety pools, that are larger with longer and higher exposure to quetiapine than the MDD and GAD pools, the risks for MDD/GAD patients are sufficiently characterized.

The first safety topic we will review from a longer-term safety data perspective is tardive dyskinesia. The most useful, succinct information

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explaining tardive dyskinesia is the language in Section 5 of the current label for approved indications, specifically, Section 5.7, Tardive Dyskinesia. The label reads: "A syndrome of potentially, irreversible, involuntary dyskinetic movements may develop in patients treated with antipsychotic drugs, including quetiapine." The label continues, "The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relative brief treatment periods at low doses."

Looking at our clinical data, overall, there were very few reported adverse events of tardive dyskinesia. In total, there were 53 adverse event reports, none of which were seen in the MDD/GAD studies. For Pool B, all short-term placebo controlled studies and C, all longer-term randomized withdrawal studies, there were very few reported adverse events. Consequently, the confidence intervals are very wide.

Therefore, no definitive conclusions can be made regarding point estimates of risk. There were no reported tardive dyskinesia adverse events for Pools D and E; Pool D, the all MDD/GAD studies, and Pool E, the longer-term withdrawal studies in MDD/GAD.

In order to further characterize the potential risk of tardive dyskinesia, we employed a more sensitive research methodology. We applied Schooler-Kane criteria to prospectively collected, abnormal and voluntary movement scale AIMS data in a retrospective manner. This slide shows you the results. Using this research methodology, the risk of tardive dyskinesia is low in MDD/GAD patients in our clinical studies.

On the basis of our data, AstraZeneca concludes that even though adverse events of tardive dyskinesia have not been reported in MDD and GAD longer-term studies, the risk of tardive dyskinesia is present and is low. The current label of quetiapine for approved indications describes the risk of tardive dyskinesia accurately for patients with MDD and GAD.

The current label for approved indications addresses the risk of tardive dyskinesia in MDD and GAD patients treated with quetiapine with this language. "Given these considerations, Seroquel XR should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that is 1) known to respond to antipsychotic drugs, and 2) for whom alternative equally effective but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on Seroquel XR, drug discontinuation should be considered; however, some patients may require treatment with quetiapine despite the presence of the syndrome."

Next, we will review the data on metabolic and cardiovascular assessments. We will look at data from short-term, placebo controlled, fixed-dose studies and longer-term randomized withdrawal studies, for weight

changes, glucose control, parameters listed here, including adverse events potentially related to diabetes, and lipids, listed here, adverse events potentially related to atherosclerotic, cardiovascular disease included.

On this slide, the mean changes in weight are displayed for all indications by dose. Note, these are data, which include fixed-dose, placebo controlled studies from Pool B. In the top half of the table, we see all doses across all indications. It is important to note that the 800 milligram dose group consists solely of patients with schizophrenia, and the 600 milligram dose group includes patients with bipolar disorder and schizophrenia. The 400 milligram dose group includes patients with schizophrenia only. Across all doses, from 50 to 800 milligrams per day, the mean weight increases are small, ranging from 0.8 to 1.4 kilograms across all indications in patients treated with 50 to 800 milligrams per day.

In the bottom half of the table, we see data

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from the MDD and GAD program and include comparators. Here, we also see small mean weight changes of 0.7 to 1.2 kilograms in patients treated with quetiapine XR, doses of 50 to 300 milligrams per day. Mean weight changes in comparator treated patients were negligible. All doses, other than 50 milligrams per day, were associated with statistically significant weight gain, though not strongly linearly related to dose over the range of 150 to 800 milligrams per day.

Having shown you the mean changes in weight at all doses in short-term studies, it is important to look at outliers. We used the standard criterion of 7 percent weight increase or more to assess weight changes. In patients from short-term, placebo controlled, fixed-dose studies and in the MDD/GAD subset, increases of 7 percent or more were seen in all quetiapine doses, comparators and placebo. These observations were seen most frequently at a dose of 400 milligrams per day of quetiapine.

It is important to address what happens with changes in weight over time. Here, we see the weight change data from Pool C patients, data across all

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indications from longer-term, randomized withdrawal studies. It's a little bit complex, so I'm going to take a few minutes to take you through this, as you will be seeing slides of a similar format in this presentation.

Between the open label baseline in the lower left-hand corner of the slide and time point zero is the period of time when all patients are exposed to quetiapine. After at least 12 weeks of stabilization, patients are then randomized to either continue on quetiapine or withdraw from quetiapine to placebo. The remainder of this graph follows these patients over time to 48 weeks.

In terms of what this slide tells us about mean weight change after at least 12 weeks of open label treatment with quetiapine, mean weight increased approximately 3 kilograms from baseline, and thereafter, there was little change for patients who continued treatment with quetiapine. For patients who withdrew from quetiapine, mean weight change appeared to decrease towards baseline levels.

The sample sizes at the bottom of this slide

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decreased over time as a result of study design. Patients who relapse exit the study. Very few patients withdrew during the randomized treatment phase due to adverse events related to metabolic parameters. No patients withdrew due to weight increase in the MDD/GAD studies during this randomized treatment phase.

So in summary, small mean weight increases were seen at all doses in short-term, fixed-dose, placebo controlled studies. The largest incidence of weight gain of 7 percent or more was observed in patients treated with 400 milligrams per day. In the longer-term, randomized withdrawal studies, mean weight plateaued with continued treatment. When patients were withdrawn from quetiapine, mean weight increases appeared to decrease towards baseline levels. As a reminder, weight gain has been described during quetiapine treatment and is reflected in the label for approved indications.

Next, we will look at glucose control and associated parameters. In patients from short-term, placebo controlled, fixed-dose studies and in the MDD/GAD subset, small increases in fasting plasma

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glucose were seen in all quetiapine doses, comparators and placebo. The only statistically significant difference from placebo was in the 600 milligram per day quetiapine treated group.

In this analysis, we looked at shifts in fasting plasma glucose in two patient categories. First, patients with normal fasting plasma glucose less than 100 milligrams per deciliter at baseline, shifting to 126 milligrams per deciliter or greater at any one time during the study. In the second category, patients with impaired fasting plasma glucose 100 to 125 at baseline, shifting to 126 or greater at any one time during the study. Across all quetiapine doses, comparators and placebo, shifts to 126 milligrams per deciliter or greater were seen. In patients shifting from normal to 126 or more, there was no difference compared to placebo in doses less than 300 milligrams per day for quetiapine treated groups. This same pattern was seen in the MDD/GAD subset. In patients with impaired fasting plasma glucose, 100 to 125 at baseline shifting to 126 or greater, there was no significant increase with quetiapine treated patients

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compared to placebo.

This slide shows fasting plasma glucose changes from Pool C across all randomized withdrawal studies. After open-label treatment with quetiapine, patients who were randomized to quetiapine had a mean increase of fasting plasma glucoses of approximately 5 milligrams per deciliter at 12 weeks of randomized treatment with a plateau thereafter through Week 48. Patients who were randomized to placebo following open-label quetiapine treatment tended to have less of an increase at 12 weeks, and then appeared to be trending towards baseline by 48 weeks.

We will now look at hemoglobin A1C, treatment emergent shift in Pool B, all short-term, fixed-dose, placebo controlled studies across all doses and indications. These data show the proportion of patients with hemoglobin A1C of less than 6.1 percent at baseline who shifted to post-baseline values of 6.1 or greater. Shifts were seen across all quetiapine doses, comparators and placebo. The only significant differences from placebo were at doses of quetiapine of 600 milligrams per day or more.

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This slide shows hemoglobin A1C mean changes over time from Pool C, across all longer-term, randomized withdrawal studies. Small mean increases in hemoglobin A1C were observed in both the quetiapine and placebo treated groups.

This slide shows hemoglobin A1C mean changes in the MDD/GAD Pool E. These Pool E data are shown here to demonstrate that small mean decreases in hemoglobin A1C were seen in both quetiapine and placebo treated groups in MDD/GAD patients where doses of 50 to 300 milligrams per day were used.

Now, we will look at glycosuria data in patients from Pool B. On this slide, we see the proportion of patients with glycosuria in each dose group, from short-term, fixed-dose, placebo controlled studies. The dose related signal appears to emerge at doses from 300 milligrams and higher, noting that there are too few data at the lower 50 and 150 milligram doses to interpret the effect of these lower doses on glycosuria.

Having observed higher proportions of patients with increased fasting plasma glucose, we examined

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reported adverse events potentially related to diabetes. These data were provided in the briefing document. This slide also includes the data on comparators used in the program and Pool D. The list of 20 MedDRA preferred terms was provided in the briefing document, and these ranged from diabetic ketoacidosis to glucose urine present.

It is important to consider, when we look at these data, that these adverse events were captured as reported by the investigator. In the descriptive Pool A across all studies in the quetiapine program, the incidence rate for reported adverse events

potentially related to diabetes was 2.5 for quetiapine versus 2.8 for placebo. Similarly, in the short-term, placebo controlled studies, Pool B, the rates of reported adverse events were numerically lower for quetiapine compared to placebo. In the MDD and GAD longer-term studies, Pool E, the relative risk of reported adverse events was 1.01 for quetiapine versus placebo. In the longer-term, all randomized withdrawal studies, Pool C, the rate of reported adverse events was higher for quetiapine compared to placebo.

We further examined this higher rate of reported adverse events in this larger Pool C by examining the predisposing risk factors for all 31 patients treated with quetiapine with reported adverse events, potentially related to diabetes, these 31 patients, out of 2,043 patients, treated with quetiapine in this pool of longer-term studies.

We examined the data from each of these 31 individual patients in detail. There were 11 patients with preferred terms of diabetic ketoacidosis, diabetes mellitus, or Type 2 diabetes mellitus reported. Each of these patients either had diabetes or risk factors for diabetes at baseline. There were 21 patients with less specific preferred terms reported, shown in the two boxes on the left-hand side. Of these 21, 16 had diabetes or risk factors of diabetes at baseline. One was receiving concomitant valproate, which is associated with weight gain, while the remaining four patients were without risk factors at baseline. Each of these four had fasting plasma glucose levels in the normal range at baseline and at the time of the reported adverse event.

Again, it is important to note that of the 31 patients described on this slide, all but four patients with reported adverse events, potentially related to diabetes, had diabetes, risk factors for diabetes, or a confounding concomitant medication. The remaining four patients had normal fasting plasma glucose at the time of the reported adverse event.

In summary, small increases in fasting plasma glucose were observed, primarily at doses of 300 milligrams per day or more, that were not progressive over time and decreased towards baseline after drug withdrawal. Small increases in fasting plasma glucose were also observed with placebo and other antidepressants. Significant shifts above 6.1 percent in hemoglobin A1C were seen at doses of quetiapine of 600 milligrams per day or more. Glycosuria was observed at doses of 300 milligrams per day or more.

In longer-term studies, an evaluation of reported adverse events, potentially related to diabetes, revealed that all but four patients who had fasting plasma glucose of less than 100 milligrams per

deciliter had established diabetes diagnosis or conventional risk factors at baseline. As a reminder, changes in glucose have been described for quetiapine, and the approved label includes a warning for hyperglycemia diabetes.

Now, I will review total cholesterol triglycerides, LDL, HDL, and LDL/HDL ratio.

On this slide, the mean changes in total cholesterol are displayed for all indications by dose. For the mean change in total cholesterol from baseline to endpoint, all doses of quetiapine were significantly different from placebo. However, only doses of 300 milligrams per day or more were associated with increases in total cholesterol. For MDD-GAD, the same observation can be made for quetiapine XR. Numerical increases in total cholesterol were also seen with escitalopram and paroxetine.

On this slide, we see the proportions of patients shifting to above 240 milligrams per deciliter, from a normal baseline, meaning below 200 milligrams per deciliter, and patients shifting from a borderline baseline, between 200 and 240.

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Shifts to above 240 were seen in all treatment groups, including comparators and placebo. The highest proportions of patients shifting to above 240 in patients with normal baseline were seen at doses of at least 600 milligrams per day. In patients with borderline baseline total cholesterol, the highest shift was seen in the 800 milligram per day dose group. For MDD and GAD patients normal at baseline, no significant shifts for quetiapine, placebo and comparator were observed. For patients borderline at baseline, significant percent of patients shifted on quetiapine, 300 milligrams per day dose and paroxetine.

Next, we will look at total cholesterol in the longer term. Consistent with the short-term studies data, a small increase in mean total cholesterol was observed during the open label phase. During randomized treatment, both treatment groups showed decreases in mean total cholesterol to below baseline at 48 weeks. The decreases were greater in the placebo group.

Here, we see triglycerides in short-term, placebo controlled studies. All doses of quetiapine,

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except 50 milligrams, were associated with statistically significant increases in mean change. No clear linear trend was seen as all doses other than 50 milligrams were associated with similar increases in triglycerides. Numerical increases in triglycerides were also seen for the escitalopram treated group.

On this slide, we see the proportions of patients shifting to above 200 milligrams per deciliter from a normal baseline, meaning less than 150, and patients shifting from a borderline baseline between 150 to 200. Shifts to above 200 milligrams per

deciliter were seen in all treatment groups, including comparators and placebo. The proportion of patients who shifted to greater than 200 milligrams per day was similar across doses of 150 milligrams per day, or more, when examined within both baseline groups. The proportion of patients who shifted greater than 200 was lower in the 50 milligram dose group and was similar to placebo. For MDD and GAD, the same observations can be made.

The longer-term, fasting triglyceride data are shown here. There are mean increases of approximately

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20 milligrams per deciliter that plateau over time in patients treated with quetiapine. For patients withdrawn from quetiapine on to placebo, fasting triglyceride levels appeared to be trending toward baseline.

In the interest of time, I will not show the data today, but I will briefly summarize the LDL, HDL, and LDL/HDL ratio data.

The LDL/HDL ratio is an important parameter predicting atherosclerotic cardiovascular disease risk. In short-term studies, small decreases in HDL were observed at all doses, including placebo. No clear change in LDL was seen, and there was no clear change in the LDL/HDL ratio. In longer terms studies for these parameters, with continued quetiapine therapy, changes did not appear to progress, and upon discontinuation, changes trended towards baseline.

A potential consequence of changes in metabolic parameters is atherosclerotic related cardiovascular adverse events, which we will look at next. We searched the clinical studies database using a standardized set of adverse event terms for death,

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myocardial infarction, and cerebral vascular infarction. This slide shows that across all pools, there was no evidence of an increased risk of adverse events potentially related to atherosclerotic cardiovascular disease for quetiapine compared to placebo. The relative risk for quetiapine versus placebo in Pool B, all short-term, placebo controlled studies, was 0.73, and relative risks for quetiapine versus placebo in Pool C, all long-term, randomized withdrawal studies, was 0.14.

To summarize, in short-term studies, total cholesterol increased at doses of 300 milligrams per day or more. Triglycerides increased at doses of 150 milligrams per day or more. Small decreases in HDL were observed at all doses, including placebo, and no clear changes in LDL and the LDL/HDL ratio were observed.

In longer-term studies with continued therapy, changes did not appear to progress, and upon discontinuation, changes trended toward baseline. There was no evidence of an increased risk of adverse events potentially related to atherosclerotic

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cardiovascular disease for quetiapine compared to placebo. Changes in total cholesterol and triglycerides are described in the warning and precaution section of the approved label.

Now, we will look at sudden cardiac death. We will not review the preclinical or Phase I studies that were discussed with the FDA in 2001 because they did not demonstrate a potential for QT prolongation at clinically relevant doses. No increased risk for sudden cardiac death has been detected in the quetiapine clinical development program. However, a recently published retrospective cohort study in the Tennessee Medicaid Database by Dr. Ray and colleagues, published in the New England Journal of Medicine in January of this year, has suggested that antipsychotics, including quetiapine, may be associated with an increased risk of sudden cardiac death. The Agency has asked us to include this topic in our discussion today, and the next few slides will summarize our review of the data from the quetiapine clinical studies database.

Sudden cardiac death is commonly defined as

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unexpected death occurring within one hour of symptom onset in the absence of a prior condition that would appear fatal. Ventricular tachyarrhythmia is often the proximate cause of sudden cardiac death, with the majority of patients having underlying coronary artery disease. Prolongation of the QT interval is one of many risk factors for a potentially life-threatening form of ventricular tachyarrhythmia, particularly a form of polymorphic ventricular tachyarrhythmia, known as torsades de pointes. Many drugs are now recognized to prolong the QT interval. Patients with depression are recognized to be at risk for sudden cardiac death. The findings from two recent observational studies have found an increased risk of sudden cardiac death among patients with symptoms of depression.

We evaluated the risk of sudden cardiac death in our clinical studies using multiple approaches. These included an analysis of all-cause mortality, an analysis of adverse events as reported by the investigator, potentially related to sudden cardiac death as detailed in the briefing document, and these reports were not adjudicated. To provide a more robust

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analysis of sudden cardiac death, all reports of death, excepting homicide, non-overdose suicide and accidental injuries, in the clinical studies database were adjudicated by an expert cardiologist blinded to treatment.

Cases were adjudicated as sudden cardiac death, using the definition of Dr. Ray, "a sudden pulseless condition that was fatal, that was consistent with the ventricular tachyarrhythmia and that occurred

in the absence of a known, non-cardiac condition as the proximal cause of death." We also reviewed the potential for QT prolongation with quetiapine, based on centrally read ECG measurements, and adverse events that may be related to a potential proarrhythmic effect.

Here, we see the all-cause mortality data from all safety pools as provided in the briefing document, Table 30, page 90. There is no difference in all-cause mortality on quetiapine compared to placebo. The relative risks for Pool B quetiapine versus placebo was 1.08. And relative risk for Pool C quetiapine versus placebo was 0.24. It is also important to note that

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when examined within each indication, including MDD and GAD, there was no difference in the risk of death for quetiapine treated patients versus placebo.

This slide shows the findings from the adjudication of all reports of death by an expert external cardiologist blinded to treatment. The cause of death was adjudicated as sudden cardiac death in 23 patients treated with quetiapine and for 8 patients treated with placebo. In each pool examined, there is no evidence of an increased risk for sudden cardiac death for quetiapine as compared with placebo. Within the MDD and GAD pools specifically, where we see three deaths in the quetiapine treated group and one death in the placebo treated group, the incidence rate of sudden cardiac death for quetiapine compared with placebo was 0.21 versus 0.23 per 100 patient-year exposure.

Next, we will discuss QT changes during quetiapine treatment from the clinical development program. QT prolongation is recognized as a marker for an increased risk of potentially serious ventricular arrhythmia and sudden cardiac death. It is important to understand how these data were collected.

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Since 2001, all multicenter studies in the quetiapine development program have used a central ECG laboratory for the reading and interpretation of ECG tracings. Data from centrally read ECGs are available for more than 15,000 patients treated with quetiapine and more than 5,000 patients treated with placebo. For short-term, placebo controlled studies, data are available for more than 10,000 patients, more than 7,000 patients treated with quetiapine and more than 3,500 patients treated with placebo.

With that context, this slide shows changes from baseline QT Fridericia in these patients. For patients treated with quetiapine, changes from baseline QTF are small and are similar to placebo. Findings from Pool A, the all studies pool, are similar. Shifts from baseline of greater than 60 milliseconds, or to a QTF of greater than 500 milliseconds, are generally

recognized as ECG findings of potential clinical importance. Shifts to potentially clinically important QTF values were infrequent among patients treated with either quetiapine or placebo.

The incidence rate per 100 patient years for

QTF increases of greater than or equal to 60 milliseconds from baseline and shifts to greater than or equal to 500 milliseconds appear similar to placebo. Shifts to greater than or equal to 500 milliseconds occurred at an incidence rate of 0.117 and 0.189 for quetiapine and placebo respectively.

To evaluate the risk of serious ventricular arrhythmia in sudden cardiac death, we searched the clinical studies database using a standardized set of adverse event terms that may suggest a significant proarrhythmic effect or a QT prolongation. QT prolongation is a qualitative marker for potentially fatal ventricular tachyarrhythmias, including a form of polymorphic ventricular tachycardia known as torsades de pointes. Among the terms included in the standardized broad list of adverse events are syncope related terms. Syncope is a recognized adverse event of quetiapine due to its effects on blood pressure and is not necessarily indicative of proarrhythmia.

As you can see in the top half of this table, in the initial analysis that includes the reported adverse events of syncope, there appears to be an increased incidence rate for quetiapine versus placebo; however, the majority of the adverse events were syncope related terms. When the adverse events of syncope and vasovagal syncope were excluded from this analysis, the incidence rate for quetiapine was similar to placebo. There were no cases of syncope temporally related to adverse event reports of QT prolongation. Importantly, there were no reports of ventricular fibrillation or torsades de pointes reported for the 26,454 patients treated with quetiapine in the clinical studies program.

Consistent with the preclinical, clinical and post-marketing data, the analyses discussed today do not identify a higher risk for sudden cardiac death associated with quetiapine as compared to placebo, and the data demonstrate that there is no difference in all-cause mortality between quetiapine and placebo.

In conclusion, we have looked across our entire quetiapine database, which included more than 26,000 patients in short and longer-term clinical studies across all indications and doses up to 800 milligrams per day. When considered in total, the risks of tardive dyskinesia, metabolic changes,

including cardiovascular adverse events, and sudden cardiac death have been well quantified within the limitations of the clinical program and provide sufficient data to inform the label, medication guide and risk management plans.

AstraZeneca Chief Medical Officer Dr. Howard Hutchinson will now discuss the benefit-risk assessment and the risk management plan.

DR. HUTCHINSON: Thank you, Dr. Rak, and good morning.

My name is Howard Hutchinson, and I'm the Chief Medical Officer for AstraZeneca. In my role, my most important responsibility is the ongoing benefit-risk assessment for our marketed products as well as our products in development. Given the importance of risk management in helping us to maintain a positive benefit-risk profile for our drugs, I wanted to be here today to discuss how we would continue to ensure the safe use of quetiapine in patients with major depressive disorder or generalized anxiety disorder if approved for the treatment of these

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indications.

As you heard, quetiapine was extensively studied in over 26,000 patients in our development program, and over 22 million patients have been prescribed quetiapine worldwide. Over 6,000 patients were studied in our MDD and GAD programs. We believe that the results of these studies support a benefit-risk assessment for a dose range of 50 to 300 milligrams in both MDD and GAD. We recognize that the potential benefits of a 300 milligrams dose in GAD are less clear, but the dose may offer value to some patients.

The potential risk of quetiapine use in MDD and GAD are no different from those observed in schizophrenia and bipolar disorder, as you heard today, where the drug is already approved, and these risks are identified in the existing labeling for quetiapine. In addition, our safety database in MDD and GAD suggests that the incidence of some of these risks may be less because of the lower doses used in the treatment of these disorders. Importantly, our development and marketing experience indicate that the risk can be

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managed or minimized, and an appropriate risk management plan will help in this regard.

Note that we are not looking to promote the use of quetiapine for all patients with major depressive disorder or generalized anxiety disorder. Our programs study patients with moderate to severe disease, and our goal is to provide a safe and effective option for patients where first-line therapies may not be appropriate.

Let me briefly discuss with you some of the elements of our risk management plan for MDD and GAD. AstraZeneca's plan includes both risk assessment and

risk minimization activities. Risk assessment involves appropriate pharmacovigilance and post-approval studies. Our risk minimization activities start with a label that properly communicates benefit and risks, as well as a revised medication guide. In order to reinforce our risk management plan, several educational activities will be employed.

Let me give you a little bit more information on each of these three important parts of our risk management plan.

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With regard to risk assessment, AstraZeneca has well established methods of pharmacovigilance. Our safety surveillance activities include collection and evaluation of safety data from spontaneous post-marketing reports and a review of FDA's adverse event reporting system. We monitor for new safety signals as well as changes in existing signals for the serious reports of tardive dyskinesia, diabetes, cardiovascular events and sudden death. Questionnaires are sent to the reporter to obtain additional information to further evaluate the report.

AstraZeneca employs a benefit-risk team that meets regularly to monitor the safety profile of quetiapine. This team identifies signals and evaluates issues and inform the labeling and/or interactions with regulatory authorities. We submit aggregate safety reports to the FDA annually in our periodic safety updates.

Now, the second method we will use for risk assessment is appropriate post-approval studies. As you are aware, FDA expressed concerns about the potential longer-term risks related to metabolic

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changes and the possibility of tardive dyskinesia in an expanded patient population. With this in mind, we intend to conduct additional studies, examining the longer-term risks for tardive dyskinesia, diabetes, cardiac events and mortality.

Designs currently under evaluation are shown here. One design is a prospective, large, simple trial, where patients are randomized between quetiapine XR and usual care. Following randomization, all patients will be treated and followed according to usual clinical practice. A second design option is a prospective observational cohort study, where patients receiving quetiapine or usual care will be treated according to usual clinical practice and followed.

In addition to these proposed studies, AstraZeneca has two ongoing observational studies. Both studies include patients with a diagnosis of bipolar disorder or schizophrenia, but these studies can be modified and extended to include MDD and GAD patients. The outcomes evaluated in these studies will provide additional information on the risks we're discussing today. Currently, AstraZeneca is seeking

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advice from the FDA on study designs that will contribute the most robust and meaningful risk management information on the long-term risks of quetiapine.

Risk minimization for any drug begins with appropriate labeling. As you saw earlier in Dr. Rak's presentation, the labeling for quetiapine XR clearly communicates the risk of tardive dyskinesia and contains instructions to the prescriber on how to identify and manage the risks. In addition, weigh gain and information on fasting blood glucose, total cholesterol and triglycerides are in the warnings and precaution section of the label. These warnings inform the prescriber that patients with diabetes, or those with risk factors with diabetes, should undergo blood glucose testing before and during treatment. It includes recommendations for prescribers to monitor all patients for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia and weakness. And finally, the current label also displays the changes in metabolic parameters seen in clinical studies with quetiapine XR. This information gives prescribers

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insight into the potential changes that may be seen in their patients.

To provide an additional level of risk minimization, AstraZeneca proposed a revision to our approved medication guide, which was tested with patients. The medication guide informs patients about potential risks, including hyperglycemia, diabetes, hyperlipidemia, weight gain, and tardive dyskinesia, and is written in patient-friendly language. The medication guide is required to be distributed by the pharmacy each time a prescription for quetiapine XR is filled. In addition, the medication guide is included with various educational materials that are left in physicians' offices or sent by direct mail.

Finally, to ensure the proper communication of safety messages to healthcare providers, AstraZeneca will conduct educational activities focused on the disorders of MDD and GAD, as well as on the appropriate use and long-term risks associated with quetiapine treatment.

At the core of all of our educational materials and activities is the approved label. Our

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methods of communication are shown on this slide. These methods have already been used successfully to communicate both benefits and risks for quetiapine in schizophrenia and bipolar disorder, so we are confident in their value. Our educational messages for patients are comprehensive and include concise messages about important risk information. Our attempt to reach the patient and caregiver takes into consideration different intervention points by using print communications, direct mail, a toll-free telephone service, a web site, and a multicultural outreach

approach. What all of these interventions have in common is that they provide the patient and the caregiver with important information, resources and practical information to encourage discussions between the patient and the doctor about important benefit and risk information.

So, in summary, I believe the risk management plan briefly outlined with you today will help ensure the safe use of quetiapine in patients with major depressive disorder and generalized anxiety disorder. It contains the important elements for risk assessment

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and risk minimization, as well as educational activities, to ensure the appropriate communication to healthcare providers and patients the risks associated with quetiapine. Major depressive disorder and generalized anxiety disorder are serious diseases with potentially devastating consequences. The evidence for benefit following treatment with quetiapine is compelling. Some risks are present, but these risks are well known, are recognizable to practicing physicians either through physical examination or laboratory testing, and they can be managed.

Quetiapine XR offers a much needed treatment option. I am optimistic about the potential for this medication to help patients with major depressive disorder and generalized anxiety disorder, and I look forward to the Committee's discussions today.

I will now turn over the podium to Dr. Alan Gelenberg of the University of Wisconsin, who will provide a clinician's perspective for today's discussions. Thank you.

DR. GELENBERG: Thank you, Dr. Hutchinson, and good morning.

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I'm Alan Gelenberg of Healthcare Technology Systems and University of Wisconsin. I've been a practicing psychiatrist for 36 years. Today I am here to address the question, is there a need for a new medicine to treat major depressive disorder and generalized anxiety disorder, one with a distinct mechanism of action and a profile of adverse events different from existing therapies.

For both men and women worldwide, depression is the leading cause of disease burden as reported by the World Health Organization in 2008. GAD causes as much impairment as major depression and may also increase the risk of suicide. When GAD and MDD coexist, as they commonly do, the level of disability days is much higher than for GAD or MDD alone, and considerably higher than in people who do not carry these diagnoses.

GAD impairs people's ability to work, diminishes their lives at home, and compromises their relationships with others. This study by Allgulander, et al. demonstrates that the greatest impairment in GAD occurs when patients are also in an episode of major

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depression. GAD patients typically go in and out of episodes of depression throughout their lives. Depressed patients are also less able to care for their children. As reported by Gunlicks and Weissman, when parents recover from depression, children benefit.

MDD patients are at a specially high risk to die by their own hands. Suicide is the eighth leading cause of death in the United States. Between 8 and 19 percent of hospitalized MDD patients eventually commit suicide. In adults, a GAD diagnosis more than doubles the likelihood of a suicide attempt. Treating depression appears to reduce the suicide risk. Among Star*D patients, achieving remission substantially and significantly decreases the likelihood of treatment emergent suicidality.

In addition to suicide, depression threatens lives in other ways. People with cardiovascular disease or diabetes face an increased risk of dying if they are also depressed. Even people without an underlying illness are at greater risk for sudden cardiac death when they are depressed. Beyond that, depression typically leads to poor health habits and

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lower motivation to seek needed medical care and follow doctors' advice.

Why don't depressed patients follow doctor's advice? Recently, a patient advocate who had suffered many bouts of depression told doctors that depressed people often do not wish to take steps to prolong their lives. On the other hand, GAD patients do seek medical attention to calm their constant fears and address their worries, but these patients often define their problems around physical symptoms and seek medical diagnoses from non-psychiatric physicians.

For both MDD and GAD, chronicity and recurrence are the rule. Of the MDD patients in Star*D, 25 percent were chronic and 75 percent were recurrent. In the recently published Baltimore ECA study, it was reported that half of first episode patients recover, 15 percent become chronic and unremitting, and 35 percent become recurrent. GAD also is a chronic condition, as confirmed by the Harvard/Brown Anxiety study. Symptoms wax and wane, but full remission is uncommon. Only 38 percent of GAD patients can expect a remission over the course of five

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years and relapses are common. For both MDD and GAD, long-term care is usually required.

The Holy Grail for the treatment of depression and anxiety is to personalize intervention. Someday we should be able to diagnose biologically distinct diseases that underlie the syndromes of major depression and generalized anxiety. For the time being, however, we are left with empirical algorithms. Current treatments leave considerable unmet needs. For MDD patients in Star*D, the remission rate after

Phase I treatment, open- label citalopram, was only 28 percent. Patients who went through all phases of Star*D had a remission rate of 67 percent. This means that even with optimized treatment, a third of MDD patients do not achieve remission; only 30 to 60 percent of GAD patients in clinical trials achieved remission.

Another unmet need of MDD and GAD patients concerns how rapidly antidepressants work. Today's antidepressants typically take several weeks to show initial onset and additional weeks to achieve maximum therapeutic benefit at a given dose. Benzodiazepines

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can alleviate anxiety and insomnia earlier than antidepressants, but carry their own burdens of side effects and risks of dependency. Existing antidepressants have their own adverse effects. Both SSRI and SNRI antidepressants cause a high degree of sexual dysfunction, which troubles patients and often leads to abandonment of the therapeutic regimen. Weight gain, sweating and insomnia also can be bothersome and affect adherence to treatment. SNRIs may cause hypertension.

In the elderly population, special concerns are risks of bleeding, osteoporosis and resulting fractures and they syndrome of inappropriate antidiuretic hormone secretion. Recent evidence suggests that, like tricyclics, SSRIs can contribute to the development of diabetes mellitus. If a patient has undiagnosed bipolar disorder, antidepressants can have adverse behavioral consequences.

Two second generation antipsychotics have recently been approved for the treatment of MDD patients, aripiprazole as an adjunct for MDD and olanzapine fluoxetine for treatment resistant

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depression. Both bring a different range of adverse effects to play in this population. Stimulation treatments are available for more difficult MDD cases. Electroconvulsive therapy, vagus nerve stimulation, and repeated transcranial magnetic stimulation have FDA approval in MDD. Deep brain stimulation now is approved for OCD and is being studied for MDD. These treatments carry different types of adverse effects, which are not trivial.

Another intervention for MDD and GAD patients is psychotherapy. Some therapies have been studied rigorously and demonstrated to be efficacious, but even psychotherapy is not without potential to be disruptive and cause unwanted consequences. Many complementary and alternative medicines are widely used throughout the population to treat anxiety and depression. These cause their own range of adverse effects and potential interactions with prescribed medications.

Differing classes of medications are often used off label to treat depression and anxiety. Included are modafinil and other stimulants,

antipsychotics, and benzodiazepines. The Canadian Psychiatric Association guidelines for GAD treatment suggest for second-line options, imipramine, buspirone, benzodiazepines and pregabalin. Ultimately, every treatment option for MDD and GAD has its own limitations and adverse effect profiles.

Concerns about labeling an antipsychotic for long-term treatment of MDD and GAD, particularly with a likelihood of many patients taking this agent for years, reminds me that we have been down this road before. In the 1960s and '70s, there was widespread use of thioridazine, trifluoperazine and the perphenazine-amitriptyline combination, among other antipsychotics, for mild to moderate cases of depression and anxiety. Perhaps these patients could have been treated with safer agents. I saw patients with tardive dyskinesia and was troubled by the fact that they might have been spared this irreversible syndrome by better care.

A current fear is that excessive and unnecessary use of quetiapine could lead to unhealthy weigh gain, adverse cardiovascular and metabolic effects, and new and unnecessary cases of TD. Today, off label use of antipsychotics is common in the treatment of anxiety, mood symptoms and insomnia. An advantage of labeling is to open opportunities for education and monitoring.

The question that the Committee faces today is that if quetiapine is approved for MDD and GAD, is it worth the public health risk. My answer is yes. MDD and GAD are serious, painful, debilitating and life-threatening disorders. Current treatments leave many patients suffering and carry their own risks and discomforts. Non-treatment exposes patients to even greater risks. A compound with a distinct mechanism of action expands treatment options for MDD and GAD patients. Quetiapine appears to be a worthwhile treatment alternative, offering an earlier onset of benefit, a distinct AE profile that allows clinician-patient dialogue about treatment options, and a distinct mechanism of action. Clinicians, patients and their loved ones much weigh relative risks to achieve freedom from disease. There are indeed risks with quetiapine, much as there are risks with every other treatment for these conditions, on label, off label, and over the counter. Worst of all are the risks of no treatment or inadequate treatment, which is the norm for most patients with these disorders.

I believe labeling quetiapine to treat MDD and GAD could bring knowledge and improved care to what is a current and common practice. Clinicians and patients would have an opportunity to compare and contrast available treatments in terms of efficacy and adverse effect profiles and reach informed decisions. My hope

is that more patients will be successfully treated and fewer people will carry the pain and impairment of depression for years of their lives. Thank you.

DR. SCOTT: Thank you, Dr. Gelenberg.

Before we take questions from the Committee, AstraZeneca is joined today by a number of internal and external expert scientists that have been involved in the preparations for today. I'd like to make mention of Dr. James Gavin, who's the past president of the American Diabetes Association and the Chair Emeritus of the National Diabetes Education Program. You just heard from Dr. Alan Gelenberg from the University of Wisconsin; John Kane, who's professor and chair at Long

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Island Jewish Medical Center; John Newcomer, who's the couch professor of psychiatry at Washington University in Saint Louis; and Annette Stemhagen, who's the Vice President for Epidemiology and Risk Management at United BioSource.

We would now like to take questions from the Committee.

DR. GOODMAN: The schedule does call for that, but I'd prefer to take a 10-minute break first, and then come back, and then we'll engage you in some questions.

DR. GOODMAN: Great. Thanks.

(Whereupon, a recess was taken at 9:46 a.m.)

DR. GOODMAN: Hello, everyone. We're reconvening.

I see somebody else has joined us at the table.

Dr. Stone, would you identify yourself?

DR. STONE: Hi. I'm Marc Stone. I'm a medical officer in the Office of New Drugs.

DR. GOODMAN: Okay. Thank you.

We now have approximately 20 minutes for the

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panel to ask clarifying questions of the sponsor. Please limit to questions of clarification. We'll have time later for discussion. And if we don't get to all your questions, we'll have some time for that later as well.

I'm going to take the chair's prerogative and start it off. I have two questions.

Do you have an explanation for why the escitalopram versus quetiapine study failed?

DR. SCOTT: Dr. Willie Early or Dr. Hans Eriksson.

Dr. Eriksson will come up to speak to that.

DR. ERIKSSON: First of all, I'd like to say that this was the only study that failed. And as we know, it's not uncommon that studies fail in development programs for studies in MDD. We've been looking closer at the data, and we have seen some characteristics of the patients. For instance, these patients had a somewhat lower number of previous depressive episodes.

What we also found out was that the placebo response was higher in this study for -- this is an overview of the change from baseline for the placebo treatment arm. So we can see that in Study 4, this change was 15.61, so it was a relatively large placebo response. And I think it's well recognized that high placebo response often are a challenge to the demonstration of clinical efficacy in studies in depression.

DR. GOODMAN: Another question I have is, reference was made several times to quetiapine demonstrating efficacy within one week of treatment. I want some clarification of that because it's certainly true that you can look at a number of antidepressant trials, say, with SSRIs, and notice a statistically significant change between drug and placebo as early as one week. That doesn't mean that you're only going to treat patients for one week or be satisfied with the response at one week.

So I just wonder if you could clarify that statement.

DR. SCOTT: I think that we'll bring Dr. Eriksson back up to speak to that. I think we saw consistently that we saw statistically significant effects at one week across the clinical trial program.

DR. ERIKSSON: For patients with depression or anxiety, it's generally important to achieve good efficacy early on. And as we saw in the slide I showed you previously today, there was a separation already at Day 4 in this Study 1. So what we have seen here is that this is a statistically separation occurring early on during treatment. We fully recognize that the difference between active treatment and placebo here is not of the magnitude that we are seeing at endpoint. So this is a herald of an effect that is coming. And also, on the slide that will come up on the screen here right now, we can see that for all the studies in MDD -- all the MDD studies, except Study 1 and except Study 4, which was the failed study, we did see this early separation from placebo. It's important also to emphasize that this effect was associated with effect also on core items of the rating scales, both for MDD and for GAD.

DR. GOODMAN: I'll given an opportunity for the other members of the panel to speak, starting with Dr. Temple.

DR. TEMPLE: I just wanted to say we've historically been very reluctant to let people claim the first time the p value is significant for a multitude of concerns. I'm not sure we're not over-conservative on this, but we have historically been very reluctant. For example, maybe it's just the station giving you that effect and it's not really the antidepressant. So we have long been quite reserved in

allowing people to claim early success before the plan study endpoint.

DR. GOODMAN: Thank you.

Dr. Potter?

DR. POTTER: This is a variation on the same question, whether or not the sample sizes are large enough or the sponsor has had the opportunity to look at a detailed item analysis to see, given the pharmacologic difference of this compound from the comparators, whether or not you could distinguish through an item analysis any difference in the pattern of response ultimately, or anything to suggest that there is a unique therapeutic difference with this compound versus either duloxetine or citalopram or

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anything else you might have out there.

DR. SCOTT: We have looked at the individual item analyses, and I think what we said at the start is we're not seeing -- the trials are being conducted with positive controls, were there for positive controls. They weren't to distinguish quetiapine from placebo with them. But we have looked at the individual item analyses for quetiapine.

I'll bring up Dr. Willie Early, who's looked at this very closely.

DR. EARLY: Good morning, everyone. My name is Dr. Willie Early, and I'm a psychiatrist with AstraZeneca.

We have looked at the item analysis for each of the studies in the MDD and GAD program, and what we have shown is really that we really do see efficacy not just on the sedation. And I know that that point was raised earlier, if the earlier effects were with just sedation or were the other 10 items affected. And so, what I want to show you is the item analysis for Studies 1 and 2 combined. And what it shows is that not only do we see it on sedation, as mentioned, but we

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also see at an anxious mood, intention -- or apparent sadness and reported sadness in the MDD program.

In comparison to duloxetine, which also separated -- it's not shown in this slide, but we see a separation on similar items. Essentially, we had 8 of the 10 items separating on MDD, and when we compare that with GAD, in the GAD program, what we show is that in the 50 and 150 milligrams, we have 13 out of 14 items showing separation from placebo on individuals items that are hand made. This contrast favorably with escitalopram and paroxetine, where only 6 of the 14 items separated.

DR. POTTER: So the specific question, though, was, was the item analysis different or not, or did you just not have enough numbers to look at that? In other words, was the shift of the items, in terms of improvement, different with this compound than it was with duloxetine or escitalopram?

DR. EARLY: Well, in the first -- in

duloxetine, which is Study 2, we did see the shift in that first week. We didn't do an item analysis for -- we don't have that slide for the first week, but

we do know is that in that first week, duloxetine and quetiapine -- quetiapine separated from placebo whereas duloxetine did not, in that first week.

DR. GOODMAN: Dr. Harrington?

DR. HARRINGTON: I want to begin to try to understand the cardiovascular and the metabolic issues here, so I have a series of questions that I'll throw out to you.

First off, in the Pool A data safety set of 26,000 patients, can you be more specific about how many are elderly patients? Let's define that as above the age of 65. How many had known coronary disease, known heart failure, previous myocardial infarction, previously revascularization procedures, et cetera?

Do you have that demographic data?

DR. SCOTT: I know we've looked at that data set very closely.

Dr. O'Dowd or Dr. Bjork.

DR. BJORK: Good morning. My name is Elizabeth Bjork, and I'm an endocrinologist working for AstraZeneca, and I'm hoping to get up the slides with the demographics for the Pool A, the bigger pool. This

is the slide showing the long-term exposure. I was hoping to get the baseline demographics.

DR. HARRINGTON: While they're searching for that, perhaps they could start searching for the second piece of data that I'm interested in, which is we hear about these weight outliers, these glucose outliers, these lipid outliers.

Are these different people or does everything track with the weight? In other words, is the weight the key variable that needs to be considered from the practitioner's perspective?

DR. BJORK: I think that's a very good and important question. And when we had looked at our data, we couldn't find a clear correlation between the increase in weight and the increase in blood glucose. Having said that, when you look at baseline BMI, that is a very clear predictor of the changes in glucose.

DR. HARRINGTON: So the changes in the metabolic parameters don't necessarily track together.

DR. BJORK: Correct.

Do you have the demographic data for me?

DR. SCOTT: Do we have the demographic data?

We're still searching for it, and if we have it, we'll get it for you.

DR. HARRINGTON: Okay. That's fine.

Could I do one more question?

So I think it was your chief medical officer, I'm sorry, Dr. Hutchinson. In his presentation, he made note of the fact that you have this large, what is

it called, Sapphire database, 22 million people have been estimated to have been treated with the drug. But you didn't present us any data from that database.

Do you have any data that might be informative on the metabolic consequences of the drug, the sudden cardiac death issues, et cetera? I understand the limitations of observational data, et cetera, but it is a rather large data set.

DR. SCOTT: All right. I'll bring up Dr. Bjork to speak to those points. But the Sapphire database is, therefore, like the AERS database, is there for signal detection. And signal detection then leads us to clinical trials, other epidemiologic investigations.

So Dr. O'Dowd will come up and speak to that.

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DR. O'DOWD: Good morning. My name is Lisa O'Dowd. I'm an intensivist, and I work in Clinical Neuroscience at AstraZeneca.

What I'll start with is the AERS data for sudden cardiac death because I think it's one of the questions that you asked. So they didn't know what I was going to come up with first. I'll give them a second to cue up the slide.

When we looked at the AERS database, we looked at a couple of different trends. We looked at a bucket of seven cardiac death terms, very similar to that which we described in our briefing document. We also looked at terms which would suggest a potential proarrhythmic event. So we looked at the standard medical query for ventricular tachyarrhythmias.

As this panel I'm sure well understands, AERS data is good for signal generation. And what these numbers present is not absolute risk but rather look for signals of a potential event. So these numbers shouldn't be looked at -- only for signal detection, and that we look for numbers -- in AstraZeneca, we look at 1.8 events at signal detection.

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So for sudden death terms with quetiapine, we have an EB05 of 1.21, which below the 1.8 level that we look at. Similarly for terms of ventricular tachyarrhythmias, we have an EB05 of .738. I could also tell you that the individual terms were 1.8 or below for all the individual PTs that contributed to these events.

You also asked for AERS data regarding cardiovascular events, and we can provide that data for you as well. And I can tell you the findings are actually very similar. There is no evidence of the signal. I'll get to the exact numbers in one second.

DR. TEMPLE: You need to make it clear. These are data mining analyses.

Everybody know that?

DR. HARRINGTON: I understand that, yes.

DR. TEMPLE: Okay, fine.

DR. O'DOWD: Okay. Again, for quetiapine, for

the SMQs of ischemic heart disease, myocardial infarction, both the broad SMQ as well as the narrow SMQ, just more specific, we don't see a signal in the AERS database.

DR. HARRINGTON: Thank you.
DR. GOODMAN: Okay. Dr. Neaton?
DR. NEATON: I have three questions. Maybe I'll just start with two, that kind of build on two of the earlier questions, just to stay with the cardiovascular events.
You showed a slide where you looked for terms related to atherosclerotic cardiovascular disease. Could you just tell us how you collected these data? And specifically, when people stop taking treatment -- and as I understand it, about roughly 20, even up to 30 percent of people, stop taking treatment, even during the shorter-term phases.
Were adverse events of this nature collected afterwards and for how long?
DR. SCOTT: These were getting adverse events, reported adverse events, in our clinical trials. I know we have as part of our protocol's follow-up periods. And Dr. Early's about to speak to how we followed cases across our clinical trial program.
DR. NEATON: I mean, the reason for asking is the metabolic effects might be presumed to have effects on cardiovascular disease sometime after you stop the therapy. And so if you stop a -- quit collecting the data, I guess I'd like to be certain about that.
DR. EARLY: Within the MDD and GAD program, we had a two-week follow-up period.
DR. NEATON: I see.
DR. EARLY: And so within that two-week follow-up period --
DR. NEATON: Pretty short.
DR. EARLY: -- we had a --
DR. NEATON: All right.
My other question, built on that, was concerning the questionnaires. And so the range in these scores is up to 56 and 60.
Can you help me put into some clinical context the differences that were seen in the studies, which I believe were around 4 or 5 for the MADRS and 2 or 3 for the Hamilton, and how that kind of relates to the morbidity, days lost from work, and other things that were highlighted in the other presentations. I mean, help me understand the significance of these small differences.
I understand, I think, from other literature what the differences in glucose and weight and cholesterol might mean, so what does this mean?
DR. SCOTT: I think we'll have Hans Eriksson to come up and speak to what we found in our clinical trial program, and then bring Dr. Alan Gelenberg up to

speak to the clinical relevance as well.
DR. ERIKSSON: I think the effects we have seen, both in MDD and GAD, are very much in line with the effects at endpoint that have been seen in other studies.
DR. NEATON: I'm not really interested in what other studies have shown. I'm more interested in terms of what this means clinically for patients with these conditions.
DR. ERIKSSON: Yes. I would like to show some data on response and remission if I could get that slide, please.
When we are showing a slide like the one that is on the screen right now, we are talking about changes on a population level, mean changes. I agree with you, it's important to translate that into

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something that is meaningful for an individual patient. And for that reason, we are using more of a patient-centered approach, looking at the proportion of patients who fulfill criteria for response or remission.
This slide that's coming up here now shows the improvements in the MADRS response across the MDD studies. So these are patients who are having at least a 50 percent improvement from their baseline score. And this is something that should be interpreted as a clear significance for the individual patient to achieve this score. Perhaps even more informative, is going over to look at remission.
As I said previously, we used a very stringent remission criteria of a MADRS of 8 in our studies. And I think most psychiatrists would probably agree that having a MADRS score of 8 is being virtually free of significant depressive symptoms. So what we can see here is a proportion of somewhere of 20 to 40 percent of patients become virtually free of depressive symptoms.
DR. NEATON: This is fine to use this, too,

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but the net difference between placebo and active drug here is about 10 or 15 percent. And so help me understand that.
DR. SCOTT: I'll bring Dr. Alan Gelenberg back up to speak more about interpretation.
Please?
DR. GELENBERG: Well, let me start with the good news. The good news, if you focus on the dichotomously defined group of patients who are in remission across all treatments in the last decade or two, that's where you see the good stuff. The good outcomes will be the return on investment in terms of work productivity, quality of life enhancement, and data that I only saw recently from Star*D, and that is the actual reduction in suicide attempts. So the good stuff happens with patients who achieve remission.
The bad news is this waning signal of active

treatment against placebo in the last decade or more, and a number of people in the room, Dr. Potter's done a lot of work on the issue of signal detection. If we took away drugs that only beat placebo by 2 to 3 Hamilton or MADRS points, we would go back to the 1940s. I mean, we would lose all of our currently approved agents because we beat the .05 by powering up to very large sample sizes. That's been a product of recent years at the rising placebo rates and difficulty with clinical trials. More than 50 percent of antidepressant trials fail.

DR. NEATON: Okay. Maybe I can just go to a third question, then we can come back to this later.

You showed a slide from your withdrawal study, and either one is okay. I think the one I'm looking at is on -- I guess the 11th slide possibly, in the core safety -- reducing the risk of relapse, and this could be for MDD or it could be for the other condition, the anxiety condition, the GAD. I think that was on Slide 89. The GAD one is probably the most dramatic one.

DR. SCOTT: It's coming up.

DR. NEATON: This is the maintenance phase, and the Kaplan-Meier curve.

DR. SCOTT: This one, Study 5.

DR. NEATON: This one or the other; they're pretty similar. And so I was thinking about the title of this, and I'm not sure that I kind of buy it, so convince me.

Isn't there a concern about the exacerbation of symptoms when you stop treatment? So one way of interpreting this study is that when you stop treatment, after achieving kind of a good response, very rapidly you have renewed symptoms. And so I'm not sure that -- you're reducing the risk of relapse, but another important feature of this, which I don't fully understand from your data is, what are the risks to the patients when they stop therapy, for whatever reason?

DR. SCOTT: Well, we can address the first part. We have looked at that. Because of the pattern of relapse we're seeing, we have looked at what happens among patients who didn't relapse during the first 14 days.

Dr. Early, you can come up and speak to that.

DR. GOODMAN: Dr. Laughren, you also had a comment on it.

DR. LAUGHREN: I think they're going to say --

DR. EARLY: That is a very good question. And, in fact, we consider that as well. So what we had done is took in consideration, within the MDD program, we looked at an analysis, looking at patients who had events after 28 days of exposure. And then within the GAD program, we looked at after 14 days. And so in both instances, it showed similar effects that

separation from placebo was still significant.
DR. GOODMAN: Dr. Temple, then Dr. Greenway.
DR. TEMPLE: I just want to say, we worry about withdrawal effects, but the general idea, when you're talking about a withdrawal effect, you're talking about something that happens relatively rapidly. Paxil is famous for having a lot of withdrawal effects. But in those cases, you probably should titrate the withdrawal, which we ask people to do sometimes. But as was just said, if you still see recurrence late, that's reassuring that it's not just a withdrawal effect; although, of course, when you take the drug away, the disease might come back. I mean, I don't know if that's a consequence of withdrawal or consequence of the drug not being there anymore.
DR. GOODMAN: Dr. Greenway, then myself, and then we'll turn to the FDA presentations.

Dr. Robinson, you had one, too? No.
Dr. Robinson as well.
DR. GREENWAY: I just wanted a clarification on Dr. Harrington's question.
It's usual, when people gain weight, to see a trend upward in triglycerides, a trend towards a reduced HDL and rising glucose. And I thought the answer to that was that these are all different patients.
Is that really true? Isn't this being driven by the weight gain?
DR. SCOTT: Could you repeat the question, please?
DR. GREENWAY: Well, I think that -- if I understood it correctly, when Dr. Harrington asked about is weight gain driving some of these metabolic problems, like the rise in triglycerides, and the rise in glucose, and the trend towards a reduced HDL cholesterol, that these were different people, and they weren't being driven by weight gain.
DR. SCOTT: I'll have Dr. Bjork come and address that question, and then perhaps Dr. Gavin.

DR. HARRINGTON: That was, Dr. Greenway, the essence of the question because if in fact there's something different, that they're in different people and we don't necessarily understand why HDL's dropping, LDL's dropping, that could be problematic in terms of monitoring people. It required much more intensive monitoring, as opposed to just noting that they're getting heavier.
(Dr. Greenway nods yes)
DR. BJORK: What we did see in these studies, we were not able to demonstrate a clear correlation between the changes in the different parameters. Having said that, of course, many of the patients had changes that went together. But often like that, that if you saw a big change in one parameter, that that always went together with a big change in the other

ones. But many of these parameters of course correlated.

Maybe I can ask my colleague, Dr. John Newcomer, to come up and command further on the correlation and interactions between these parameters.

DR. NEWCOMER: John Newcomer, Washington University School of Medicine. I think this is an important question, but what I would emphasize is that in large data sets, whether it's our NIH funded data set or an industry funded data set, if you look cross-sectionally at the correlation between body mass index or some direct measure of adiposity or body weight, and any of the metabolic parameters of concern, triglyceride levels, you will find a very powerful correlation. When you go to look for the correlation between change in one of those variables and change in the other variable, now you have a real statistical problem because the variance around one of those items, something like body weight, is very different than the variance around something like triglyceride. So it's very hard to achieve the statistical significance.

I don't think that that undercuts what we know about physiology, that increases in adiposity are going to drive that signal in populations. But I think that when this company or any other goes to look at the correlation between change scores, they're not going to find it.

DR. GOODMAN: Thank you very much.

Dr. Temple?

DR. TEMPLE: I have one slightly different question.

The proposed labeling is for people in whom first-line therapy is not appropriate. That implies that that has two components; people don't tolerate the other drugs or you don't want to give them to them, and people who don't respond to the other drugs.

In depression, you actually have a study showing that when you add on to the drug that didn't do very well, you actually get a response. So that's pretty good. You don't have a study like that in anxiety. And I just wondered whether you were thinking of doing either that kind of study or the study that I promote all the time and no one ever does, which is to take the drug people failed on and randomize back to that drug or the new drug, and show that you've actually identified a population that responds to the new therapy, which is really what Dr. Gelenberg was talking about. We all believe in individualization, but, in fact, no one ever demonstrates it because no one ever does that study.

Were you thinking about that?

DR. SCOTT: We have actually a study that has recently completed -- we don't have the data here. The data hasn't been final as of yet, but quetiapine as an

adjunct antidepressant in GAD. So that study's being finalized.

Now, as for the broader question, when we had the discussions back in 2005 about this development program, we chose to have an all-comers program. And recognizing the potential risks for quetiapine, I think physicians realize that when they look at the data we have right now, they're seeing it not as a first-line agent. And so we're kind of caught between the right patient and the development program that we did. So we hope the discussion here might be able to inform, is there labeling like that we could perform on the basis of the data that you've seen today.

DR. TEMPLE: So you would at least consider doing the trial I asked you about, that is, take people who don't do very well on something else, randomize them both to that and to the new drug, and see if you found a subpopulation that responds to one drug but not

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the other.

DR. GOODMAN: You'd have to get that through IRB, too, Dr. Temple.

DR. TEMPLE: Okay. Put me on the IRB; it'll go through.

DR. SCOTT: We have to have that dialogue with you to see what's the best way we can achieve that.

DR. GOODMAN: We're running a little bit behind schedule. I want to give Dr. Robinson and myself the last chance to ask questions before we move on.

DR. ROBINSON: In the sort of schizophrenia literature, in terms of the metabolic side effects, they seem to be much worse in younger patients. I'm struck with like your own CAFE trial, where the metabolic outcomes for young patients were much, much worse than what you've been -- what you've presented for the group.

So I was wondering, do you have data in terms of the MDD and GAD populations for people like under 40, which is the oldest you had in CAFE?

DR. SCOTT: Dr. Bjork.

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DR. BJORK: We have not specifically looked at the metabolic parameters across the ages. 4A (ph.) is for example, and also 4A is related to diabetes. They seem to be similar across the ages, but we haven't looked for the metabolic parameters that way.

DR. ROBINSON: Well, because I was concerned, in CAFE you got a 52 point increase in triglycerides after 12 weeks of treatment for people under 40. So you haven't looked at all about the triglycerides?

DR. BJORK: Not for age.

DR. GOODMAN: Okay. In Dr. Gelenberg's presentation, there was a slide in which you seemed to be making the case that there's already widespread use of long-term antipsychotics in both GAD and major depressive disorder, and we might as well go ahead and

approve them because at least, then we'd have some measures in place with labeling and monitoring.

One of the questions I had about that slide is, in my own experience, my own clinical experience, I don't see much use of antipsychotic monotherapy for either GAD or major depressive disorder. So I wanted to see if you had any other data that would suggest otherwise.

DR. SCOTT: I don't have any data at all.

Dr. Gelenberg, you want to come up? That's fine.

DR. GELENBERG: No, I don't have data, Dr. Goodman. I wasn't saying, just for clarification, that since there's widespread use, so we might as well just go ahead and approve it. The leap there is that I think it certainly requires demonstration of efficacy and acceptable safety. But in terms of the actual data, it's probably out there in terms of prescription patterns.

My personal experience would square with yours, that I think it's seldom used by primary care doctors or psychiatrists as single therapy. I think most commonly with antipsychotics, particularly the more sedating ones, they're used for anxiety, agitation and insomnia, as add-ons.

DR. GOODMAN: Okay. Thank you.

Ms. Lawrence, I'm going to give you the last word, and then we're going to move on to the series of FDA presentations, which we'll start with Dr. Ray.

MS. LAWRENCE: In following Dr. Robinson's comment and question, has there been any study in patients with schizophrenia under the age of 40 for adding to their life span in using this drug in combination with other drugs, as far as metabolic and the sudden death?

DR. SCOTT: We have completed a study in adolescence that's been submitted to the Agency that will be reviewed at an FDA advisory committee in June of this year.

MS. LAWRENCE: Not in adolescence, but say 20 to 40?

DR. SCOTT: Not in that specific patient population.

DR. GOODMAN: Okay.

Is Dr. Ray here?

You must be Dr. Ray. Welcome.

DR. RAY: Thank you very much for inviting me to present our recent study. Sudden cardiac death has been defined as the unexpected natural death from a cardiac cause, heralded by an abrupt loss of consciousness within a short time period, generally less than one hour from the onset of symptoms. It is a cause of death that accounts, according to some data, for the majority of cardiovascular deaths with more

than 400,000 each year. Some studies suggest that 85 to 90 percent of these deaths result from ventricular tachyarrhythmias and medications may contribute to the risk of these underlying arrhythmias.

Typical antipsychotics have long been suspected to cause or increase the risk for sudden cardiac death with case reports dating back to 1963. Many typical antipsychotics have electrophysiologic effects that are consistent with an increased risk for sudden cardiac death. There have been numerous case reports of torsades de pointes and sudden cardiac death among users of typical antipsychotics, and four separate epidemiologic studies, one conducted by us, have demonstrated increased dose-related risk for sudden cardiac death with typical antipsychotics.

When the atypical antipsychotics were introduced, there was hope that these newer agents would be less likely or would not at all increase the risk for arrhythmias and sudden cardiac death.

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However, the atypical antipsychotics have electrophysiologic effects that overlap with those of the typical antipsychotics, and indeed, there have been case reports of torsades de pointes with atypical antipsychotics, including a published report for quetiapine.

This slide shows data from one electrophysiologic effect, the study of the blockade of potassium channels. And all I wanted to point out from this slide is that the effect on the potassium channel of one atypical antipsychotic, risperidone, is very similar to that of a typical antipsychotic, thioridazine, well recognized to increase the risk for sudden cardiac death. And similarly, there are data from the few comparative studies of antipsychotics and their effect on the QT interval that, again, suggest overlapping. In this particular study, although the numbers were small and several of these were not statistically significant, but you see the effects of typical antipsychotics, such as haloperidol and atypical antipsychotics clearly overlapping.

Now, of course, these are surrogate endpoints,

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and they may or may not predict a true risk of increased risk for ventricular arrhythmias or sudden cardiac death. And so the question we undertook to address was do typical and atypical antipsychotics differ with regard to the risk of sudden cardiac death. And this study was conducted as a retrospective cohort study for the period 1990 to 2005, and we conducted it in the Tennessee Medicaid population, using an extensive computerized database. We used this database because there was a defined population characterized by an enrollment file. We had records of prescriptions filled at the pharmacy, which for large populations serve as an excellent surrogate for medication exposure. We had information on hospitalizations,

outpatient encounters and death certificates, which allowed us to construct a definition for sudden cardiac death.

This slide depicts schematically how this study worked. The X axis here is time. And we began by identifying all users in the study population of antipsychotics, and we set the first day of follow-up, or T-knot, as close as possible to the beginning of

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antipsychotic use. We then required, prior to T-knot, a 730-day baseline period, which allowed us to collect information on covariates that were indicators of important potential comorbidities.

We then, subsequently, for each day of follow-up, classified the cohort member according to likelihood of antipsychotic use. Current users were those for whom the information on the filled subscription suggested that they were actually likely to be taking the antipsychotic on that particular day. Once the prescription supply lapsed, the persons went into a period of indeterminate use and then ultimately became former users. The former user group is important because they may resemble current antipsychotic users more than non-users.

For each antipsychotic user in the cohort, we then matched two non-user controls according to the data follow-up age and gender. For both antipsychotic users and controls, the following inclusion-exclusion criteria applied. Age, between 30 to 74 years of age. The younger persons were not studied because sudden cardiac death is a somewhat different phenomenon in

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this age population and is also extremely rare. We had an upper age limit of 74 because the computer definition of sudden cardiac death that's used was found to be less accurate in older populations. Similarly, the cohort excluded persons in nursing homes because our experience suggests, again, that our case definition for sudden cardiac death is less reliable in this population.

Further requirements were a full two years of enrollment prior to baseline. To ensure that everyone in the cohort was under medical surveillance, we required in each of the two years proceeding T-knot a filled prescription and some kind of outpatient medical encounter. We excluded persons with non-cardiac, life-threatening illnesses, such as cancer, HIV, and we also excluded persons with evidence in the files of recreational drug use.

For each cohort member, follow-up began at T-knot and terminated at the end of the study, when the person no longer met the inclusion-exclusion criteria, with enrollment loss, or death. Person time excluded hospital stays and the subsequent 30 days. We studied

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sudden cardiac deaths that occurred in the community. For that reason, hospital stays were excluded, and,

furthermore, the database of prescriptions filled at the pharmacy did not include medications received in the hospital. And for that reason, we excluded the 30 days following hospital discharges.

So for our study, there are really two definitions that have to be kept in mind for sudden cardiac death. The first was the clinical definition, and that was defined as a sudden, fatal, pulseless condition, or collapse, occurring in the community, consistent with a ventricular tachyarrhythmia, occurring in the absence of a known, non-cardiac cause as the proximate cause of death. And this excludes deaths in the hospital, those that were not sudden, those that there non-cardiac or of a different cardiac etiology.

For the purposes of this study, which is a very large study, we constructed a case definition using information available in the computerized files. For this definition, we began with death certificates and looked for deaths that were not in the hospital,

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and that had a cause of death compatible with sudden cardiac death and, indeed, had a relatively high positive predictive value.

For example, our previous work has found that deaths with an underlying coded cause of diabetes, that about 40 to 50 percent will actually be sudden cardiac death if they occur out of the hospital. We did not include that in our case definition because it had a low positive predictive value. On the other hand, a death coded as myocardial infarction that occurs out of hospital has a high likelihood of meeting the clinical definition for sudden cardiac death, and so it was included. We further excluded deaths for which there was emergency department care on the day of death, such as thrombolytic therapy, that was inconsistent with sudden cardiac death.

We validated the computer case definition by medical record review, and this was done for two separate databases, one from 1990 to 1993, using a previous study, and one from 1994 to 2005, using a sample from the cohort that I'm presenting today. And in both cases, the positive predictive value was

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between 86 and 87 percent. And for the sample from the cohort I'm presenting today, the positive predictive value did not vary according to antipsychotic use.

One important clarification. We classified a death as sudden cardiac death if it met our criteria for either probable sudden cardiac death, which meant that there was a witnessed collapse or that the person was seen alive less than one hour prior to death. But we also, as have done other studies, included possible sudden cardiac deaths, which means that the person had been seen less than 24 hours previously alive. Approximately 62 percent of the deaths accepted were probable and 38 percent were possible.

We controlled for an extensive set of potential confounders. These included demographic factors. Within the database, we identified more than 60 variables that were potential markers of cardiovascular comorbidity. These included drugs, such as a prescription for insulin; diagnoses, such as a prior diagnoses of heart failure; and medical care utilization. And we essentially used statistical techniques to combine these covariates into a single

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cardiovascular risk score. And this was helpful for purposes of describing the cohort were the antipsychotic users at different baseline cardiovascular risk than the non-user, as well as facilitating statistical analysis. We collected extensive information on baseline psychiatric and neurologic comorbidity, to the extent that it had been diagnosed, and we measured changes in these factors as well as hospital admissions, emergency department visits, and other drugs that are associated with sudden death occurring during follow-up.

So at baseline, we had identified 93,300 antipsychotic users, about half typical, half atypical, and 186,600 controls. Demographically, the characteristics of these populations were relatively similar. The mean age was 46. About 35 percent were male. And the clinicians are probably wondering why this is, and this reflects the fact that it's set within a Medicaid program, which for this age group gives preferential enrollment to females.

The antipsychotic users did have a higher prevalence of enrollment due to disability than did the

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controls. Interestingly, the baseline cardiovascular risk score, in high numbers indicate a greater degree of risk, was slightly higher for the non-users than for the antipsychotic users. However, it was a different story with regard to psychiatric characteristics, as you would expect. The antipsychotic users had much greater rates of diagnosed schizophrenia and related psychoses, affective disorders, and other types of psychiatric conditions in use of psychiatric medications.

The study cohort had slightly more than a million person years at follow-up. During that million persons years at follow-up, there were 1,870 deaths that met our definition for sudden cardiac death or about 1.8 deaths per thousand person years.

This table shows the incidence of sudden cardiac death as a function of use of antipsychotic medications. And when I present the incidence rate ratios, I'm going to use this group of non-users of any antipsychotic as a reference group. We found increased risk of sudden cardiac death for both current users of the typical and atypical antipsychotics, with

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approximate doubling of risk for each group that was

highly statistically significant. And we chose a priori six individual drugs to look at, the two most interesting typical antipsychotics, and then the four atypical antipsychotics for which there were at least five expected cases under the null hypothesis. And we found significantly increased risk for each of the six individual drugs.

There was a significant dose response for both typical and atypical antipsychotics, and to help you interpret these, we converted all doses to chlorpromazine equivalence. And this group represents less than 100 milligrams; this is the 100 to 299 milligrams, and this is 300 or greater milligrams chlorpromazine equivalence. And, indeed, for both typical and atypical antipsychotics, there was a statistically significant dose response. Similarly, there was dose response, at least a trend, for individual drugs, and this was statistically significant for thioridazine. And high doses of thioridazine actually had the highest incident rate ratios, slightly above 5, and risperidone.

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One limitation of the analysis I presented is that we were comparing antipsychotic users to non-users, and that these groups differed markedly according to psychiatric characteristics. So we conducted a secondary analysis that sought to compare antipsychotic users to a more comparable group of non-users, those with a similar range of psychiatric conditions and medications. And to do that, we first excluded all persons with evidence of diagnosed schizophrenia or other psychosis because there simply are really no alternative medications for those conditions, and we couldn't compare a schizophrenic on an antipsychotic to a comparable non-user.

We then used propensity scores to match according to psychiatric comorbidity. And in this context, it's just helpful to think of propensity scores as a very efficient way to achieve matching on a large number of potential patient characteristics. And, indeed, if you look at the -- the cohort included some 68,000 users of antipsychotics and 116,000 non-user controls, and there was much better balance on psychiatric conditions with about 65 percent and

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70 percent having some evidence of an affective disorder; 15 percent, a prior hospitalization, psychiatric hospitalization; and comparable proportions, use of various psychiatric medications. The findings were entirely similar in the propensity score-matched cohort with increased risk for both typical and atypical agents and a significant dose response for both classes of medications.

We performed a number of alternative analyses to test various potential limitations. One was a new-user analysis to assure that the results weren't influenced by deaths that occur early in therapy. To

exclude potential effects of long-term metabolic changes, we conducted an analysis restricted to those with no more than -- or less than one year of total antipsychotic use. And finally, for concerns about secular trends, we restricted the study to the latter half. And in all of these analyses, the findings were very similar to those of the primary analysis.

The study had several limitations. We used a computer case definition, however, this case definition was validated in two separate medical review studies

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and found to have a positive predictive value of 87 percent, and the PPV did not differ according to antipsychotic use. Confounding we'll talk about in a bit more detail. And final limitation is generalizability. This was conducted in a Medicaid population. In some ways, that's both a limitation and a benefit. I think it's important because many persons with serious mental illness end up in Medicaid, and it's a population that has a higher comorbidity level than many other populations. So, in a sense, it's a bit like the canary in the gold mine. If there's a problem in that population, there may well be a problem in others.

Confounding was a major issue to be addressed in this study. With regard to cardiovascular disease, we think that we did a good job insofar as these conditions were diagnosed or treated. And we required, for that very reason, everyone in the cohort to have a pattern of regular encounters with medical care just to increase the likelihood that any conditions present would actually be diagnosed or treated.

Smoking is a potential concern, however, much

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of the effect of smoking will be mediated by cardiovascular disease. We conducted a sensitivity analysis that suggested that smoking could not be responsible for our findings. And finally, in the propensity score-matched cohort, we had similar findings.

Poor self-care is another issue in this population. Again, for that reason, we required the cohort to have regular medical encounters. The lack of increased risk for former users in the dose response suggests that this was not responsible for our findings, as do the similar findings in the propensity score-matched cohort.

Psychiatric illness per se, one comment, let's be sure before we blame the psychiatric illness that we're fully taking into account the medications. But in any case, in our analysis, the propensity score-matched cohort, with comparable levels of psychiatric comorbidity, suggests that this was not responsible for our findings.

So in conclusion, atypical antipsychotic users had a dose-related increased risk for sudden cardiac

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death. The magnitude of the increased risk was not different than that for typical antipsychotics. And several lines of evidence indicate that the increased risk is due to the effects of the drugs per se.

DR. GOODMAN: Thank you very much.

Let's hold questions until after Dr. Stone's presentation.

DR. STONE: Good morning.

The Vanderbilt study that Dr. Ray described to you uses death certificates to identify cases of sudden cardiac death. I'd like first to introduce some issues about using this kind of data and then some other possible explanations for his findings.

I found two published studies that look specifically at the accuracy of death certificates for identifying sudden cardiac death. The first was done in Seattle. This was a prospective study of 30,000 Seattle area patients, hospitalized for suspected myocardial infarction. They identified 407 deaths outside the hospital with complete paramedic report and death certificate data, and the paramedic finding were used as a gold standard. These are patients who are

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very likely to have good medical records and close medical follow-up. These are probably the best possible circumstances for the death certificate to be accurate.

If we consider cases where paramedics could identify definite arrhythmic cause of death, that being ventricular fibrillation or ventricular tachycardia, and an underlying cardiac cause to include a situation like electrocution, death certificates do no better than a random selection of about three-quarters of the cases. It's not just that death certificates identified cases where the paramedics could not confirm or refute an arrhythmic cause, there were no more likely to identify the cases confirmed by the paramedics, which should be slam-dunks. They missed nearly a quarter of them.

If the definition is expanded to include asystole, the performance of death certificates have improved; it's doing much better than chance. But asystole is not at all specific for a cardiac cause of death; all deaths lead to asystole. The improvement in accuracy comes from the paramedics assigning a cardiac

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cause to the death, based on information available to them. They may be able to exclude sudden cardiac death if they arrive premortem, if there's an obvious trauma, or if there's someone who can provide a history. But in other cases, all they may be able to find out is that the deceased had been hospitalized for heart problems or find a bottle of nitroglycerin at the scene. Cardiac death could be just a circumstantial or presumptive diagnosis made by exclusion. Note that even when paramedics could identify a different cause of death, death certificates still identified them as

sudden cardiac death in over 40 percent of the cases.
Something else here is worth noting. Loosening the gold standard should cause the sensitivity to go down and the specificity to increase. With more liberal standards, the paramedics are more likely to identify some deaths as sudden cardiac deaths that really aren't. If the death certificate algorithm has validity, it should be less likely to classify the deaths that paramedics got wrong as sudden cardiac death and the ones that paramedics got right. This should produce a number of classifications by the

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algorithm, which would be counted as false negatives, even though the algorithm in fact got it right. The reverse is true for specificity because with a strict gold standard, the paramedics or more likely to miss genuine sudden cardiac death cases that the death certificate algorithm is able to classify correctly but would still be counted as false positive. This is less likely with a more liberal gold standard.

In this case, however, liberalizing the gold standard resulted in the sensitivity going up from 78 percent to 85 percent. This would suggest that the death certificate algorithm is more sensitive to deaths classified as sudden cardiac death on the basis of presumption or circumstantial evidence than it is to cases where the evidence is direct and unequivocal.

To strike an analogy, the paramedics are setting up a lot more targets, and many of the additional targets are decoys. If the algorithm is good at spotting the decoys, it would deliberately avoid hitting the decoys and the percentage of targets hit would go down. In this case, however, the percentage of hits goes up because the algorithm is

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better at hitting the decoys than the targets you really want to hit.

A second study using different methods found very similar results. This was a community-based study with an established infrastructure for monitoring cardiac disease. The intention of this study was to modify risk factors in the community and look at their impact on cardiac disease. The age range is exactly the same as the Vanderbilt study. Also like the Vanderbilt study, death certificates listing COPD, neoplasm, poisoning, injury, accident suicide or homicide, were considered sufficient to rule out sudden cardiac death. Now, 911 of those deaths met those exclusion criteria. The remaining 1,124 deaths were reviewed by physicians using medical records, an interview with the next of kin in over 95 percent of the cases, and autopsy reports of nearly 20 percent of the cases.

If we exclude the cases where death certificates were assumed to be accurate and use strict criteria for the death certificate definition of sudden cardiac death in order to reduce the number of false

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positives, by only counting death certificates that listed cardiac arrest as the first contributory or underlying cause, the death certificates have no accuracy at all. In fact, they do worse than chance expectation. If a broader definition is used, including any ischemic heart disease diagnosis, as well as sudden cardiac death, some accuracy may be found with the death certificate data, but the specificity is extremely low, only 30 percent, and there are lots of false positives. This is because many of the deaths included in the broader definition were due to coronary artery disease, but they were not sudden deaths.

The two studies concluded, respectively in Seattle, we conclude that the death certificate can be used to identify cases of sudden cardiac death in patients at high risk; however, there's a substantial rate of false positive, sudden death classification. In a Minnesota study they concluded that death certificate diagnosis of out-of-hospital sudden cardiac death included many erroneous cases and may not have been suitable for study of etiologic factors, such as cardiac dysrhythmias.

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What implications does this have for the Vanderbilt study associating antipsychotic use with sudden cardiac death? As you probably know, positive predictive value is dependent on prevalence. If no one in the population has the disease, any positive test will have a predictive value of zero. And if everyone has the disease, any positive test will be certain to be correct.

This graph shows that relationship. The dash diagonal line represents an algorithm that has no predictive value, and the four curves near it represent the death certificate algorithms used in the Seattle and Minnesota studies. Here you see one that seems to do worse than random chance; then there's one that does almost exactly the same, and then two that are slightly better.

The Seattle curves represent the same algorithm with two different gold standards, leading to two different prevalences, while the Minnesota curves represent two different algorithms with the same gold standard has no change in prevalence. The curves for a perfect algorithm would go straight up from zero and

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then straight across. The orange dots show the positive predictive value. Twenty-six percent of the deaths in the Minnesota study that were classified as sudden cardiac death by the broader algorithm actually were sudden cardiac deaths, as were 85 percent of the deaths in the Seattle study when they used the liberal gold standard.

The Vanderbilt study is claiming the same positive predictive value, actually, a higher positive predictive value, than the Seattle study, even though

their population selection is very similar to the average risk Minnesota study. This applies a much better performance of the death certificate algorithm in the Vanderbilt study than in the studies I've just discussed. In fact, it's pretty close to perfect.

How much better did the death certificate algorithm perform in the Vanderbilt study than in the other two studies? This can be calculated by deriving the positive likelihood ratio, which is the ratio of the sensitivity or true positive rate to the false positive rate or 1 minus the specificity. And that can be derived from the prevalence in the positive

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predictive value. So if 23 percent of non-excluded, out-of-hospital deaths are sudden cardiac deaths, which was the prevalence in the Minnesota study, and the positive predictive value of death certificates is 86 percent, the positive likelihood ratio is 20.6. And if you push that 86 percent up to 87.4 percent, it actually becomes 23.

Compare that to likelihood ratios of 1.24 in the best case of the Minnesota study and 2.02 in the best case in the Seattle study. A positive likelihood ratio of 20.6 requires greater than 95 percent specificity.

(Brief pause)

There was a small change in the slides. For example, in the Minnesota study, the citation had a slight error. It said 1997. It is 1998. So I came up with some revised slides, which they're only just able to load, just to show you that. It's 1998.

So the algorithm performance in the Vanderbilt study is vastly superior to what was seen in the other two studies. It's very difficult to understand how this could be the case. They are getting a result that

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was not replicated in two studies that are arguably better designed. They were prospective and they had more methods of verification.

Could this be because of a prevalence higher than in the Minnesota study? And once the prevalence is much higher, such as sudden cardiac deaths constituting more than 50 percent of the cases considered by the death certificate algorithm, at 50 percent prevalence, the likelihood ratio would still be 6 and specificity would have to be almost 85 percent with 100 percent specificity or 90 percent with 60 percent specificity. And once you get above a 50 percent prevalence, the sensitivity starts to matter more.

Another point I want to make about the Vanderbilt study is that the positive predictive values for both groups are about the same, but the study's implying that the prevalence of sudden cardiac death is higher among antipsychotic users. This would mean that the algorithm performed worse in the antipsychotic group. If the algorithm were equally accurate in both

groups, the positive predictive value should be higher
among antipsychotic users because the prevalence is higher.

If the prevalence of the group not taking antipsychotic drugs is 25 percent and the odds ratio is 2, then the prevalence among antipsychotic users would be 40 percent. And then you end up sliding down the curve from 25 percent to 40 percent, and the specificity goes down. If the prevalence in the comparison group were 50 percent, and the prevalence among antipsychotic users would be 67 percent, the specificity would slide down here. In either case, with the same positive predictive value in both groups, the rate of false positives in the antipsychotic group would be about twice the rate in the comparator group.

Although the Vanderbilt study is implicitly claiming very high specificity for its death certificate algorithm, the algorithm is actually designed to be more sensitive but less specific than the Minnesota study, which only had 30 percent specificity, by casting a much broader net. In the Minnesota study, only those diagnoses shown in color were considered to be indicative of sudden cardiac death. The Vanderbilt algorithm includes many other diagnoses, most of which are not specific for sudden cardiac death. They even include cases where the cause of death is said to be completely unknown, patients who are just found dead.

The results of the Vanderbilt study has certainly shown association between antipsychotic prescriptions and something captured in death certificates; if it is not sudden cardiac death, what else could it be? What the study is attempting to estimate is the ratio of the prevalence of sudden cardiac deaths among antipsychotic users to the prevalence of a comparator group. Every sudden cardiac death is either a true positive, because it was detected by the algorithm or a false negative because it was missed, and this is what we want to try to estimate. But what we end up measuring is true positives plus false positives in the two groups. And aside from missing the false negatives, the algorithm will mistakably identify some false positive cases as sudden cardiac deaths.

If we have a very good algorithm and the numbers of false positives and false negatives are both very small, then the difference between what we want to estimate and what we end up estimating will be very small. And what if there are substantial numbers of false positives and/or false negatives?

Let's consider first the possible impact of false negatives. If the ratio of false negatives in the antipsychotic cohort to false negatives in the comparator cohort is the same as for true positives,

then it shouldn't be a problem. But what if this isn't the case? Is there any reason to think that the false negatives could be more common in the comparator group than in the antipsychotic group? Well, the Vanderbilt study excluded a number of deaths, deaths in nursing homes, deaths in hospitals, and deaths occurring 30 days after hospital discharge. Could these be more common in the comparator groups?

Well, could the comparator group have more hospital and nursing home admissions, longer stays, and even more importantly, admissions that coincide with a period of high risk for sudden cardiac death? In order to be included in the Vanderbilt study, subjects had to

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have had a visit to a physician. For antipsychotic users, that may have been necessary only for the psychiatric illness. Subjects in the comparator group in contrast were more likely to have had a non-psychiatric illness. That may have made them more likely to be admitted to a hospital or a nursing home. The more time the subjects spent in an excluded period, the more likely the subject would be to have a sudden cardiac death event occur during that exclusionary period. Non-psychiatric hospital admissions are also more likely to coincide with periods of high risk for sudden cardiac death. Someone admitted for myocardial infarctions probably are a higher risk than someone admitted for acute psychosis. It's also not just a question of sudden cardiac deaths being excluded, someone is more likely to be successively resuscitated in an hospital or nursing home.

Finally, in an acute, life-threatening condition, such as pulmonary embolism or severe infection, that would be falsely classified as a sudden cardiac death if it occurred outside a hospital or a nursing home, is more likely to be accurate diagnoses

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and even successfully treated if it occurred in a nursing home or hospital.

The results of the Minnesota study suggest that there should be three or four times as many false positives as true positives, at least in the comparator group. Could the Vanderbilt results be more about a greater rate of false positives among antipsychotic users than among comparators?

I would pose the question this way. If someone dies and no one else is around to see it, would it be more likely to be classified incorrectly as a sudden cardiac death? Mental illness severe enough to require antipsychotic drugs, particularly in the 1990s, may also increase the chances of someone being homeless or living alone with little social contact. They may also be less likely to seek medical attention or disclose to anyone symptoms of a potentially rapidly fatal condition, such as infection, pulmonary embolism, anaphylactic shock or drug overdose, to name a few. Prescription of an antipsychotic drug, and even the

dose of an antipsychotic drug, may simply correlate with the risk of dying alone.

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Dr. Ray mentioned some other possible confounding factors that I'd like to touch upon briefly.

Smoking as an important risk factor for sudden cardiac death is unlikely to appear in the Medicaid claims data used in this study. Dr. Ray did a sensitivity analysis, which suggested that the differences in prevalence of smoking were not sufficient to explain the observed difference in sudden cardiac death, based on current estimates of the difference in smoking prevalence between groups, which were not specific for the Medicaid population; they were just published estimates, and the relative risk for sudden cardiac death attributable to smoking taken from epidemiological studies. Neither of these estimates are, however, known with any precision, particularly for these specific populations. The wide uncertainty about these estimates, coupled with the possibility that antipsychotic users are heavier smokers, means that smoking cannot be ruled out as being a sufficient explanation.

Dr. Ray also argued that some of the risks

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attributable to smoking is manifested as other risk factors, such as hypertension or preexisting coronary artery disease, that can be detected on Medicaid claims and may be accounted for in his risk adjustment model. My concern here is that the model may not work the same way in antipsychotic users as in non-users.

I said before that the prevalence of sudden cardiac death among antipsychotic users would need to be higher than among comparators to be consistent with the results. This is not necessarily true. They could be claiming, for example, that the rates are equal in both the antipsychotic users and the comparator group, but that the rate among antipsychotic users should be lower than the comparator group because they have fewer risk factors. Antipsychotic users may be less likely to have their risk factors, however, recognized, because they may get less non-psychiatric care. They may also be less likely to have any coronary artery disease symptoms or risk factors recognized or entered on claims even when known because their severe psychiatric problems may take precedence. This problem carries over to the effectiveness of care.

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Antipsychotic users may have less opportunity or be less willing or able to communicate symptoms of cardiac disease to medical personnel or to cooperate with treatment.

So to conclude, death certificate data are unlikely to be a reliable means by identifying sudden cardiac death. They may have adequate predictive value in high-risk populations; however, if the prevalence is

so high, an effect should be detectable looking at total deaths. Death certificate classification should be unnecessary and would be more subject to bias. And if you take a step in that direction and say, let's just compare rates with out-of-hospital sudden cardiac death, then you begin to realize some of the other problems. The rate of out-of-hospital deaths, total deaths, may be higher among antipsychotic users than non-users. But we can think of a lot of explanations for that, particularly if the inpatient death rates are different, are lower. Also, the findings in the Vanderbilt study could have been significantly influenced by false positives and false negatives. And finally, confounding could also strongly influence the

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results. Thank you.

DR. GOODMAN: Okay. Thank you.

First, a housekeeping issue. My intention is to start our open public hearings on time, as scheduled at 12 noon. That would give us 10 minutes for clarifying questions and only 30 minutes for lunch.

Do panel members see any problem with that?

Okay. So that's how we'll proceed. I would also encourage Dr. Ray to make comments because I do detect some difference of opinion between -- so maybe we'll give him the first chance to comment, and then we'll go around to panel members.

DR. RAY: Well, I'm not going to -- respecting your schedule, I'm not going to address every one of the issues that was raised in the FDA presentation, but I do want to say a couple of things.

First, our study was an observational study; it was not a randomized clinical trial, and the possibility of confounding is present. What I would claim is that added to the other evidence, our study presents further evidence that this whole class of drugs may increase a side effect that is of extreme

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concern to patients. Other corroborating evidence that I didn't mention, of course, is the clinical trials in the elderly, where we have seen that atypical antipsychotics are associated with an increased risk of all-cause mortality.

The second point is most of the FDA comments seemed to relate to the case definition, and I simply note a couple of points. First, there were differences in the gold standards used. I believe some of the studies shown in those slides used as a gold standard what we would call a probable sudden cardiac death, which was that there was a witnessed collapse or the person had been seen less than one hour previously.

We used a broader definition as the gold standard, which included probable and possible. In several of our previous studies, we've analyzed the data according to which standard was met and have never found a difference. And it's been our practice to include both probable and possible, because one of the

best ways to make a drug look safe is to have an exceedingly rigorous case definition and reject all of the potential cases because they don't meet it. So our

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practice is to be broad rather than narrow in that respect.

It's not clear that the screening criteria used were similar. For example, one interpretation of one of the Minnesota slides is that they used all deaths except the 900 or so that were related to injuries or other clear conditions that weren't sudden cardiac death.

Finally, to clarify a point about nursing homes, we didn't exclude deaths occurring in nursing homes; we excluded people in nursing homes from the entire cohort. So our cohort, that's not going to be a factor introducing bias; it's simply going to be a question of generalizability.

Let me stop there and give the panels time.

DR. GOODMAN: Yes. Why don't you stay there for a moment.

Among the criticisms of the methodology were the differences and possible ascertainment between the psychiatric group on antipsychotics versus the control group.

Could you just elaborate a little bit more on

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what kind of contribution to the error that might have accounted for?

DR. RAY: In our opinion, really, it would make very little difference. What would have to happen is that there would have to be differential misclassification; that is, that the definition of sudden cardiac death was substantially better or substantially worse, according to antipsychotic use. And we simply didn't find that, and we used a very straightforward method of ascertaining it.

DR. PINE: I have a question.

DR. GOODMAN: Well, let me --

Dr. Pine?

DR. PINE: I mean, related to the argument that was presented from the FDA, one would think, though, that the characteristics going into the study of patients on antipsychotics, typical or atypical, could very easily be different from the characteristics of patients not on antipsychotics in some unmeasured way. For example, the sicker, more at risk, more isolative, patients who were more concerning, physicians might be more eager or rigorous in giving

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them antipsychotics.

How plausible is Dr. Stone's idea that these patients also might be differentially misclassified since their deaths might be unwitnessed? I mean, is that a plausible explanation or not?

DR. RAY: I think the first part, that there's some unmeasured confounder, is a far greater concern,

because we hope that in the real world, patients aren't assigned to antipsychotics at random.

DR. PINE: Right, of course.

DR. RAY: There has to be some reason that they're on an antipsychotic rather than on a mood stabilizer. But the second part, how would that manifest itself, I think given our data, it's very unlikely that differential misclassification is the explanation. I mean, I just don't see it.

DR. PINE: But the thing about them being unwitnessed dying, couldn't you also imagine a situation where the same thing that leads to this one group to be not randomly assigned medications also leads them to have an unwitnessed death? I mean, that seemed, on the surface, plausible to me. You seem to

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think that that's not plausible.

DR. RAY: There are several pieces of evidence that would argue against that. And the first, of course, is the fact that the positive predictive value we found in the validation study to be the same in both groups. The second is the similarity of the effect for former users and current users, because the former users, in fact, these may be people who against medical advice stopped their antipsychotics. These should be the ones who would have the greatest risk of these kinds of deaths. Third is the dose response. Why would that misclassification correlate very strongly? Fourth is the propensity score-matched cohort, where we excluded schizophrenics with the greatest likelihood of this scenario. We matched very closely on prior psychiatric hospitalizations, bipolar disorder, use of other medications; exactly the same finding.

So while any single finding you may be able to argue plausibly, the entire picture just suggests strongly it's the drugs.

DR. GOODMAN: Laughren and then Harrington.

DR. LAUGHREN: Yes. I just have two

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questions.

I guess of the 223 deaths in atypical users and the 895 deaths in non-users, can you tell us what proportion of those were found dead as opposed to witnessed deaths? You see what I'm saying?

What I'm trying to get at is the point that Dr. Pine was raising. Is there something different about the patients getting antipsychotic drugs, and particularly getting high doses, that makes it less likely that you're going to know about other causes of death? And so, if you could give us the data on the proportion that were found dead and, therefore, considered sudden cardiac death because there's just not enough information to say one way or the other.

DR. RAY: We can't do that for our study because our definition is a computer definition for the entire cohort.

So it's based on death certificates and hospital

visits, emergency department care. So --
DR. LAUGHREN: But --
DR. RAY: -- in the sample, we found no evidence that that was occurring, but that's a sample.

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DR. LAUGHREN: The only other question I wanted to raise, quickly, AstraZeneca looked at its own database for sudden death, and they had a large number, a large sample, like 26,000 patients. What I understand from your data is that the excess risk of sudden cardiac death here is somewhere in the vicinity of 1 to 2 per thousand patient years, if you look at the risk difference between users and non-users. I don't know if I'm right about that. But it looks like their analysis should have been able to pick up a difference in sudden cardiac death, and they didn't find any difference between drug and placebo.
DR. RAY: I would just urge you to be cautious about using spontaneous reports for this purpose.
DR. LAUGHREN: No, this is a clinical trial. This is their clinical studies database. They've done 118 studies.
DR. RAY: Okay. So we're not talking about the second one.
DR. LAUGHREN: No, no. We're talking about a clinical trial's database.
DR. RAY: Well, again, the clinical trials, I

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was somewhat troubled when I saw that presentation because, as I understood it, the safety calculations were done by pooling the data from all of the clinical trials, dividing them into placebo and active drug group, and then just calculating -- treating it as though it were one large data set. It's well known that this is subject to something called Simpson's paradox, and it's the whole reason that we do meta-analysis. And if you read the sudden text on meta-analysis, you'll see a clear explanation of this.
That said, I've seen similar analyses for all of the Cox-ibs that shows that none of them causes myocardial infarction. For many, many reasons, this kind of pooled analysis of an unstructured safety database, where there was no prospective attempt to detect the specific events, is useful, but it's very dangerous to take it as definitive.
DR. LAUGHREN: Except that here we're talking about a pretty definitive event, sudden death.
DR. RAY: Another factor, too, is you have to keep in to account the dose. If you look at our numbers for quetiapine, if the sample size is

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sufficient, you'll see that for the 75 milligram dose, we were seeing a risk ratio on the order of 1.2. So for all of these drugs, the real action seems to be at the higher doses, which would be 250 to 300 milligrams for quetiapine, and that's another consideration for those trials' databases.

DR. LAUGHREN: Right. But even there, you can argue that dose, perhaps, might be a marker of how severely ill a patient is and how likely they are to have poor medical care and more social isolation.

DR. RAY: One final comment. I'm basing this on my memory of what I saw this morning. But I think, although there were some 22,000 patients, there were far fewer patient years. I think it was in the order of a few thousand patient years. And again, in a relatively healthy younger population at relatively low doses, the expected number of such deaths would be small. You just have to simply do a careful power calculation.

DR. GOODMAN: Stand by, please, Dr. Ray.

Dr. Harrington, Ms. Lawrence, and Dr. Neaton.

DR. HARRINGTON: I want to make a comment and

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ask a couple of questions of Dr. Ray.

First is, this is certainly the challenge we're going to face this afternoon. I mean, observational data, we have two very smart people looking at it very different ways. So it's pointing out the limitations of observational data.

Having said that, I actually applaud you, Dr. Ray. I think you've done everything you can do with a very limited data set, but I have a couple of questions for you.

Your cardiovascular risk score, have you published this as a validated cardiovascular risk score? And tell me what does it mean when you come up with a risk score of 9.6 versus 9.2? What does that a risk of? Have you actually validated that the cardiovascular risk score correlates with subsequent cardiac death, or myocardial infarction, or anything like that?

DR. RAY: Yes. And thanks for the opportunity to explain that a little greater length.

What the cardiovascular risk score really is, is a measure that's internal to the specific study, and

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it's a way of summarizing many variables. So, for example, we would have had a table 1 with about 80 variables reflecting cardiovascular risk, and we simply used regression techniques to put those into a single number. Then, the way that score was calculated, it ranged from zero, for the lowest level of risk, to 19 for the highest level, and they were 5th percentiles, each one comprised in equal proportion of the cohort. So, basically, around 9.5 is actually the median of the cardiovascular risk for the entire population.

If you compare the highest 5 percent of the population, according to risk score, with the lowest 5 percent, after adjusting for everything else, there's a 10-fold greater risk of sudden cardiac death. So it does a very good job of differentiating or identifying high-risk patients. And the factors that weigh most strongly in it are prior hospitalization for

cardiovascular disease, heart failure, diabetes, and prescription of loop diuretics and digoxin. Those are among the factors that have the greatest weight.

DR. GOODMAN: Go ahead with your follow-up, Dr. Harrington.

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DR. HARRINGTON: So my follow-up is that, assuming that there is this relationship between cardiovascular risk and sudden cardiac death, did you test for an interaction between cardiovascular death, the drug, and sudden cardiac death?

DR. RAY: In this study, we did not. In our prior study, we actually found that the risk was greatest for the higher levels of the score. But we haven't done that, and that's a good question.

DR. GOODMAN: Ms. Lawrence?

MS. LAWRENCE: Thank you. I don't have a question. I just want to thank you as a layperson, Drs. Ray and Stone, for really explaining things and showing both sides of the illness and the people that are at risk. Thank you.

DR. GOODMAN: Thank you.

Dr. Neaton?

DR. NEATON: Thanks for the presentations, both of them.

Dr. Ray, can you maybe reach to this issue by -- did you look at, for example, the outcome of just all cardiovascular mortality?

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DR. RAY: We didn't. And, you know, that's kind of an interesting thing to do, but it's addressing several questions. For example, these drugs are known to have metabolic effects, and those metabolic effects are almost certainly going to increase the risk of heart failure a long time down the road. And we were specifically interested in kind of the arrhythmogenic side. And so, for that reason, we restricted our analysis to sudden cardiac death.

DR. NEATON: So you really can't speak to how specific these findings are to kind of sudden cardiac death versus other forms of cardiac and cardiovascular mortality?

DR. RAY: No, we cannot.

DR. NEATON: Just one related question that kind of came up in the FDA presentation. I noticed the average follow-up was shorter in the non-users.

Is that because of more exclusion of data from hospitalizations or how is that arrived?

DR. RAY: No, it's not. What happens is that we allow persons to enter the cohort multiple times. So if someone started out as a non-user in 1993 and

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then in 1997 began to use an antipsychotic drug, at the time they used the antipsychotic drug, they would be switched to the user status, and that's the reason.

DR. GOODMAN: Okay. We need to break now.

Dr. Ray, you'll be around this afternoon?

DR. RAY: If you'd like me to be, yes.
DR. GOODMAN: Yes, very much. I have a feeling there may be additional questions.
DR. RAY: Certainly.
DR. GOODMAN: And so, we're going to take a 30-minute lunch break; come back at 12. Please take your valuables with you. Reminder to panel members there should be no discussion of meeting issues outside this public forum.
(Whereupon, a lunch recess was taken at 11:29 a.m.)
DR. GOODMAN: I'm going to begin. We're reconvening the meeting.
DR. WAPLES: For all open public hearing speakers who signed up or registered before the deadline, please make sure that you go to the front desk to sign in. Thank you.

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DR. GOODMAN: So we're reconvening the meeting, and this is the open public hearing portion of our meeting today.
Both the Food and Drug Administration, the FDA, and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes 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 for 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 choose not to address this issue of financial

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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.
Because of the number of speakers that have signed up today and the limited time we have, each

speaker will be limited to three minutes of comments.
Do we have the slide for the first speaker?
Excuse me if I mispronounce your name. Our first speaker is Vince Boehm.
MR. BOEHM: Can everybody hear me? The name is Boehm.

Good afternoon. My name is Vince Boehm. I'm an unpaid volunteer. I edit a private news e-mail list that brings news items to a group of mental health professionals and other interested parties. Disclosure, one of my readers contributed $100 toward my expenses today. He is a psychiatrist in Ohio.
The following is a note from a bereaved Arkansas mother.
"On December 20, 2005, my energetic, healthy, happy go-lucky 15-year-old child, who was above average and enjoyed swimming and skating, was administered Seroquel. Within less than eight months, I found her lying dead on her bedroom floor. Her autopsy report reads that she had passed away due to a possible fatal heart arrhythmia although she had never had an history of heart disease, heart attack, heart failure, or irregular heart beat related issues.
After beginning Seroquel, she had an incident of making a suicide gesture, although she had never made such a gesture in her life. She was always very happy with life and had nothing but reason to live. As disturbing as that was, her doctor adjusted her dosage

and assured me not to take concern. All would be okay after the adjustment. However, after this increase, my daughter became increasingly agitated, gained 50 pounds, experienced neck rigidity, sleepiness, tremor in her hands, uncontrollable movements, weakness. And these are clearly effects caused by Seroquel.
As time progressed, she became confused and was even aggressive on occasion. A drug was, at the time, started due the diagnosis of depression after experiencing the loss of a loved one. Nothing will bring my daughter back. But if she was here today, she would please say don't give this medication to anyone.
I know today Misty Angel is not here with me, all because of a drug that was supposed to heal, instead took her life away along with a large part of mine. My stand is to set the record straight. Seroquel is dangerous and should not be given to anyone. If a 15-year-old child who never had had --"
DR. WAPLES: Thank you.
DR. GOODMAN: The time has expired. I'm sorry. We have to limit it to three minutes.

MR. BOEHM: Okay.
DR. GOODMAN: Thank you.
Everyone watch that red, yellow and green light on your podium.

Our next speaker is Eileen McGinn, MPH.

MS. McGINN: My name is Eileen McGinn. I have a master public health degree. I have no competing priorities to disclose.

Based on my analysis of the data presented here, as well as an extensive review of the literature on schizophrenia and bipolar disorder, I ask you to reject these applications for the approval of Seroquel for all indications. There are large databases available to be mined before making these crucial public health decisions.

If we objectively weigh the benefits and harms from these trials, we would have to conclude that the harms outweigh the benefits. We should also recognize that there are many other drugs and interventions for symptoms of MDD that do not have the associated adverse effects of atypical antipsychotic drugs. Further, if we are trying to move toward the science of comparative

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effectiveness, these trials reveal little of interest. Benefits are not robust. A few of the arms even reached a difference of 3.5 on the scale between drug and placebo groups. Even in the short trials, 20 to 30 percent of the people dropped out. Even in the short term, many of the adverse effects we know from the schizophrenia and bipolar literature were seen. These adverse effects are not uncommon, potentially exposing many people to premature disability and death.

There are now two black boxes for Seroquel, one for 100 percent increase in suicidal thoughts and behaviors, another for 70 percent increase in mortality in older adults. These are the warnings from the label. They were updated in January of '09. We've talked about some of them today but not all of them.

The issues of glucose and lipid dysregulation are important, but there are other important health effects as well; sudden cardiac death, weight gain, obesity, breast cancer, cataracts, motor dysregulation, neuroleptic malignant syndrome, dementia related mortality. There are two black boxes with Seroquel, but perhaps there should be another, for hyperglycemia

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and diabetes. Europe and Japan have stronger warnings than we do for this adverse effect.

It is important to recognize that CNS drugs can induce unexpected and unwanted mood changes, like anxiety, agitation, irritability, suicidality, and drug-induced dysphoria. These drug-induced mood changes are routinely attributed to the illness or to the patient, rarely to the treatment. Since these drugs are already being extensively used off label, we can mine the databases to find out the long-term, real world benefits and harms before we consider approving them for a larger population.

DR. GOODMAN: Thank you very much.

DR. PARTRIDGE: My name is Dr. Patricia Partridge. I'll be presenting for Ann Blake Tracy.

This is her presentation. She was ill today. She is executive director of the International Coalition for Drug Awareness and author of Prozac Panacea or Pandora: Our Serotonin Nightmare. This is her presentation.

For 17 years, I have testified in court cases involving antidepressants. The last 19 years of my life have been devoted to researching, writing and

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lecturing about drugs affecting serotonin. I have no financial ties to any drug company. I request that you not approve Seroquel for any additional applications. If anything, what should be considered is additional restrictions in the use of this drug due to the serious adverse reaction reports. And the thought of even considering approving for use in children is preposterous, almost as preposterous as the FDA's recent approval of Lexapro for children, which came two weeks after the Justice Department filed fraud charges against the manufacturer for concealing data on Lexapro, causing suicide in children.

What has been ignored for far too long is the use of all these serotonergic medications and the accumulative effect of impairing serotonin metabolism in a wide population base. Why should that be a concern? Because the research on serotonin has been clear from the very beginning, if anyone would bother to read the research, that the most damaging thing that could be done to the serotonin system would be to impair one's ability to metabolize serotonin. Yet, that is exactly how SSRI, SNRI and atypical

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antipsychotics exert their effects.

What are those symptoms of impaired serotonin metabolism? They are migraines; hot flashes; pains around the heart; difficulty breathing; a worsening of bronchial complaints, tension; anxiety, which appears from out of nowhere; depression; suicide, especially violent suicide; hostility; violent crime; arson; substance abuse; psychosis; mania; organic brain disease; autism, anorexia, reckless driving, Alzheimer's, impulsive behavior with no concern for punishment; and argumentative behavior.

The end result of impairment of serotonin is the fatal reaction, known as serotonin syndrome that produces death by a multiple organ failure. This generally is caused by taking two or more serotonergic agents together but can be caused by only one. Patients often go from antidepressant to another or from an antidepressant to a serotonergic atypical antipsychotic with no washout period, leaving them exposed to two serotonergic agents and, therefore, putting them at risk for serotonin syndrome.

How anyone ever thought it would be

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therapeutic to chemically induce the above reactions is beyond me; yet, these reactions are exactly what we have witnessed in our society as a result of the

widespread use of these drugs. And after two decades of these drugs, we now have multiple millions of people who have symptoms of impaired serotonin metabolism as a lingering effect of these medications.

I and thousands of those in my organization ask, how long are you going to allow this serotonin nightmare to continue?

DR. GOODMAN: Thank you very much.

Our next speaker, please.

MR. JONES: My name is Allen Jones. By way of disclosure, I'm the relator in a unsealed ketone lawsuit in the state of Texas against the makers of the drug risperidone. The suit alleges drug industry corruption of government decision-making in the marketing of psychiatric drugs.

Recent press attaches the term "smoke and mirrors" to Seroquel science. Smoke and mirrors is a term contained in internal AstraZeneca documents describing the manipulation and burial of unfavorable

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clinical trial data on Seroquel by Lisa Arvenitis, Seroquel project doctor. Arvenitis was responsible for disseminating Seroquel data to the FDA and scientific community. She authored scores of articles and gave presentations worldwide on the properties of Seroquel. She has been cited thousands of times by other authors. Prior to Seroquel's approval, Arvenitis herself certified to the FDA that the World Press contained no negative Seroquel data, which would adversely affect Seroquel's approval.

Now, we learn that Arvenitis was conducting a smoke and mirrors job with Seroquel data and that she operated in a corporate climate, which openly condoned this behavior. We also know that Arvenitis researched and published early Seroquel data with Richard Borrison. Borrison served a lengthy prison sentence for research-related crimes, and yet the Borrison-Arvenitis Seroquel data remains in the literature.

The body of scientific knowledge regarding the properties of Seroquel has been hopelessly polluted in a deliberate manner. All we know for certain about

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Seroquel is that we cannot rely upon the accuracy of AstraZeneca's data. If executives and scientists at AstraZeneca were charged criminally for research fraud, they would be entitled, under law, to be presumed innocent until proven guilty. Their data and their drug doesn't have that presumption of innocence.

I ask instead that this panel presume the potential future victims of this drug to be innocent. Protect them. There should be no expanded usage of this drug under this cloud of uncertainty. Over 19,000 victims allege in lawsuits that they've been seriously harmed by Seroquel. The harms alleged in the suits align directly with the properties of the drug AstraZeneca explicitly covered up, buried and subjected

to smoke and mirrors. We have no way of knowing how much more data AstraZeneca has buried. There should be no discussion of expanded Seroquel usage unless and until AstraZeneca releases every shred of Seroquel data in their possession for independent scientific review. Consequences, not rewards, should arise from AstraZeneca's intentional deceptions.

The FDA has been compromised by drug industry

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influence and money. The industry has run roughshod over regulations and over regulators, and it will continue to run until somebody tackles them. Please, tackle them. Please place the health and safety of the American people foremost in your deliberations. Please separate the money changers from the temple. Thank you.

DR. GOODMAN: Thank you.

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman. I'm president of the National Research Center for Women and Families, and I have no conflicts of interest.

Our center is dedicated to looking at scientific and medical information to compare the safety and effectiveness of various treatments. In addition, I'm a fellow at the University of Pennsylvania, Center for Bioethics. My doctorate's in clinical psychology and I was trained in epidemiology at Yale Medical School, where I did research on depression, and I've also worked with schizophrenics, depressed patients, and patients with anxiety.

The key question for you today is do the benefits of Seroquel outweigh the risks for the

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treatment of depression and anxiety. And although there are statistically significant improvements as a result of Seroquel, it's clear that there's a huge placebo effect that is accounting for most of the improvement for depressed patients, and that Seroquel actually adds just a couple of points on a depression scale.

Compare that to the unanswered questions, and that's what I ask you to focus on today. It is not appropriate to approve a drug with this many unanswered questions. Seroquel has been studied for too short a period of time. Six to eight weeks is not a long enough period of time to look at serious adverse reactions. And, obviously, diabetes is a very serious one. We need to find out more about how big of problem that might be; obesity as well. And I wanted to say a few words about tardive dyskinesia, a condition that I saw in the psychiatric hospital early in my training, and one that you would never forget.

When you look at these symptoms of tardive dyskinesia, the grimacing, the tongue protrusion, and other very embarrassing symptoms, and you know that you

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can't control them once they start, and that there's no really good effective treatment, or at least not ones

that always work, you need to avoid that at all costs. And so, when you look at the unanswered questions about diabetes, tardive dyskinesia and possible sudden cardiac death, those questions must be answered before this drug could possibly be approved for these other uses because there are other drugs on the market that are safer. And perhaps we will find out with long-term studies that these are not problems, but we haven't found that out yet. We must know the answer to that before an approval can be made, and you can't rely on labeling to warn patients or to warn doctors.

So I ask you, because I see that as your position, your job, is to recommend to the FDA not to approve this product until long-term, well-designed studies are done that can conclusively determine whether --

DR. GOODMAN: Thank you.

Next speaker, please.

MR. WHITE: I'm Stan White from Cross Lanes, West Virginia. Our youngest son, Corporal Andrew Ryan

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White, U.S. Marine Corps, died while taking Paxil, Klonopin and Seroquel, that was prescribed to him by both private and VA psychiatrists. The chief medical examiner of West Virginia ruled the death to be accidental intoxication of painkillers, Paxil and Seroquel.

In a research that my friends and I have done, we found at least 87 military men had died in the past six years. I've contacted several families. Most of the families I've contacted say they were taking Seroquel. Andrew exhibited all of these side effects that were listed a few minutes ago, yet he was taking sixteen to 1800 milligrams a day. We did this research too late.

My plea to you is to revisit the side effects of these antidepressants, painkillers and antipsychotic medications, especially Seroquel. My belief is that overuse of these medications has caused our soldiers and Marines to die. I believe that's really what caused Corporal Andrew White and others to die in their sleep.

In the past few months, six people have died

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from food poisoning from peanut butter. What we did, we shut down the factories and recalled. However, 81 men died; no alarm sounds. I'm trying to sound that alarm.

MS. WHITE: I'm Shirley White, mother of Andrew White, who died in his sleep while taking prescribed medications for PTSD. Andrew handled his own medications for approximately four months, until I was contacted by the VA and suggested to become involved with his treatment and to monitor his medications. PTSD patients do not remember to take medications.

When I started doing this, following the

regimen of his daily doses of Paxil, Klonopin and Seroquel, including Seroquel HR, his behaviors and physical conditions started to deteriorate. Andrew had extreme weight gain, at least 40 pounds in just a few months. He experienced tremors in his hands and feet, as well as many other side effects. When he complained about these conditions to his physicians, he was told, yes, there are side effects, but then the medications were increased. If there were any warnings about the

seriousness of these drugs being prescribed together, Andrew was not aware of them. He was told, as I his mother was told, these medications will not harm you.

His anger and lack of self-control kept escalating. He kept withdrawing even further from the outside world. I monitored the medications because I wanted to make sure that he was taking them correctly. I trusted the doctors to do what was best for my son.

DR. GOODMAN: Thank you.

Next speaker, please.

MS. VANDE BURGT: My name is Diane Vande Burgt. I'm the spouse of retired veteran, Staff Sergeant Vande Burgt, from Charleston, West Virginia.

In 2006, my husband began treatment for his PTSD, and one of the medications he was given by the VA for off-label use was Seroquel to be used as a sleeping aid. Our feeling is that this medication caused my husband to behave more erratically and increased violent behavior to the point that I was strangled in April of '08. He had many issues while on this medication, such as enuresis, increased sedation, sleep apnea issues, increased sugar levels, increased

cholesterol, weight gain, increased confusion, problems with kidneys, twitching or jerking movements of limbs that were causing frequent nighttime awakenings, suicidal thought, increased memory loss, increased violent tendencies, and he appeared and sounded extremely drunk while on this medication at only 50 milligrams maximum.

It also appears that Seroquel has an addictive quality to it, and for a recovered alcoholic, this was another serious concern. Even though some of the behaviors were PTSD related, it's hard to say what was worse, the PTSD or behavior, and the side effects from the medication. His manner changed drastically when he began using Seroquel in 2006, as did his behavior becoming increasingly odd and dangerous. These side effects appear to increase 10-fold when taken in combination with other narcotic prescriptions.

One of the things my husband explained to me -- when he was taking this medication, I could see that he was stoned for hours, and I quote -- "I could take a maximum of 50 milligrams of Seroquel and I felt stone for hours. I cannot imagine anyone taking more

than 50 milligrams and being able to even function. I

was so out of it on 50 milligrams, when I fell asleep, a bomb couldn't wake me. And if there had been a fire in the house, I would have slept through it. The worse part was, after I woke up, I felt hungover or like I had crashed. I could not stand noise or anyone really talking to me, and I became extremely irritable and aggressive.

If someone at home or work got in my face, I would literally be psyched out to beat them down. You could not talk to me for anything else. Once I was finally off of it and recovered from the side effects, I'm a whole different person. It is to me just another legal high, and as being a recovered alcoholic, it was not a medication I should have been using. I got the same effect I did from it when I was drinking heavily. And if I did not have my Seroquel, I had serious problems, and I would become extremely aggressive and angry because I felt both mentally and physically I needed this drug. I guess what you might call addicted because that is how I behaved when I was actively drinking."

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It was after throwing my husband's Seroquel away in 2008, October, and dealing with his withdrawals and anger, it was then that our family all noticed a decrease in all the extreme symptoms and an improvement in his mental thinking behavior and a lessening of the medical side effects. His PTSD remained severe, but it's more manageable with him off the Seroquel, and his sleep apnea symptoms have all pretty much subsided.

My concern is that this drug has contributed to the death, medical problems, and should not be used off label for anything until testing is done to rule it out, being 100 percent safe and effective. Many veterans are given this and other drugs without disclosing it as an anti-psychotropic or the side effects that they need to be watching for. Why should I troops be Seroquel's guinea pigs?

DR. GOODMAN: Thank you.

Next speaker, please.

MS. LAYNE: Do I just start?

DR. WAPLES: State your name. You can start.

MS. LAYNE: Janette Layne. I am the widow of Sergeant Eric Layne. I found my husband dead when I

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son Shamus was 17 months old. I was six months pregnant with our daughter, Jubilee. Eric and I both served in Iraq during Operation Iraqi Freedom. Eric did not want to take the medication, but the VA could not accommodate his work schedule for therapy. Eric was told that he would get his life back once the VA got his medications right.

In the summer of 2007, he began taking Paxil, Klonopin and Seroquel. By October, Eric was suffering from incontinence, severe depression, continuous headaches. He ate excessively, he would fall asleep with food still in his mouth, and he gained a massive

amount of weight in a very short time. He became listless, and the medications were exacerbating his distant and cold demeanor. Then they said -- they told me I could take Seroquel during the day for anxiety. It made him like a zombie.

By Christmas Day, I was unable to wake Eric after he took his medications. Eric was dramatically worse, having tremors, extreme lethargy, and his genitals had shrunk in significance. His breathing was labored. He developed sleep apnea. A few days before

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his return home, I spoke with Eric on the phone. His speech was slurred to the point, I couldn't tell what he was saying.

The day Eric graduated from the PTSD rehab program, he was confused, lethargic and very sick, and not able to urinate. He said he had been having hallucinations all that week and that he thought he had food poisoning. Eric did not have any of these problems before he took the prescription medication. He took his Seroquel and laid down, and he never did urinate. So he sat on the toilet trying to go almost all evening, and Eric died that same night at 29 while his family was sleeping.

This video is of my husband on Christmas Day.

(Video played)

MS. LAYNE: That was 45 minutes to an hour after taking his prescription medication. He had nothing else that day. Thank you.

DR. GOODMAN: Thank you.

Next speaker, please.

DR. GREENHILL: Good afternoon. I'm Larry Greenhill, president-elect of the American Academy of

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Child and Adolescent Psychiatry. Over the past 24 months, I have, just for disclosures, received research support from a number of sources, including the NIMH, Otsuka, Johnson & Johnson, Forest, but no support from the sponsor today, AstraZeneca. I practice child psychiatry and have been a member of the American Academy of Child and Adolescent Psychiatry for 30 years. This organization is a medical membership organization of 8,000 child and adolescent psychiatrists, established back in 1953. And it's a leading medical association dedicated to treating and improving the quality of life for the estimated 7 to 12 million American youth under age 18 years of age, who are affected by emotional, behavioral, development and mental disorders.

All of the focus today is on adults and their treatment. We as child and adolescent psychiatrists note these findings with respect and concern. Expanding indications from the use of an atypical antipsychotic in the adult population secondarily may expand the off-label use of this medication in pediatric patients. Although a few clinical trials

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have suggested use of this medication may be effective, the lack of systematically collected safety data in this age group strongly indicates a need for large-scale pharmacoepidemiological studies to more accurately identify and perhaps estimate the risk of side effects for youth from quetiapine or Seroquel, including the metabolic changes tardive dyskinesia and sudden cardiac death that we heard about earlier.

We ask this committee to carefully consider their votes on the two questions that have been raised and are sitting before them. As for Vote 1, Seroquel's efficacy, when it comes to youth, there are no trials showing its efficacy for major depressive disorder or generalized anxiety disorder in youth. A positive vote for this question, we encourage you to accompany by the demand for a clearer package insert statement that individuals below the age of 18 have not been studied, and are, therefore, off label for use of this medication. As for Question 2, AstraZeneca has yet to show that Seroquel XR is acceptably safe in youth. Dr. Robinson's comment earlier today, that the CAFE study showed increased triglycerides levels in

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53 percent of individuals treated with Seroquel just adds to this concern.

While Seroquel and other atypical medications may be helpful and even life-saving for some people with mental disorders --

DR. GOODMAN: Okay. Thank you very much.

Next speaker, please.

MS. GALBREATH: Laura Galbreath. I'm with the National Council for Community Behavioral Health Care. The National Council represents over 1,600 community behavioral health organizations, providing treatment and rehabilitation to individuals with mental illness and addictive disorders. National Council members represent the public sector safety net for millions of individuals with severe and persistent mental illness, and provide a wide array of recovery-oriented and person-centered support services and treatment.

As we continue to invest in America's future through prevention, early intervention and research on mental illnesses, we must remember how far we've come but also how far we still have to go. The class of antipsychotic medications have helped thousandths of

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millions of patients with psychosis lead to a more normal and fulfilling life by relieving symptoms. And we know that early antipsychotic medications often have stigmatizing side effects.

Today's meeting provides us an opportunity to ensure that individuals who experience mental illness, and their providers that support their recovery, have the information to make meaningful decisions and access to treatment options that work best for them. Providers and patients continuously weigh symptoms relief with side effects to develop prescription plans

that are tailored to individuals and take into account history and preference.

Given the limited options available to people who experience mental illness, we need to ensure that clients have the information needed to make treatment decisions that include community support, education about their illness, ongoing reviews of the effects of prescription medications, and arranged rehabilitative services. Mental health providers are implementing shared decision-making to enable clients to participate actively and meaningfully in their treatment by

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providing them information and choice.

Research must continue to inform the treatment options for mental illness, and to inform us as to the relationships with other chronic diseases, such as asthma, cardiovascular disease and diabetes, so that we can help individuals effectively manage their whole health. Given the nature of mental illness and the fact that one medication that works for one person often doesn't work as well for another, brings to bear the need to access a wide range of options.

Finding the right medication is critical, as research has repeatedly shown that those who take their medications often do better than those who do not. That's why the search for new treatment is vital. Consumers want and need choice of treatment options in order to decrease the possibility of tragic outcomes like suicide and increase the opportunities for protective, healthy lives.

To conclude, healthcare reform will provide new opportunities and challenges for our country. As articulated in discussions of the patient-centered medical home, we are shifting away from a focus of

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episodic acute care to a focus on managing health, especially those living with chronic conditions. Individuals with mental illness must have access to an array of service options and vital information to prevent delays in early and successful treatment. We support the valuable role that this --

DR. GOODMAN: Okay. Thank you.

Next speaker, please.

DR. BAUGHMAN: I'm Dr. Fred Baughman. I'm a retired neurologist. I have discovered and described real diseases. You have heard of the sudden, unexpected deaths of the four West Virginia veterans and mention of the fact that there are as many 70 or 80 more. Each of them had so-called PTSD, each a lethal mixture containing the cardiotoxic Seroquel. Only the military and perhaps Congress and the FDA know how many such deaths there have been. Try as they might, they haven't been able to cleanse the Internet where new cases keep appearing.

We have a still raging psychiatry-prescribed epidemic of sudden cardiac deaths, one that could be stopped immediately if it was acknowledged. There must

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be immediate full disclosure of every such medical record. There must be an immediate halt to all new cases of psychiatric drug prescribing in the military.
Going to the Internet, one readily finds new veterans almost by the day. Jared Arn (ph.), 21 years of age, was found unresponsive in his barracks. Christopher Aiden, 20 years of age, was found dead on a Monday morning in his barracks. Blake Branagh (ph.), 25 years of age, was found dead last Thanksgiving Day. His brother Barry talked to him on Thanksgiving Day and said he seemed fine. Jordan May, 26, fell into a deep sleep and never woke up. There are more questions than answer in the state-side deaths of May and 13 other Fort Hood troops in the past eight months. Kevin Marsh, 41 years of age, found dead in his barracks room. Authorities were already investigating at least five such deaths at Fort Hood. Matthew Rhodes (ph.), 29, was found dead at Fort Bragg. There have been nine deaths at Fort Bragg. Scott Vickery, 23, was found dead in his barracks room at Fort Hood, Warrior Transition Unit. Vickery was the second soldier to be discovered unconscious in a barracks room over the
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weekend.
These are, undoubtedly, sudden cardiac deaths with Seroquel as the likely culprit. Furthermore, young men in our military are still --
DR. GOODMAN: Okay. Thank you.
Next speaker, please.
DR. WAPLES: Before OPH Number 12 speaks, I must make a statement that he has been given four minutes to speak in a combined talk with another registered speaker.
DR. WIRSHING: Good afternoon. My name is Dr. Willie Wirshing. I have previously been a paid consultant by both Astra and AstraZeneca. Currently, I am not, but I am currently engaged in litigation involving patients taking Zyprexa, Seroquel and risperidone.
I'm speaking today because I am gravely concerned about the possible expansion of approved indications for quetiapine. In my opinion, the expansion of the indications for quetiapine in such a manner will exponentially increase the number of patients who will suffer from the toxic effects of this
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powerful, mind-altering, and indeed potentially addictive substance. I consider the expanded use of quetiapine for less psychiatrically serious and more common conditions of depression and anxiety to be medically unsound, socially irresponsible, at least based on the currently available data.
My concern is three-fold. Firstly, quetiapine will not provide the population suffering from major depressive disorder of generalized anxiety disorder with any therapeutic advance over the currently

approved available treatments for these widespread conditions. When considered in schizophrenia patients across many trials, quetiapine has consistently been shown to be about 10 to 20 percent less effective than conventional medications, and about 50 percent less effective than the other second generation medication, olanzapine. Those less than stellar results are largely mirrored in the trials and have been performed to support the indications under consideration by you today.

There's nothing in the available results to even suggest that quetiapine is better in any

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syndromatic domain than the currently approved and available treatments. It is important to note that many of these treatments are generically available and are literally a hundred-fold less expensive. For example, sertroline at 200 milligrams per month is $4 versus $385 per month for a 300 milligram dose of quetiapine. Secondly, quetiapine treatment in these populations will unnecessarily expose millions of additional patients to the serious metabolic toxicities that they would not otherwise experience, including but not limited to diabetes mellitus.

If there is no superior clinical efficacy, then the increased risk of patient exposure to toxic side effects from quetiapine are not justified. Although the company continues to deny any causal link between quetiapine and diabetes, distinct and clinically serious weight gain increases and axiomatic, metabolic dysregulation were well known to AstraZeneca, even before launch of the drug in 1997. Other potential causal mechanisms of quetiapine-induced hyperglycemia and diabetes, disassociated with weight gain, are to this day being discovered and researched.

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This toxicity has clearly emerged during the post-marketing surveillance period and has been published upon extensively in the observation literature.

This morning, we heard comments touting the post-marketing experience of the drug, but no mention that there are at least 10 epidemiologic studies that report a statistically increased risk of diabetes and several others that support data supporting this conclusion. Two papers reported a significant risk in Seroquel users taking low mean doses, 203 and 64 milligrams per day.

Due to the long-term nature of depression and anxiety treatments, during which patients consume antidepressant and antianxiety medications over a course of years, not weeks or months, the increased toxicity of quetiapine treatment cannot be justified, particularly in light of the fact that there's no evidence of increased therapeutic benefit. If the Committee were to recommend approval of quetiapine for MDD and GAD treatment, and the FDA so approved, then

the medical monitoring at baseline, and consistently
throughout the early months of treatment, at least every eight weeks for the first six months, including weight gain, waistline measurements and glucose and lipid parameters, must be mandated for safety of quetiapine users. Later signs of increased adiposity or other signs of glucose intolerance would trigger renewed and continued monitoring over the course of quetiapine treatment. I note that conspicuously absent from AstraZeneca's monitoring proposal are either regular weight measurements or blood glucose. This is simply astounding

Lastly, it is disturbing to me that there has been nothing mentioned of the potential addictive propensity of quetiapine. Clinical experience in a number of case reports have suggested that certain patients will abuse, divert for sale, and become physically dependent on quetiapine. I've published about this for the last decades of time. Though not mentioned here today, quetiapine abuse led to --

DR. GOODMAN: Okay. Thank you.

Next speaker, please.

MS. WITCZAK: Hi. My name is Kim Witczak, and I'm from Minneapolis. I come here today as a drug safety advocate who lost my 37-year old husband almost six years ago due to an antidepressant and due to suicide. Woody was given Zoloft for insomnia by his GP, and five weeks later hung himself with no history of depression or any other mental illness. I'm also a newly appointed patient rep for this committee.

I am concerned that there are too many unanswered questions and a strong indication of conflict of interest in the initial approval process before this panel can make a decision about recommending to expand the use of this drug. I believe there are many lessons and correlations that can be drawn between antidepressants and now Seroquel. One of the lessons we learned has to do with the conflicts of interest on this important decision. Last weekend, it was reported that few members of this board had ties to AstraZeneca, including the chair of the Committee, who is not here today. You've been entrusted with a huge responsibility. Conflicts of interest don't belong there.

Before granting approval for a wider market share of Seroquel, maybe we should look at the initial approvals first. Recently, there have been allegations in the media about misconduct during the trial process, leading to the application for approval. You should ask, is it possible that the original approval was made under false pretenses with evidence compiled by individuals with conflicts of interest? Look at the situation with the former U.S. medical director being accused of exchanging sexual favors with both a

clinical researcher and ghostwriter for the studies involved. These women were responsible for compiling and presenting evidence; or what about the unpublished study called Study 15 from 1996? This is your responsibility to get to the bottom of this.

The FDA does not have the ability to go into the drug company files, so they rely on what the sponsor and what people bring forward. There's already a lot known about these drugs, but what looms still in the files? As in the case of the antidepressants, many issues didn't come to light until legal. In fact, I brought out some of these documents to the FDA that showed the suicidality risk was known long before black

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box warnings. There are outside experts that are familiar and have seen those inside documents. Why wouldn't you want them to make a presentation up here today?

The only way to make a recommendation is to get a full 360 degree perspective of those that might have a different, unconflicted point of view. But what's really concerning is the ability to expand it to an additional 20 million adults or eventually kids. Of course, you're going to hear AstraZeneca presenting data that shows that it works. But, however, the real clinical trial begins when millions of people start taking Seroquel for various indications. Pretty soon these drugs will be advertised and handed out for everything like antidepressants by GPs, who know relatively little about the powerful mind-altering drugs these are, and often layering these drugs.

I'm guessing that many of the general physicians have never heard of serotonin syndrome, like Woody's doctor had never heard of akathisia being a precursor to suicide.

DR. GOODMAN: Thank you.

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Next speaker, please.

MS. LIVERSIDGE: I'm Number 15?

DR. WAPLES: Fifteen is good.

MS. LIVERSIDGE: My name is Ellen Liversidge from Silver Spring, Maryland. I'm a board member of the Alliance for Human Research Protection. My remarks today are my own, given in memory of my son, Rod, who died of profound hyperglycemia from Zyprexa in 2002. I'm also speaking on behalf and in memory of all the loved ones who have died of Seroquel, Zyprexa, and all the other drugs in the class atypical antipsychotics. My suggestions to the Committee are of following: 1) no, there should be no expanded use of Seroquel XR approved by the FDA, based on existing evidence and documentation; 2) Seroquel and Zyprexa should be removed from the market in a one-year phase in, based on existing evidence and documentation; and 3) the FDA should initiate criminal charges against responsible parties of AstraZeneca and Eli Lilly for these two drugs for manslaughter, based on existing evidence and

documentation. Radix malorum est cupidatis, money is the root of all evil. Thank you.

DR. GOODMAN: Thank you very much.

I believe that was the last speaker and concludes the open public hearing portion of our meeting today. I wish to thank all those speakers for presenting their opinions, their experiences, point of view, to us today.

According to the agenda, we're supposed to engage in some clarification questions, but I wanted to see what the feeling was of the panel, including FDA, about going directly into discussion of the questions, both those that we have to vote on, ultimately, and the other ones. So that discussion does not preclude us from posing clarification questions to the FDA or sponsor or our guest speaker today.

Does that seem reasonable? Okay.

What I'd like to do is I'd like to show the slide of the questions, not the ones in which we're taking a vote, but the questions that are designed to outline our discussion today, to guide our discussion.

So those questions for discussion and comment are as follows: Number 1, what are the public health consequences of expanding the use of Seroquel XR into a much larger psychiatric population with major depressive disorder and generalized anxiety disorder?

The second question is, in particular, how should less well-defined concerned about longer-term metabolic risk, potential risk for tardive dyskinesia, and a concern for an increased risk of sudden cardiac death be considered in this risk-benefit discussion?

What I'd also like to do is I'd like to fast forward a bit to get a preview of what the questions are on which we've been requested to cast the vote.

Yvette, could you turn to the original questions? These questions are as follows.

Number 1, has Seroquel XR been shown to be effective for the treatment of major depressive disorder and GAD? And Number 2, has Seroquel XR been shown to be acceptably safe for the treatment of major depressive disorder and GAD?

Could you show the next slide, too?

Based upon discussions so far today and opinions offered, instead of having lunch, I drafted this slightly modified version of those two questions, which basically splits them apart. And this is only for our discussion, modification and approval. These are just suggestions to stimulate discussion. So let me explain what I did here.

The first question lumped together major depressive disorder and GAD as it was originally worded. So I thought that in the voting question, we might want to vote separately on major depressive disorder and GAD. And I think there's also separate

considerations for whether we're talking about using Seroquel as an adjunct in the case of major depressive disorder or as a monotherapy, either in the case of major depressive disorder or GAD.

So I entertain any comments, and I'm fine, too, with leaving the questions as they originally were. I offer this for your consideration.

Any comments from the panel?

So does that mean that you like it? You like it. Okay. It gives a little bit more resolution to the questions and our vote.

Number 2, likewise, analogously, reworded, divided up into three categories.

Has Seroquel XR -- there's one other change,

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too, I need to point out.

Has Seroquel XR been shown to be acceptably safe as a second-line treatment of? And then we have it broken down into the three categories in the first question.

So if we vote, say, in favor of 2A, B or C, it would imply that we're not recommending it for a first-line treatment. We could have a separate question that asks whether it should be accepted as first-line question -- based upon our discussions, I'm not --

Go ahead, Dr. Potter. Dr. Malone, go ahead.

DR. POTTER: Could you just help clarify -- again, this gets to the question of what is the nature of evidence.

So is the evidence for effectiveness as a second-line treatment uniquely different than evidence of effectiveness as a first-line treatment? I mean, do we have an understanding of that?

DR. LAUGHREN: I can just speak to the issue of when we have used that kind of language in labeling. And, basically, there are two situations. Clozapine is

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approved for the treatment of treatment resistant refractory schizophrenia. And that is based on an actual trial that looks at patients who have failed on standard therapy and were shown to be superior to standard therapy in a controlled trial. So that would be one situation where a drug, in a sense, has second-line therapy.

But there have also been situations in Geodon, ziprasidone is an example of that, where it has not been studied explicitly as second line, but because of concerns about the risk of, in that case, QT prolongation, we've included language in labeling, basically in the indications section, suggesting that clinicians should think about other drugs first, before that drug, because of the concern about QT prolongation. So that's even in the absence of having any specific data that shows a benefit as second line.

So that's just to give you some examples of how we have thought about that. And this, of course,

would fall into that latter category. There aren't any data here. Now, you can argue that the adjunctive therapy data for MDD sort of fall into that category,

but we have distinguished between an adjunctive claim and a claim for a treatment resistant condition. But that's just to give you some background on that.

DR. PINE: Can you say more about that? What's the difference between adjunctive versus treatment resistance in the eyes of the FDA?

DR. LAUGHREN: Well, the usual studies that support -- as was the case here -- an adjunctive claim are patients who have had a suboptimal response to available therapy, and where a clinician might think it's reasonable to -- rather than to switch entirely to another drug, to add something to that underlying therapy. And so the design there is to take patients who are already taking a drug for which they've had a suboptimal response, and add either the new drug or a placebo, and show a benefit in that setting. That was the design for this study.

Treatment resistant, we recently approved Symbyax for treatment resistant depression. And there, the design -- now, that's a particularly complicated example of that because it turn out to be a combination product. But, basically, patients who have failed on a

particular drug are randomized back to that drug, or the new drug, and you show superiority. So that would be the design to support a treatment resistant claim.

But admittedly, those two conditions are somewhat overlapping, and it's a somewhat artificial distinction. But, again, in this case, what we would be talking about -- except for the adjunctive claim, but the second line, it's more just directing clinicians, because of a particular set of risks, to think about other drugs first, and think of this as somewhere down the line.

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

DR. TEMPLE: Well, as I indicated before, we would like to see trials in which people are randomized back to the thing they failed and to the new one to pin that down. In this case, the failure of the first drug is sometimes going to be because of the lack of effectiveness and sometimes going to be because the side effects aren't well tolerated. It's a little more plausible in that case to think that a drug with a different array of side effects might be useful even without the study that I like most.

If you really wanted to know that it works when the other one didn't work, the add-on study tells you something about it, but it doesn't tell you how it would do alone. It tells you that when you add it on, it does something, which is very good information. And we've had these discussion with many, many advisory committees. A lot goes to how well you believe that

people really are different and things like that. But there's a lack of data on this. There's not much data on whether there's individualized responses to most drugs, hardly any. We have a couple of very successful examples, but there aren't very many. So there has to be a judgment about how much persuasive data.

As Tom said, we don't hesitate to say think about other things first because there's a safety problem. It's still a perfectly good question, do you know enough to say that it's worth trying the other drug. And the way to pin it down is to do the study I described, but we plainly have not always insisted on that.

DR. GOODMAN: Dr. Jenkins?

DR. JENKINS: I would just like to raise a

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question about your proposed rewriting of the voting questions. When I look at Slide 3 of the sponsor's presentation, I don't see anything about their request being for second-line therapy. So when you rewrite the questions to presuppose second-line treatment without already having discussed and reaching the point where you don't think it's appropriate for first-line treatment, I think we're missing some of the conversation.

So that would be the concern I have about the way you've rewritten the question. It presupposes that the Committee's view is that it's not appropriate as a first line, but that's not what the sponsor requested on Slide 3. They seem to be asking for the standard indications for the drug. I did hear them say during their presentations, they didn't think this was the right drug for everyone, but I don't recall them saying they were seeking explicitly second line.

DR. GOODMAN: I think your point's well taken. And we should let the sponsor weigh in on that. We shouldn't try to interpret what the request is.

So would you address -- thank you.

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DR. SCOTT: Mark Scott from AstraZeneca. Indeed, the package we filed at the end of last year was based on an all-comers approach, and the indication that we sought was predicated on MDD and GAD in general. However, again, we studied only moderate to severe symptoms, and demonstrating efficacy in both of those, that was the labeled indication that we felt was appropriate.

Now, after having reviewed the briefing materials from FDA, having the conversations with the FDA, is a way to address this through, in fact, a different form of labeling. So we'd like to be informed by the conversation here, where that labeling actually could be appropriate in the context of the program that we've conducted.

DR. GOODMAN: Is that fair, Dr. Jenkins?

DR. JENKINS: Well, I think the Committee needs to discuss whether you want to include second

line explicitly in your conversation a priori, or whether you want to get there over the course of your conversation. I'm just highlighting the questions that were originally proposed didn't jump to second-line

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therapy and these questions do.

DR. GOODMAN: In terms of process, I totally agree with you, that we do not have to decide on the final wording of these questions at this point. We should have our discussion first, so let me say that this is a proposal. And before we get to the vote, we'll reexamine the questions, including the originals.

Dr. Malone?

DR. MALONE: Actually, I have a question. If it's labeled second line, what difference does that make for prescription or detailing or monitoring of the drug? I mean, I can imagine some drug rep coming to my office and saying that it's a second-line treatment, but we do have other data that we'll show you, and then show all the monotherapy first line or however you might want to think of it.

So I'm not clear what difference would it make ultimately.

DR. TEMPLE: Well, if somebody does that, you should report the incident to the Division of Marketing, Advertising and Communications because they're not allowed to do that. You can't undermine

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the label by your statements. That is not an assertion that it never happens, by the way. But we would very much like to know about those things. It is supposed to restrict and inform all promotion and all other promotion -- I mean, all written promotion and advertising, and anything that representatives says. And second line is pretty clear. It means you're supposed to try something else first or have a very powerful reason for thinking the other thing's inappropriate. That's pretty straightforward.

DR. GOODMAN: I'm going to call on others, but the other thing that we could do to make it simpler is just take out the second line and consider the vote with the only changes being the gradations with respect to separating out GAD, major depression, and whether we're talking about monotherapy or adjunctive.

But having said that, who's next? Dr. Neaton?

DR. NEATON: Actually, my question has been addressed because I was going back to hear from the sponsor what exactly are they requesting, because in Dr. Hutchinson's second slide, he said the goal was to provide an option for patients for whom first-line

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therapies were not appropriate. And so I've been confused since the very first slide.

Actually, I'd like to argue against the gradation. I actually think the issues are kind of similar and might interfere with kind of a broader discussion on efficacy and then a broader discussion on

safety more generally.
DR. GOODMAN: We certainly should have discussion, but my opinion is that monotherapy and adjunctive are different situations, and we can discuss that.
Dr. Harrington, you have a comment?
DR. HARRINGTON: So I'm hoping that my psychiatry colleagues around the table can help me understand a couple of things.
One of the themes that emerges here is the broad-spread usage, obviously, of these drugs as we move from the schizophrenia population to these much more prevalent diseases. And so I'd like my colleagues around the table to give me a sense of how large a population are we talking about? What is the potential number that one might think about as people being

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affected with these two diseases? That's question number 1.
And then question number 2 gets to the heart of how I might consider whether or not the trials have provided a persuasive level of evidence. So the question is, where are these trials done? What I'm hearing is that the majority of this prescribing is going to be done in the primary care physician's office with some prescribing done in the psychiatrist's office. And so I want to get a sense of how these trials are typically done. Are these the trials that I see advertised in the newspaper every Sunday, where patients come in and agree to participate for six weeks, or are these trials that are done in a broad, clinically applicable setting?
Then my third question -- I asked the same question yesterday, Dr.Goodman. Maybe you or Dr. Pine or others can tell me, is this the bar, typically, for major depressive trials, general anxiety trials?
DR. GOODMAN: I think I count four questions in there, Dr. Harrington. I'm not sure I can keep track of all them.

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DR. HARRINGTON: I've got pages more.
DR. GOODMAN: I know. I understand that.
With regard to when we talk about expanded prescriptions -- maybe I'll just give an actual number. But I think it's a vast increase. And maybe the sponsors or the FDA would be able to give us an estimate of --
DR. HARRINGTON: A public speaker, I wrote down, said 20 million. Is that too big?
DR. GOODMAN: I don't know.
DR. PINE: To put some numbers on it, prevalence is very tricky to measure for these kinds of things. A typical cross-sectional point prevalence in the community, a lower bound for these two conditions is probably 10 percent. That's a lower bound.
DR. HARRINGTON: Ten percent of the --
DR. PINE: Ten percent of the United States

population will at sometime, as lower bound, be afflicted by major depressive or generalized anxiety disorder episode. When you do prospective studies, where you serially assess people multiple times, you find the prevalence to be even higher. So we're

talking about a potential substantial increase in use and prevalence. And this is talking about a relatively high bar, maybe not quite as high as the company talked about, moderately severe, but that still is talking about the kind of compilation where typical clinicians would at least think about pharmacologic treatments. So it's huge, much bigger than schizophrenia, for example.

DR. GOODMAN: Dr. Malone?

DR. MALONE: And I think those numbers might more be related to what psychiatric surveys may give. I'm not sure what would happen in a general practitioner's office if a patient comes in and says, I've been upset or depressed. I'm not sure they're so -- those numbers would even be bigger I guess.

DR. PINE: They're higher. They would be higher.

DR. GOODMAN: Gail Griffith?

MS. GRIFFITH: I think one of the things that we heard at the open public hearing is very telling. One of the things I know that the mental health community is very concerned with is the returning

veterans from the Iraq and Afghanistan operations. Most of these people are seen in clinics, oftentimes not adequately. The signature wounds of these wars are PTSD and other psychiatric illnesses. And I think that we can grossly underestimate those numbers. So that's something we have to factor in that we hadn't thought about before when we're looking at the general population.

DR. GOODMAN: We'll circle back to some of your questions, Dr. Harrington, but I wanted to try to respond to Dr. Neaton's question and kind of put things in perspective or context here.

Our recommendations to the FDA may lead to some actions on their part that would be precedent setting. And where the precedent setting would be, approval of an antipsychotic as a single therapy for major depressive disorder or as a single therapy for an anxiety disorder, generalized anxiety disorder.

There's already precedent for using an antipsychotic as an adjunctive therapy for treatment resistant depression. Unless I'm mistaken, I think that's where the -- so that was my rationale for

splitting it apart, because of the change it would represent in practice and what we teach to our trainees.

Dr. Temple?

DR. TEMPLE: I wonder in terms of numbers if

you would comment on the number of people who you think would be affected if it was for people who explicitly had failed other therapy. Maybe that's hard to put a number on, and maybe nobody would pay attention to it, but if they did.

DR. PINE: Yes, well, for all the reasons you bring up, it would be very hard to -- the data in epidemiologic studies also suggest that most people are not treated with anything, particularly for an adequate trial of what you guys would consider a first-line treatment. So it's hard to say. It's hard to say. But I think we need to be very wary of the very real possibility that approving this, particularly without any statement about adjunct or second line, potentially really opens the floodgates. And that's why I actually liked Dr. Goodman's change, and that's why I like separating the two questions.

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Personally, in thinking about this issue, I have a much easier time for communicating that, given the data we've seen, this is a reasonable thing to consider in somebody who hasn't responded to a reasonable treatment. And that's actually how I heard the company, just like you did, even though maybe it wasn't explicitly said.

I am very uneasy, to be blunt and frank about it, about proposing, or advocating for, or approving an antipsychotic medication as a first-line treatment in a condition like generalized anxiety disorder, given a lot of the things we've heard and a lot of the things that we haven't talked about. I mean, I do think we should talk about that, but as a psychiatrist -- and maybe this is what Dr. Goodman was thinking about -- my discussion is going to be pretty brief about is this a reasonable first-line treatment. In my eyes, it's probably not.

DR. GOODMAN: The Chair recognizes the sponsor.

DR. HUTCHINSON: Thank you.

Howard Hutchinson, chief medical officer. I

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just thought it was important to reiterate that the language Dr. Pine has just suggested is what we're looking for. It's a question of how to craft that language. We realize that there are other drugs out there that would be more commonly used for first-line therapy in these diseases, so we're looking for that option for the patients who are not able to tolerate that therapy for some reason or are failing despite multiple attempts with the first-line therapies. Thank you.

DR. GOODMAN: Dr. Temple, then Ms. Lawrence.

DR. TEMPLE: I just chatted with Tom. I think you can assume that we're not likely to say yes to something without limitations of that kind, and the question is whether we should do it then and what the limitations should be.

DR. GOODMAN: Lawrence, then Pine.
MS. LAWRENCE: Dr. Goodman, how long has Seroquel been on the market in treatment of schizophrenia? Ten years; 12 years?
DR. GOODMAN: We should ask the sponsor. They're closer to the data than I am.

DR. SCOTT: It's been on the market since September of 1997.
MS. LAWRENCE: Okay. Thank you.
And I guess in looking back at all the studies and the side effects of everything, your study is recent. Has there been a prior study to the side effects on the patients with schizophrenia?
DR. SCOTT: We had clinical trial programs in schizophrenia and in bipolar disorder. All that data was submitted to the FDA, and it's reflected under the approved labeling for both of those. So it's been broad programs in those other disorders, and the tolerability profile you're seeing here is really not dissimilar to what you're seeing in those disorders.
MS. LAWRENCE: Because I'm concerned if, as others have said, your major family doctor is going to be prescribing this drug, it's not going to be good. I don't think -- I mean, I think there are enough risks with the medicine itself, but if people are going to be prescribing this, maybe not really understanding the full extent of the drug, I think we're asking for the Pandora's box to open.

DR. GOODMAN: I think we are being asked -- maybe we should go back -- well, I'm glad that my revision of the question stimulated discussion. We can return to the crafting of the questions later. Let's go back to the slides or the discussion, that guide our discussion.
Here, I think in part, we are being asked to look at the unintended consequences. And one in my mind, naturally, is how much uptake will it be by primary care physicians and will some think now that we have one size that fits all? Even if I'm unsure of the diagnosis, I can prescribe Seroquel for whether or not it's schizophrenia, it's generalized anxiety disorder, major depression or bipolar disorder.
That elicited a response from the sponsor. Please, come up. And then Dr. Harrington, and who was next? Dr. Pine?
DR. GELENBERG: Dr. Goodman and members of the Committee, I just wanted to respond. I'm Alan Gelenberg again. I wanted to respond about the concerns about the primary care doctor.
If this medication gets the requested labeling

for MDD and GAD, it's reasonable to worry about the prescribing patterns of family doctors. I worry about those all the time, but it's not unique in this instance. I worry about the primary care doctors not

making appropriate psychiatric diagnoses. And I worry about their under-prescribing as well as over-prescribing various treatments and then not monitoring them. So it's not unique in this instance. There are cardiac, diabetes, obesity risks from non-treatment or from inadequate treatment, and there a series of risks from the existing treatment.

I think our best bet would be to educate and illuminate and help the primary care doctors diagnose, monitor and prescribe appropriately to patients. In terms of the specific concerns with quetiapine, I think primary care doctors are probably better suited for monitoring those adverse events than psychiatrists. In psychiatric practice with quetiapine and other second generation antipsychotics, patients are typically not weighed, don't have -- one of the things we heard about, waist measurements and so forth. Primary care doctors, by contrast, typically start off each visit by

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putting you on a scale and checking your blood pressure, and usually, periodically, monitoring your lipids and your glucose.

So I think in terms of the risks of this agent, I think the primary care doctor may actually do a decent job.

DR. GOODMAN: Dr. Pine, Harrington, and Robinson.

DR. PINE: So two comments that kind of came up during the discussion. One is to get back to Dr. Harrington's question about the magnitude of the effect. This relates to some of Dr. Neaton's questions earlier when the data were presented.

I would say that this is consistent with the effect that we see for these conditions with most medications. Probably on average, the results might be a little more consistent in terms of the number of studies that were done and the consistency of the placebo controlled difference. On the other hand, the differences are usually not large, and it's troublesome. And the field has troubled a lot with, as was mentioned in the open public hearing, the magnitude

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of the placebo response. And when you looked at all those different studies on one of the slides, you saw that there is a really big placebo response, which consistently happens across studies.

One of Dr. Temple's frequent points is that usually if you do a open trial and do a placebo substitution, that is less likely to happen. And it was interesting that that was not the case here, that the effect was not dramatically larger. But I think in the realm of the work on the efficacy of most agents for mood and anxiety disorders --

Oh. Did I misquote you?

DR. TEMPLE: Maybe a little. What I've said is that -- I mean, people have been remarking on how the small the effect -- of all the antidepressants,

it's only 2 or 3 ND (ph.) points and stuff, and that's absolutely true. Tom's been accumulating this stuff over years. Fifty percent of trials can't show anything, like their escitalopram study.

But when you do a randomized withdrawal study, now, that's sort of a fixed study of people who can, a) tolerate the drug, and b) think they're doing well

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on it, so it's enriched with responders.

DR. PINE: Right.

DR. TEMPLE: But what you see there typically is what you saw here. There's quite a dramatic difference between the relapse rate. So, you know, everybody has to decide which think is more important and stuff like that. But those trials almost never fail.

DR. PINE: Yes. But the bottom line, this is typical. And I would say, given that they recruited a somewhat more severe population, we should be very reassured in terms of that the evidence for efficacy is very strong, even though the clinical effect is no more than moderate.

The second point was, it would be really helpful in dealing with this issue of adjunct treatment or to get some standards in general, because, obviously, this question is going to come up again for other agents. It looks like there are two main issues on the table, although it doesn't sound like the FDA is being as explicit as I think would be helpful. In terms of, number one, there's a safety concern. But

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then, number two, there's also the need to show some evidence of efficacy in patients who have failed, or some kind of design where you go beyond just take all-comers and randomize them to this new drug that is thought to be less safe compared to placebo.

That's going to come up again when we talk about the difference between GAD and major depression. But, again, in my mind, it will be helpful -- and I would think it would be appropriate to, particularly in conditions where there are a lot of other treatments that are available, insist on both, to insist on a rigorous evaluation of the safety data so that you can say something about the relative merits of the first-line and the second-line medication, but also some direct experimental data that directly speaks to the issue of has this medicine been shown to work in people who don't respond to the typical things that they respond to.

DR. GOODMAN: Dr. Laughren, and then Harrington, and then Neaton.

DR. LAUGHREN: If a company is seeking a specific claim for treatment resistant something or

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adjunctive treatment for something, then there's a clear path forward. We have fairly clearly laid out what a company needs to do, and that needs to be

definitive trials to support that.
The third position is, in very few situations, in the absence of having such data, we feel we've been, I suppose, sort of flexible in labeling, in the sense of including some language, not a specific claim, but some language just to direct clinicians, because of a risk, to using this drug somewhere down the line rather than as first line.
DR. PINE: But I worry in the absence of also insisting on seeing some data, you might want to intend to the primary care practitioners that this is a risky drug and it should not be used until first-line treatments have failed. But in the absence of having data in patients who have failed, practitioners are going to be encouraged to take it right off the shelf and give it to somebody --
DR. GOODMAN: Wait a minute. Let me just add to that point. Again, the biggest concern -- I don't think this would be many practitioners, but some
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primary care practitioners, where you don't need much diagnostic clarity to make that decision.
DR. LAUGHREN: And that would be very useful advice to us. If your feeling is that the risks here are so concerning that in order to support labeling, there would have to be definitive data. As in the case of MDD, there is an adjunctive trial. There isn't such a trial that we have seen yet -- I gather one is almost completed, but we don't have the data for the adjunctive trial in GAD.
DR. PINE: So that's what I'm saying, that I look at the case of MDD differently because of those data; that that goes beyond what I would want to see.
DR. GOODMAN: Dr. Harrington? Then what's our order? Robinson, Neaton and Kelsey.
DR. HARRINGTON: Maybe my question's directed to the FDA.
I read this question a little differently about the public health consequences. At least what I'm reading into this is, as we think about moving into a population that is potentially quite large, is the bar that has traditionally been set an acceptable one?
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And what I mean by that is, largely what we're seeing measured here in the efficacy studies are what I'll term intermediate endpoints. Dr. Gelenberg I thought this morning did a nice job of convincing me that these are bad diseases where people miss time from work, they can't function at a high level, their suicide attempts.
I wonder, as we move from drugs which are affecting a rather narrow part of the population, i.e., schizophrenia, to the public health consequences of releasing these drugs to potentially millions, if not tens of millions, of people, are you asking us should the bar be higher? Should there be clinical -- should intermediate outcomes no longer be acceptable when the safety concerns are high? Because what I'm hearing,

and what I certainly do in my own practice, is I want to be able to quantify things. I want to know -- we all know that drugs do bad things. We know that they do some good things. And the way I view the Hippocratic oath is not first do no harm. I try to think of it as, on average, do more good than bad.

That's really what I'm trying to figure out here, is do we have enough information to quantify what

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the good is versus a quantification of what the bad is.

Is that what you're asking us?

DR. LAUGHREN: Well, that wasn't what I was asking. You could certainly introduce that. I mean, what I had in mind here really are two things. It's absolutely true that GAD and MDD are very troublesome disorders that cause a lot of impairment, a lot of dysfunction, a lot of pain and suffering. But on the general continuum of psychiatric disorders, they probably -- schizophrenia and bipolar disorder probably fall towards the more severe end. And also, in terms of numbers. The numbers of patients who would be affected by the adversity, if this drug were it to be approved, would greatly expand if it were indicated for GAD and MDD. And there might be certain things that you would accept, that you would be more likely to accept in terms of adversity for a treatment for schizophrenia than you might for generalized anxiety.

But you want to add an additional --

DR. HARRINGTON: No. I'm actually saying the same thing you are. Let me give you an analogy from cardiology, is that I am willing to accept a risk of

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intracranial hemorrhage if I'm having an anterior myocardial infarction, and the choice is a reasonable chance of dying. I'm willing to accept the risk with fibrinolytic therapy if having an intracranial hemorrhage. If I'm having a bout of angina, I may not be willing to accept that risk.

So I think I'm very much in line with what you're saying. I wrote down one of the sponsor's comments, which is that the risk profile here is not dissimilar from what we see in the schizophrenic trials. I think that's what they said. And so, the question I have to you, then, is, then shouldn't the bar be higher in a disease -- if the risks are still going to be high, shouldn't the clinical benefit be pretty high as well?

DR. TEMPLE: The trouble is, you have a problem. We have not figured out how to do outcome studies with highly symptomatic conditions yet, because you won't find anybody willing to be untreated in the face of recurrent depression. So if you know how to do it, that would be very good, but we haven't figured out how to do that.

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It's fine when what you're treating is lipids, which nobody feels, or the blood pressure, which nobody

feels, or the platelets, which nobody feels. You get outcome studies there. We don't really know how to do it against placebo. You can compare two drugs; on the other hand, you don't really know what difference you're looking for.

Just one comment. The thing that impresses me most about these trials, always, is the ability to prevent recurrent, nasty depression or anxiety or whatever it is. I would have said -- but we'll be interested in hearing what you say -- that that is a meaningful benefit; that people would find that useful. And the question you're posing is, what do we do about these risks, which are acceptable in schizophrenia, but we're very nervous about them in less severe illnesses, and how do we put all that together.

DR. HARRINGTON: And I'll accept your last point, Bob, that preventing a relapse may well be not an intermediate outcome, obviously, but an important clinical outcome. So I'll accept that.

DR. GOODMAN: I have a few people that have

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been waiting to speak. And after we do that, I think we need to dig a little bit more deeply into some of the specifics mentioned in Question 2, in order to answer Question 1 adequately.

So the sponsor had a comment.

DR. SCOTT: And I don't want to say that I misspoke, but I think broadly the adverse events that you're seeing in MDD and GAD, the types and kinds of adverse events that you're seeing in both schizophrenia and manic and depressive episodes, and bipolar disorder -- but I think when you look at the changes in glucose, changes in weight, changes in lipids, you're seeing smaller changes at the lower doses that we're associating MDD and GAD.

DR. GOODMAN: Dr. Robinson?

DR. ROBINSON: Also, just to sort of reiterate how prevalent these disorders are, I mean, I think the ECA studies, which are the -- NIMH paid for these big studies where, essentially, they went door to door and did very good epidemiology studies. I mean, there we were getting something like anxiety disorders maybe 20 percent of the population. So we are talking

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about -- there are data from NIMH that these are very prevalent. Because of that, again, we're thinking about primarily non-psychiatrists being the people who might be using these drugs.

Yes, I think GPs are very good about measuring weight and blood pressure. They're very bad about some of the major side effects of these drugs. I don't know very many GPs who are really good at doing tardive dyskinesia exams, nor the Schooler-Kane criteria, et cetera, for TD. And so, I think that's a big area that they're not going to know about. And they're not going to know about akathisia, a lot of the motor side effects, which can have very profound implications.

The other comment is, given that if we're talking about a very, very big population that might be exposed to these drugs, then I think it becomes very important to know the safety profiles in subgroups. Like when I was talking about, in schizophrenia, if you give a young schizophrenic first-episode quetiapine, in 12 weeks you may get 52 points increase in their triglycerides, I think it would be very important to know -- if you're going to be giving quetiapine to a

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big group of 20 percent of the population, then knowing even about side effect profiles and specific demographic groups are very important because that group can be a huge -- that can be a few million people.

DR. GOODMAN: Thank you, Dr. Robinson.

Neaton, Kelsey, and then I'll let the sponsor respond.

DR. NEATON: Well, I viewed this first question pretty much the way Bob did. I think the bar should be higher, for two reasons. One, the prevalence, and the second is what I heard the sponsor say, 25 to 30 percent of the patients be treated chronically, long term. And so, we're dealing with a set of studies that the longest is 48 weeks. Most of the data is from six or eight weeks. And so, it's a tremendous uncertainty concerning the risks in my mind.

Concerning the efficacy outcome, I accept the fact that the drug is better than placebo, but the effect is modest. And it actually may be more modest than even what is estimated because around 20 percent of the people dropped out; they're using last value

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carried forward; and if stopping the drug exacerbate some symptoms, that could underestimate kind of what the potential effect of this drug is on these scales that are being used relative to placebo.

The cardiovascular risk is uncertain I think in their studies because the person years of follow-up is quite low, so there's a power issue. Plus there's a potential for bias issue because they stopped characterizing the events two weeks after people stopped taking drugs. I agree that there are problems with the study that kind of were nicely laid out in terms of limitations, the confounding with the study from Tennessee, but at least they're there. There's kind of some methods that have been used to at least address these two issues a little bit better, the power issue and the potential for control of bias due to confounding.

So coupled with the metabolic effects, which are real, and probably also underestimated because of the dropout -- if you just look at the curves that we were shown, there's substantial falloff in patients followed over the 48-week period. And we heard that

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people didn't drop out because they were gaining

weight, but I guess I don't find that very reassuring. We didn't see enough analyses to really characterize what are the people dropping out like versus those that continued on therapy.

So I come away feeling very uncomfortable about this, that we're dealing with modest effects that may be underestimated or overestimated in terms of efficacy, and a substantial uncertainty concerning cardiovascular risks because of power and bias, and metabolic effects that in the short term are concerning, and 25 to 30 percent of the patients will be taking it long term.

DR. GOODMAN: Before we get to Dr. Kelsey, I think Dr. Laughren wants to --

DR. LAUGHREN: Just one quick thing on the effect size here.

The effect size that you're seeing in the short-term trials is very much in the ballpark of what we see with other antidepressants. The relapse prevention trials, if you look at relapse rates, it's about a 30 to 35 percent difference between drug and

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placebo in relapse. And that's a pretty good effect by most --

DR. NEATON: I guess I come back -- I mean, I heard the comment earlier that that analysis had been done, but I cannot believe, looking at those Kaplan-Meier curves that relative hazard is not different in the first four or five weeks of therapy. And so some of that's got to be the effects of stopping the treatment.

DR. LAUGHREN: We have -- and I'm sure the sponsor's done the same thing. We looked at events occurring after two weeks to get at the withdrawal question.

Do we know what those relapse rates were for that --

DR. NEATON: Why not go out --

DR. LAUGHREN: Because discontinuation effects, if they're going to occur, occur very early; expect discontinuation effects beyond two weeks.

DR. NEATON: Some of the metabolic effects continued longer.

DR. TEMPLE: Whether the metabolic effects

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really last and how long they last is one thing, but the usual ideal of a withdrawal effect -- who knows; this could be wrong, I suppose -- with the withdrawal of SSRIs, for example, or beta blockers, or whatever, is that they happen fairly rapidly because it's a response to the withdrawal of the pharmacologic effect. So, I mean, whether it should be two weeks or three weeks, I don't think anybody can say.

I think what Tom is saying is that after a plausible period of time, you still see a difference in relapse rates. And for what it's worth, we see that with all the SSRIs all the time. They're much better

preventing relapse than they are at the initial treatment, which is always a puny effect.

DR. NEATON: Okay. So let's leave it arbitrary. So how does the relative hazard, then, of relapse change over time in these trials? Let's not kind of leave it kind of an arbitrary two weeks or four weeks, just let's look at it over the time. And the curves suggest that there's a substantial difference, to me, over the first several weeks of the study compared to later.

DR. TEMPLE: So that most people relapse within the first 8 to 16 weeks as opposed to later. You have to form your own judgment. That doesn't surprise me, that relapse would occur when you take the drug away, relatively soon.

DR. NEATON: But the other side of the coin is if you make it past the first eight weeks, for whatever reason, then you do better on placebo.

DR. GOODMAN: Dr. Kelsey?

DR. KELSEY: I just had a quick question about PTSD.

If people with that diagnosis are being prescribed Seroquel, is that considered off label?

DR. GOODMAN: Yes, that would be an off label indication.

The sponsor, I know you've been waiting to respond.

DR. SCOTT: Yes. We'd like to raise a couple points with respect to the short-term trials and last observation carried forward. We've done reanalyses with respect to sensitivity, doing other methods, and the results are broadly consistent. In fact, the failed study became positive using a different method of analysis.

Now, we want to address three things, one of which is the longer-term metabolic risk. I'll have Dr. Newcomer up to speak to that. And then the cardiovascular risk with Elizabeth Bjork, and the sudden cardiac death with Lisa O'Dowd, please.

DR. NEWCOMER: Well, I think what I want to speak to is the context. I think the Committee's having a very fruitful discussion of context. And what many of us who do research in this area are concerned about is the overall burden of cardiometabolic risk in this population. Many of us, and people around the table, are certainly concerned about this. Certainly Tom Insel in some of his talks is citing a paper from -- I'm not going to go to that quite yet -- citing a paper funded by CMS and SAMHSA, looking at a 16-state study, where about six of the states had complete inpatient and outpatient data looking at those individuals with major mental disorders and minor mental disorders. Patients were losing, compared to the general population, somewhere in the neighborhood

of 13 to 30 years of life expectancy. And not much difference between major and minor mental disorders. The point is that this is an at-risk population, whether they're getting antipsychotics or not.

The other point I wanted to raise, if I can show this slide. There was just a paper published recently by Richard Rubin, who was recently president of the American Diabetes Association. And he had done a post-hoc analysis -- if I can get it to come up -- of the Diabetes Prevention Program. The Diabetes Prevention Program, recall, was a major NIH-funded effort to look at what might be moderators or things that would control risk of progression from pre-diabetes on to diabetes. A certain percentage of the patients with pre-diabetes who entered that trial had depression.

So the question was, that Richard Rubin asked in a post-hoc way and published recently, as I've got up here on the slide, that it looked as though treatment for depression was a risk factor, and most of the treatment that was taking place was SSRI use. So existing antidepressant therapies may in fact have some

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risks -- and if I had to speculate, it might be in relation to the weight gain that you often see on these medications.

Many of the psychotropics that are available -- virtually all of the psychotropics that are available for the treatment of depression and anxiety disorders are associated with some increase in body weight. So it's not shocking that there would be some increase in risk.

If we can go on to this other slide. A paper came out just this month in the American Journal of Psychiatry -- it's going to be hard to read. But, basically, it was from the UK General Practice Research database. Same question: is there an association between use of antidepressants, existing antidepressants, and the risk of diabetes for people who are taking these drugs for depressive disorders? It's going to be hard to see, but almost all of the risk ratios are greater than 1, and several of them with commonly used agents. For example, here's paroxetine, and here's fluvoxamine, and venlofaxine, have a statistically significant increased risk of

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progression to diabetes in a five-year window of observation.

Then one last slide for further context in that same UK General Practice Research database, just to put this in context of risk factors that we know very well for diabetes. For example, here's overweight, a body mass index of 25 to 29.9. We're talking about a relative risk about two times. If you go up to obesity, now we're talking -- just mild-level obesity, about four and a half times the risk, and if you go to morbid obesity, about 14 times the risk, just

to frame context for the discussion.
By the way, this is not just psychotropic drugs that are associated with weight gain and, therefore, risk of diabetes, here's beta blockers, about one and a half times the risk, statistically significant; thiazide diuretics; here's the antipsychotics, same signal; and our old friends, glucocorticoids with somewhere between two and two and a half times the risk. So it's an important broad context that you think about all of it. And I think the discussion's very fruitful.

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DR. SCOTT: Dr. Bjork?
We wanted her to go through -- there were some comments on the cardiovascular events that we had.
DR. GOODMAN: What I'd actually like to do is I'd like to return to the discussion of the questions, and then if you have any rebuttal, I would hear that.
Could we put the slide up on the questions?
What I'd like to do is, 1 is predicated on 2 and a more in-depth look at some of the risk issues.
Could we have a little bit more discussion on the metabolic risks? I think it's a good segue from Dr. Newcomer's talk. So I'd be interested in members of the panel with expertise in this area.
Dr. Greenway?
DR. GREENWAY: Well, I think it's remarkable how much a small amount of weight gain can be detrimental in terms of diabetes, or a small amount of weight loss can be in terms of improving things. One example is the Diabetes Prevention Trial that was just alluded to. Those people did have impaired glucose tolerance to start with. About the same amount of weight gain was seen in the long-term studies with

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quetiapine, were seen as weight loss in the Diabetes Prevention Trial, and there was a 60 percent reduction in the onset of diabetes over that three years that patients were followed.
Clearly, weight is something that can be easily measured, and so, one can pick this up. But I think that the magnitude of the weight gain, at least from what I understand, is greater than the other drugs that were just mentioned on that slide. So I would have certain increased concerns about this drug compared to the other ones. And I, like most of the other panel members that have said so, would prefer to use this as a second-line agent rather than a first-line one.
DR. GOODMAN: Thank you very much.
Dr. Pine, did you have some comments from earlier?
DR. PINE: I was just going to come back to the issue that Dr. Harrington and Dr. Neaton raised about raising the bar, and I guess it does relate to the concern, which everybody's been saying is pretty high about the issues on metabolic effects, not to

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mention tardive dyskinesia.
In my mind, the idea of insisting on demonstrating efficacy in patients who have failed a first-line treatment is a pretty high bar; that there are relatively few treatments that pass that bar. And that's really where I was pushing the FDA, that here we have an instance where not only is the parallel -- a few parallel studies for depression show a clear, reasonably sized effect, but there's also a clear effect in people who fail a first-line agent. That is a high bar. That is a significantly higher bar than most other agents are forced to jump over. And again, at least in my mind, for the case of depression in particular, that makes me feel a lot better.
DR. GOODMAN: Dr. Temple?
DR. TEMPLE: You were talking sort of around this. It could also identify a population that is a relatively small subset of the entire population of people who have depression or anxiety, that could be the very group that one thought it's appropriate for. It's a great narrowing, and that's one of the things we need to hear from you.
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DR. PINE: I mean, as you yourself said, and it's accurate, it's very hard to predict the characteristics of any patient group that are going to predict response or non-response to a treatment. So I think it's far more workable and sends a clear message to companies if you say to them that experimentally, you've got to show, in this treatment that we're worried about, it has added benefit to something that fails.
DR. TEMPLE: All right. Well, let me be explicit. You say there are -- and I think we agree with that -- there are pretty good data that people who don't respond can benefit when this drug is added to them in depression, and there's a study in anxiety going on.
Does that describe or could that describe the population that you think is the only population that should get this drug? We don't know whether everybody will follow that advice, whatever the labeling says, and would have to think about how to do it. That is a considerably smaller population than the entire population of people who are depressed or anxious.
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DR. PINE: Yes, I would feel very good about that.
DR. GOODMAN: You're just talking about the adjunctive treatment, not the monotherapy.
DR. TEMPLE: Well, yes, that's right. We don't know whether dropping the thing they failed would leave you still able to respond, and the labeling would presumably say that; we don't know how it would work if you took away the drug you partly responded to or something. But adjunctive use is one possible claim

that a drug can have. And, in fact, there are some that already have that, so it's not unprecedented.

DR. GOODMAN: Dr. Potter?

DR. POTTER: Yes. I just thought it might be useful to remind us all of the historical view here that -- just personally, I spent 25 years with the National Institutes of Health, and then more recently in industry. And to get to Dr. Temple's point, I think both the National Institute of Mental Health and the whole field, and industry, has had a deep interest in identifying and finding the subpopulations and then individualizing treatment in this space.

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So it's not as if we haven't spent hundreds of millions of dollars, cumulatively, and very huge efforts over the last 30 years to be able to do this. Unfortunately, as so many people have spoken to today, our science of subtyping patients and predicting exactly who responds to get the right drug to the right patient is not to the point where we would like it to be. So we are confronted with -- I think Dr. Neaton, very good questions. We are confronted with the reality that maybe when we have drugs with alternate mechanisms and we see robust efficacy by current standards, which, frankly, these trials have been more robust than a lot, frankly, because fewer trials have failed here.

So we have to ask ourselves, will this capture a population of patients, which we can't exactly cull out right now, who would really benefit from this in ways that they won't benefit from other drugs.

DR. GOODMAN: So you mean as a monotherapy.

DR. POTTER: Either as. So to get to that point, how do we estimate the positive public health consequence. And our science just doesn't give us a

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very good sense to do it. So we're thrown on the judgment of all of you ladies and gentlemen here.

DR. GOODMAN: Have we sufficiently discussed the potential metabolic risks?

Dr. Harrington?

DR. HARRINGTON: I just want to remind people, I think that Dr. Neaton had suggested this, that a year is just not adequate to fully characterize the risk. I remind people that in the lipid lowering trials, the Kaplan-Meier curves against placebo separate sometime between a year and 18 months later, and most of these trials have followed people for 4 to 7 years.

Now, there are some more recent trials, where there's an earlier effect picked up, but it does appear that if you're going to -- you're talking about disease, atherosclerosis, that has developed over decades. And I think it would be naive to assume that it can be effect -- metabolic effects can be detected in a year. We also know from the epidemiology that small changes in population -- cholesterol, for example -- translate into cardiovascular events: death,

myocardial infarction, stroke. So I don't think we have well characterized --

DR. GOODMAN: So, in part, what you're saying is we may not know the answer to number 1, what the public health consequences are, for another 10 or 20 years.

DR. HARRINGTON: I think that that would be a safe statement.

DR. GOODMAN: The sponsor wants to respond.

DR. SCOTT: A couple of points, that we believe, in the answer to the question, that could be beneficial for those patients who are properly treated and properly managed and monitored for the potential adverse events.

But I wanted to correct something -- not correct something, but just to -- you said that we didn't present some analyses. We were trying to have a scope for time. I'd like Elizabeth Bjork to come up and speak to the question about dropouts during the longer-term studies, because we've looked at it very closely to make sure that the 48-week data weren't, in fact, reflective of those who just got out there.

So Dr. Bjork.

DR. BJORK: We are very well aware of the fact that when you look at the cohorts the way we presented them, the mean, it decreases over time. And that has to do with the way these studies are designed. And that's what you have on the slide here, are the reasons for discontinuation during the randomized phase. And as you can see, the vast majority of patients discontinued the study due to closure on the study or due to development of the study specific discontinuation criteria. And they were not related to weight gain or to metabolic effects. They were related to meeting the efficacy endpoint, i.e., having a relapse of a depressive disorder.

For this very reason, we decided to look into cohorts instead of just looking at the mean values over time. We then followed patients, both for glucose and for weight. So we followed the same patients over time, and I will start by showing you the glucose effect.

So here, this is from Pool C, and this is during the randomized phase. And above, you have the blue ones. They are the patients on quetiapine. And you can there see patients who went all the way to Week 42. So it's the same patients over time. So you have a 48-week cohort, a 36-week cohort, and a 24-week cohort, and the same for the ones that were randomized to placebo. So the pattern of effect here for glucose, and we can see the same for -- I hope I have the same for weight, a very, very similar pattern. And these slides were also presented in the briefing document.

Reaching back to the discussion that we had

before on cardiovascular disease, I really want to remind everybody that the effects we saw on the important LDL ratio over time really was very minimal. So this is the same plot done for weight. So here we follow the same patients over time for the 48-week cohort, the 36-week cohort, and the 24-week cohort, and the same for placebo. And again, back to LDL/HDL, very minimal effects over time. And even with most of the patients that were included in our trials for a short term, we had substantial amount of patients, over 1,500 patients, that were treated for more than a year in the Pool A.

DR. NEATON: I just want to point out that

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this analysis got the same problem as the other one, of course, because the curves are no longer protected by randomization, because people have selected out for very different reasons in the two groups, more than likely.

DR. BJORK: That's absolutely correct. I tried to convince you that the reasons for discontinuation were not due to weight increase or to metabolic parameters. They were due to efficacy reasons and prespecified -- and the vast majority of the patients leave the study because we stopped the study because we had sufficient number of events. So, again, it was not efficacy driven or safety driven.

DR. GOODMAN: Okay. Thank you.

DR. SCOTT: We realize there are limitations to that data set, and part of our risk management plan is to be actually conducting a study which addresses that specifically.

DR. GOODMAN: So have we now, to the satisfaction of the Committee, assessed the metabolic risks?

So what I would like to do, in the interest of

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time, is to move on for further discussion of tardive dyskinesia, if that's felt necessary, and return to the issue of sudden cardiac death as well.

Dr. Neaton?

DR. NEATON: So I'm totally out of my area here, but I heard -- this is what I heard, and maybe somebody can just enlighten me. So I heard that a Schooler-Kane criteria was applied, and that, according to this criteria, 2.4 percent had evidence of dyskinesia. I believe it was characterized as being low. And I thought, well, gee, it didn't sound so low to me, given the fact that your trials were only six or eight weeks. And so, maybe you could just --

DR. GOODMAN: Dr. Kane happens to be here.

DR. KANE: Thanks. My name is John Kane. I'm from the Zucker Hillside Hospital and Long Island Jewish Medical Center. In the Schooler-Kane criteria, we proposed to help researchers and clinicians do a better job of defining a case of tardive dyskinesia. The idea was that patients would be rated on a rating

scale, and if they scored above a certain threshold, that might be considered a case. So those criteria

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were applied to the long-term data. And you're absolutely right that many of the trials involved exposure for relatively brief periods of time. Tardive dyskinesia can take many months or years to develop.

If we look at the data sets that involved long-term treatment, in a population of elderly patients, we have 389 subjects, 60 patient years of exposure. There was one case who met Schooler-Kane criteria on one occasion. And then the signs of tardive dyskinesia disappeared after that. So we would not define that as a case. But being very conservative, there was one case, so that led to an annualized incidence of 1.7 in that study. In the other group of patients followed for longer intervals, we have 2,500 patients and 743 patient years. The incidence of meeting Schooler-Kane criteria, again, on one occasion, was 0.8 percent annualized in that subgroup.

So there is a potential risk of tardive dyskinesia, and I think everyone would acknowledge that. That is in the package labeling. One of the most well substantiated risk factors for tardive

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dyskinesia is cumulative dosage. So here we're talking about a relatively low dose of quetiapine, so we would expect the incidence to be substantially lower.

I should also point out that quetiapine has been associated with a lower level of extrapyramidal side effects in other diseases treated with quetiapine. And, in fact, it is one of the two drugs that's frequently used to treat patients with Parkinson's disease who develop psychoses. So clozapine had been the gold standard; now quetiapine is very frequently used to manage those patients. And that's really attributable to a very low likelihood of causing neurologic side effects.

DR. GOODMAN: Dr. Kane, before you step down, could I ask you a question on relative risk of developing tardive dyskinesia, based upon age, gender and diagnosis?

DR. KANE: Yes. One of the risk factors is older age, particularly older women. We've seen in our studies that the risk is as much as five times greater in the elderly. So, again, it's reassuring to see in the elderly sample here that there was a risk of 1.7.

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And, again, that one case is not a case that we would truly define as a case, but meeting Schooler-Kane criteria on one occasion. So that's reassuring.

In terms of diagnosis, there is some evidence -- it's inconsistent. But in one of our studies, we found that those patients with depression did have a higher incidence of tardive dyskinesia than patients with other psychiatric diagnoses. That is not

a consistent finding across all of the studies, but there certainly is some reason to think that.

DR. GOODMAN: Thank you.

Any other questions for Dr. Kane?

Thank you very much.

It seems to me that one of the issues in evaluating risk of tardive dyskinesia, as was just mentioned, is cumulative years of exposure. And we have over the years developed some guidelines for how long we should keep somebody on antidepressant medication, like SSRI or tricyclic, depending upon their history and presentation of their illness.

As I see it, we don't have similar data here for quetiapine, so I think it's kind of hard to

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predict. I'd be interested in others' opinion or from the sponsor about what the recommendations would ultimately be in somebody who, say, was on quetiapine monotherapy for depression; how many years of exposure -- in the case of GAD, how many years of exposure might they have.

It will be interesting. I'll accept anybody's response to the question.

DR. SCOTT: We'll ask Dr. Gelenberg. Before he gets up here, I think that the label that exists for the risk of tardive dyskinesia actually characterizes in the situation. It's the lowest dose to achieve the right response

Dr. Gelenberg, the use of agents for how long they should treat in MDD and GAD, how long they should treat and risk for tardive dyskinesia.

DR. GELENBERG: Yes, thanks.

The operative word is "should," and here there's a huge disconnect between treatment guidelines and real community practice. In major depressive disorder, the recommendation is after a first MDD episode to taper and stop the medication after 6, 9, 12

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months of continuation therapy. After two episodes, you can consider maintenance treatment. And certainly after three episodes or a particularly severe earlier episode, one goes into maintenance treatment. GAD is less well characterized. The assumption is that chronic treatment probably isn't necessary; people can stop and see how they do. But I think for most patients, long-term treatment is required for maintenance of remission, for those who achieve remission.

Then you get the actual real world, and in the real world, you have studies like Greg Simon's from Puget Sound, where you're lucky if people stay on antidepressant medications for three months, and that's sort of the outside. So in the real world, people often tend to stop their medicine. So there's a huge divergence between optimal treatment, which, in fact, patients would be staying for years and decades on these treatments and what actually happens.

DR. GOODMAN: But I think it's fair to say we don't know whether those guidelines, that have, in part, developed through studies of tricyclics, apply to quetiapine.

DR. GELENBERG: Tricyclics and more recently, the latest iteration for the newer generation antidepressant, but certainly not for -- (off micrphone).

DR. GOODMAN: Right.

Unless there's more discussion of tardive dyskinesia, I'd like to spend a little time on the sudden cardiac death and then take a break, before we come back and look at the questions to vote on and actually do a vote.

So how about further attention to the risk of sudden cardiac death? There was some divergence of opinion, and I wanted to see if we could revisit it.

Dr. Pine?

DR. PINE: Yes. I think maybe there was divergence opinion about interpreting the one study, but I'm not sure I'd be interested in other people's thoughts; the cardiologists in particular. I'm not sure how much divergence of opinion there was that there is the need to be cautious in terms of the cardiovascular risks associated with atypical antipsychotics in general, including quetiapine. But maybe we should hear from the cardiologists about it.

DR. GOODMAN: Yes, that's an invitation, Dr. Harrington.

DR. HARRINGTON: I think that Dr. Pine has a fair interpretation, that what we're faced with is observational data, which Dr. Stone pointed out the limitations. Dr. Ray has done his best to consider those limitations in a variety of rather sophisticated analyses. And I would say we know that the class of drugs generally increases the QT interval. We know that QT prolongation is associated with sudden cardiac death. We also know that there are patients who, perhaps, suffer sudden cardiac death in whom it is unclear as to whether or not they had QT prolongation. The only way to really know this is in the context of randomized trials with long-term follow-up.

DR. GOODMAN: One thing we haven't seen today is a comparison of the antipsychotics with respect to QT prolongation.

Do you happen to have a slide with you that would show comparative effects? I wonder if that would be useful to you, Dr. Harrington, to take a look at quetiapine.

DR. HARRINGTON: I thought somebody showed it this morning.

DR. GOODMAN: You're confusing it with yesterday maybe.

DR. HARRINGTON: No, no, no. I think we --

DR. GOODMAN: It was today? My mistake. My mistake.

So maybe this is the first time I will see it today.

UNIDENTIFIED SPEAKER: It's an invitation to take a look, Dr. Goodman.

DR. SCOTT: Could I get Dr. Eric Michelson to come up and speak to the QT data? Because we'd like to also address a couple points that were made this morning by Dr. Ray about our analyses, and just to make sure that we give the complete things that we did in that clinical trial program.

DR. MICHELSON: Thanks. Eric Michelson, cardiologist with AstraZeneca. I also have training in electrophysiology.

I didn't have the opportunity to attend yesterday's meeting, but I did see in the handout that you provided to this committee, there was a comparison given from what was known as the Pfizer Study 054, in which there was a presentation of some of the comparative data related to potential effects on the QT interval.

Would you like us to revisit --

DR. GOODMAN: Yes, I'd like to see it.

DR. MICHELSON: Yes. So let's just take a look at that for a moment.

So apologies to Dr. Temple. And just so you understand, the look that was taken yesterday by the group, Dr. Stockbridge's group and Dr. Garnett, they have done really a tremendous service to all of us looking at these things very, very meticulously. And having taken a look at the analysis, what's here, I'd like you to focus for today's discussion on QTF. It's c probably the single best, off-the-shelf technique or subtle differences in which correction method you use. The F is only because it uses a Q function as opposed to B, Bazett, which we see on our standard ECGs, which is square function. F is a bit more accurate and reliable, and drugs may have just even small changes in heart rate.

If you'll look at QT -- let me just point out c first that quetiapine itself does not prolong the QT. It does not prolong the QT. However, when you take a look at the effect on QT corrected for heart rate, it does, using some methods, then project to cause small changes, an increase in mean QT. And in this case, c the S-MED (ph.), if I can find it here, was a mean effect of about 4.8 -- thank you so much.

Is that Dr. Temple? You're so kind. Thank you. I appreciate the assist. Thank you.

So 4.8 is a mean effect.

When we do studies looking at effect, we're

trying, in general, to exclude an effect that on the average is less than 5 milliseconds. And we even throw in some confidence intervals around that. And so, for us, the upper bound might be less than 10. It just happens -- it's not projected here, but the upper bound was less than 10. So if we were to look at this in terms of interpreting this effect, we would say that

although there was not a placebo here, and at the time this study was done, it was assumed that haloperidol was a drug at the doses given that would not have an effect on the QT interval.

Just to put this perspective, the drug study was done -- this study was done by Pfizer then, with a way of projecting a worst-case scenario. So for each of these drugs, after they were already in steady state, a metabolic inhibitor was thrown on board that would then show this drug at some multiple and its effect.

So in this case, quetiapine was studied with the addition of a large dose of ketoconazole, so that the actual concentration of that drug in this study is approximately eight fold, the concentration that you'd see now with the 300 milligram dose. And even with that high concentration, eight fold, the 300 milligram dose, you're seeing essentially what would be a negligible effect. And if you compare it to haloperidol, it's, again, half the size of the effect of haloperidol. So these data we would interpret as being very reassuring.

Now, what I really would like to show you is the data, just again, the QTF data that we actually

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have, based on 26,000 patients in our own program, because if you take a look at those mean effects --

Is that here? Do we have it?

If I see it here, I will be very happy to press it and magically have it come up.

This is okay. This has been shown before. Anyone that's showing the mean effect.

You saw a core deck before, but, basically, you saw effect. It's in the briefing document also. The effect that we have is essentially within 1 millisecond of placebo.

Dr. Temple, can I just ask -- Dr. Garnett's not here. Dr. Stockbridge isn't here from your IOT committee.

Would you sort of concede that the effect that we have is essentially -- is indistinguishable from placebo as --

DR. GOODMAN: He doesn't have to answer that question.

DR. MICHELSON: Okay. Thanks.

Okay. Furthermore, when we look at other sort of indicators, such as ours, what's the proportion of

patients that go above 60 milliseconds, which might be a threshold for concern, it's no different than placebo. The numbers are low, no different than placebo.

So if you take a look at this, this is essentially 50 patients out of 15,000 total patients, 1 in 3,000. You saw numbers yesterday that were approximately 1.4 percent of patients passing some of these thresholds. This is 1 patient in 3,000. Look at it. And density; it's less than placebo, no different. Again, if you take a look at another threshold -- as clinicians, we care about -- Bob Harrington cares about it; 500 milliseconds means something to us.

But again, 15,000 patients, five --

DR. GOODMAN: I'm sorry. Just in the interest of time --

DR. MICHELSON: Yes. Is there a question I can answer?

DR. GOODMAN: Yes. Why don't you stay there a moment.

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Let me invite any comments or questions from either Drs. Harrington, Stone or Ray, on sudden cardiac death other cardiovascular --

DR. MICHELSON: Thanks. And while you're doing that, I'd like to -- I just want to ask if we could just -- I do want to discuss with Dr. Ray what we presented.

DR. GOODMAN: Let Dr. Harrington go first.

DR. MICHELSON: Yes, please. Dr. Harrington.

DR. HARRINGTON: Yes. So I think that we've seen this this morning. This is a fair interpretation of the available QT data. My point is that sudden cardiac death is sometimes not seen in patients with QT prolongation. And so there's some mechanism at play here that we, perhaps, don't understand. We also don't understand some of the issues and conditions of, for example, hypovolemia, hypokalemia, whether or not the response to QT prolongation changes.

So, how do I then interpret all of this? I think as a class of drugs, I certainly am vigilant about the QT. I think Dr. Pine said it well. And I'm concerned when I look at data like Dr. Ray's, where,

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for all of its limitations, does at least raise some cautionary flags about the risk of sudden cardiac death associated with drugs like this. Despite, I thought the very nice rebuttal, if you will, that Dr. Stone created, I think it's one of the challenges of observational data.

So I think, Mr. Chairman, we don't adequately know.

DR. GOODMAN: Okay. Thank you.

Any further comments from Dr. Stone or Ray? I don't know if Dr. Ray's still here.

He is still here, but he has no further comments.

DR. MICHELSON: Is it okay if I just put that piece into context also? It doesn't answer the question, but again --
DR. GOODMAN: Yes. If Dr. Harrington says yes, it's fine with me.
DR. MICHELSON: That's okay.
Dr. Harrington and I, we're used to hard outcomes, and we used to things like CV deaths. So I just want to get some hard data because we agree. The

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QT is reassuring, but I want to just at c least -- because I think Dr. Ray's done us a service, too, and it's important for us to stay vigilant. And I did appreciate the presentation by Dr. Stone.
But I do want to -- SS-16, if I could.
If I have this correct, I think I've got Dr. Ray's -- some of the data from Dr. Ray's presentation, SS-16.
DR. HARRINGTON: While we're waiting, Dr. Goodman, a question. This triggered my memory from Dr. Ray's presentation this morning.
If you have the time to sudden death from initiation of drug. When did the sudden deaths occur relative to the start of antipsychotic drugs? Because that may speak to whether or not we learn enough in a year's worth of data.
DR. RAY: If you had adequate sample sizes, you would learn that in a year's worth of data because we did an analysis specifically where we restricted the cohort to those with less than 365 days of cumulative antipsychotic use, and we found, essentially, the same findings, and it was statistically significant. We

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thought that was important because we were concerned about distinguishing between long-term metabolic effects that might eventually raise someone's risk of sudden cardiac death versus the short-term arrhythmogenic effects. You see the same increased risk in the short term in persons with less than 365 days of use.
DR. O'DOWD: If I may, I wanted just to share two things regarding the presentation that Dr. Ray had this morning. One is, I thought it might be informative for you to see the time to death for patients who had cases adjudicated sudden cardiac death within the quetiapine development program. And you can see that we have, really, no clear pattern of when the events occurred. We had one death within seven days of starting therapy. We had five deaths, 7 to 30 days on therapy, and 11 days after being on therapy for more than 1 day. You'll note that this is not corrected for exposure, though, so one must be careful when interpreting these numbers. We also, for conservative purposes, included all deaths we had in the database, even if patients were off treatment. So, in fact, 6 of

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the 23 quetiapine adjudicated deaths were actually off therapy, but we included those since we didn't want to hide any data. So I wanted to provide that for a little bit of context.

The other thing Dr. Ray had found in his study was that there was a dose effect. If I may ask you for the dose slide.

We saw that there was no evidence of a dose response within our quetiapine database. This will show you that data. You could see that looking at the doses that were reported at the time of death in the development program, we had all doses basically represented. We have new evidence of the clear dose response. We thought it might be important to look at the data cut by Dr. Ray's definition of low, medium and high dose, and those numbers are on the bottom. And again, you can see that we did not -- we were not able to replicate the dose response he had found in his study.

Also, I wanted to make one small clarification to how we analyze our data. Dr. Ray had made the comment that our data was just sort of all pooled

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together. And, in fact, the Simpson paradox does not actually apply because within each pool, data was stratified by trial. So I just wanted to make that clarifying point in case it was important for you to consider.

DR. GOODMAN: Okay. Thank you.

Any comments from the panel or Dr. Ray?

Okay, put the discussion questions back up.

I would propose a sharp, 10-minute break. Come back, decide what questions we're voting on, and see if we're ready to vote on them.

Is that fine? Okay, good.

(Whereupon, a recess was taken at 2:24 p.m.)

DR. GOODMAN: I'm going to start now. All the members of the panel are present. I'm going to resume.

Based upon the discussion we just had, I'm going to recommend a change in my proposed revised questions, which are a little bit less radical than the first one.

Yvette, could you show the suggested changes for consideration by the Committee?

So I've taken out the conditional second-line

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treatment. We could still discuss the question of -- let's suppose that we conclude that for 1A, for example, or one of the others, that we did not give an affirmative answer. We could still discuss whether we felt there might be situations in which it would be effective. But I'm not sure that's what the FDA wants.

Is the FDA looking for us to vote on second line or would the discussion be sufficient without the vote?

The reason I've changed is I had a feeling that it was too radical a departure from the original

to put in the second line. We could double the questions, but I'd hate to do that.

DR. TEMPLE: Well, the first set of questions is, relatively speaking, I think, straightforward. The first question, I mean, is, relatively speaking, straightforward. That doesn't quite go to what we should do. And so, the acceptably safe, properly amplified as to who exactly, under what circumstances, with what labeling, blah, blah, blah, is probably a way for you to give us the advice we need. But I want to be sure Tom agrees with that, and maybe John has views, too.

DR. LAUGHREN: Yes, I agree. We certainly want to incorporate, in your response to Question 2, your thoughts about who should get this, and that might include some considerations of second line, or some language in labeling that directs clinicians, because of the risk, who might get this. As long as there's some discussion of that, I would be fine with this.

DR. GOODMAN: Thank you.

Members of the Committee, discussion of the questions to be voted upon.

Are you pleased with what we have? No suggested changes? I guess not.

I'm sorry? You have to use the mic.

DR. GREENWAY: I was asking if you were referring to all doses, especially for Number 1C.

DR. GOODMAN: Dr. Laughren?

DR. LAUGHREN: I don't think you need to vote on individual doses. I think it goes without saying that we will -- if we were to approve any of these indications, we would look carefully at the dose data and make some judgment about dose. Typically, we don't have committees vote specifically on different doses that were utilized in trials.

DR. GOODMAN: Dr. Pine?

DR. PINE: I have a comment about Question 2? Shall I wait until we vote for Question 1 and then comment?

DR. GOODMAN: Yes. I think you should wait.

I would propose that we go ahead and vote on Question Number 1, and then have a discussion before we vote on number 2. I think 1 is relatively straightforward.

Is that okay?

Okay. Let me read the instructions on voting, if I can find them.

We'll be using the electronic voting system for this meeting. Each voting member has three voting buttons on his or her 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. It's the last vote that counts, so keep pressing it. It's the last

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one. It won't stop flashing, so one firm press should be sufficient.
I will read the vote from the screen into the record. We will next go around the room and each individual who voted will state their name and vote into the record as well as the reason why they voted as they did.
Is that clear?
So we're voting on two questions, each of which has three parts.
Ready to arm the system? We're starting with 1A. I'll read it.
Has Seroquel XR been shown to be effective as a treatment of major depressive disorder as an adjunct? And by adjunct, we mean as an add-on therapy to another antidepressant.
(Pause)
DR. GOODMAN: The vote for 1A is 9 yes, 1 no, zero abstention. And if we could start with Dr. Malone, your vote and reason.
DR. MALONE: Richard Malone. I voted yes, and I thought they had a trial that showed that it was
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effective as an adjunct for major depressive disorder.
MS. LAWRENCE: Margy Lawrence. I voted yes also for the same reasons.
DR. HARRINGTON: Robert Harrington. I voted yes, that there was a specific trial asking the question, and it was also consistent with the information in the other trials.
DR. KELSEY: Sherry Kelsey. I voted no because it seemed like most of the data was looking at the monotherapy.
MS. GRIFFITH: Gail Griffith. I voted yes on the strength of the data.
DR. PINE: Daniel Pine, yes, for the reasons that have already been stated.
DR. GOODMAN: Dr. Goodman, yes. The evidence seemed clear.
DR. GREENWAY: Frank Greenway. I voted yes for the reasons of the data.`
DR. NEATON: I voted yes. The two trials showed efficacy in the short term, although there was no evidence for a benefit on quality of life, so I did so with some reservation, I have to say.
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DR. ROBINSON: Delbert Robinson, yes. I felt the data demonstrated.
DR. GOODMAN: We'll now turn to Question 1B.
Has Seroquel XR been shown to be effective as a treatment of major depressive disorder as a monotherapy? Meaning as a single agent.
(Pause)
DR. GOODMAN: Okay. The vote is as follows: 8 yes, 1 no, 1 abstention.
Maybe we can start with Dr. Robinson this

time.
DR. ROBINSON: I voted yes because of the findings in the studies.
DR. NEATON: Yes, for the same reasons as I --
DR. GOODMAN: You have to give your name.
DR. NEATON: Jim Neaton. Yes, for the same reasons stated before.
DR. GREENWAY: Frank Greenway. I voted yes, based on the data.
DR. GOODMAN: Dr. Goodman, Wayne Goodman. Yes, for the same reasons.

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DR. PINE: Daniel Pine, yes, for those same reasons.
MS. GRIFFITH: Gail Griffith. I abstained. I'm not fully confident of the data.
DR. KELSEY: Sherry Kelsey, yes, based on the data.
DR. HARRINGTON: Robert Harrington, yes, based on multiple trials with consistent results.
MS. LAWRENCE: Margy Lawrence. I voted no. I could have abstained, but I'm not a hundred percent sold on the data, but I voted no.
DR. MALONE: Richard Malone. I voted yes.
DR. GOODMAN: We're now voting on 1C.
Has Seroquel XR been shown to be effective as a treatment of GAD or generalized anxiety disorder, as a monotherapy, as a single agent?
(Pause)
DR. GOODMAN: Okay. The vote is as follows: 7 yes, 2 no, 1 abstention. And maybe we can start with Dr. Malone.
DR. MALONE: Richard Malone. I voted yes. I would like to just make one, I guess, statement. I do

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wonder about maybe any drug that would give a calming or a sedating effect might be able to affect the symptoms that they look at on these scales, and you wonder how many drugs could pass that.
MS. LAWRENCE: Margy Lawrence. I voted no. Still not a hundred percent sold on the data.
DR. HARRINGTON: Robert Harrington. I voted yes. Again, multiple trials, consistent results.
DR. KELSEY: Sherry Kelsey, no; concerned about the side effects.
MS. GRIFFITH: Gail Griffith. I abstained. Similarly, I have concerns about the data.
DR. PINE: Daniel Pine. The data from the efficacy trials were clearly supportive.
DR. GOODMAN: Wayne Goodman, yes; same reason as Dr. Pine.
DR. GREENWAY: Frank Greenway. I voted yes, based on the data.
DR. NEATON: Yes, based on the multiple trials.
DR. ROBINSON: Delbert Robinson, yes, based on

the trials, and, actually, also some findings on the
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individual items.
DR. GOODMAN: Now, let's pause a moment before we vote on number 2, and make sure that everyone's clear on what our answers mean, what affirmative and no means.
As I see it, it's balancing efficacy with side effects or risks. We've talked about a number of those risks: metabolic, cardiovascular, tardive dyskinesia. It would seem to me that even if somebody -- I'm glad to be corrected on this -- if somebody could vote no on this and still feel that there could be situations in which it could be conditionally approved.
Would that be fair to say or not?
MS. GRIFFITH: Dr. Goodman, wouldn't that be an abstention, then?
DR. TEMPLE: Well, I think we'd like ultimately to know whether you think there's any population with these descriptors, for which it would be appropriate, and then tell us something about what population you think that is if you think there is one.
DR. GOODMAN: I'm glad I asked for that. So if we think that there is a population --
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DR. TEMPLE: I will check with Tom, too.
DR. LAUGHREN: No, I agree. I'm a little bit worried. The way the question is worded, even if you thought that there might be some population, it might not be reflected in your answers to this question. So it would be very important here for us to know -- again, this is in some ways similar to the discussion we had yesterday. If there are some circumstances -- for example, if the labeling had some second-line language, you might be more inclined to say yes. I think there definitely needs to be that discussion.
DR. PINE: And without that wording directly in the question, for all the same reasons we talked about yesterday, I myself, personally, am uncomfortable voting for a question where we kind of agree that there's this statement about second line but it's not in the question.
DR. GOODMAN: Well, I'm willing to entertain reintroducing that qualification.
DR. PINE: So I would propose just adding as a second-line treatment or after "as a" as a second-line
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treatment or as a treatment in a, I don't know, subset of particular patients.
DR. GOODMAN: Let me hear the will of the panel.
DR. HARRINGTON: Yesterday, we added a third question or an extra question, and I wonder if that wouldn't be appropriate here, where you'd say is it acceptably safe for the treatment of ABC, as you have, and then Question 3 would be, are there specific

situations where the risk-benefit ratio may be acceptable.

DR. GOODMAN: So we could do that, though, add three questions. Then 2 would be broadly and 3 would be more narrowly.

We need to make a decision on that.

DR. TEMPLE: I mean, I think we're content with either way you do it. We're going to listen to what you say. So if you can make it clear either in one question or in two, but --

DR. GOODMAN: You're listening carefully, but it will be promulgated as it was yesterday --

DR. TEMPLE: Either way you want to do it is

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okay with us.

DR. PINE: Although, I have to say, talking about it as a general adjunct is almost like an oxymoron because you would not think about a general adjunct. So Question 2A only makes sense if you're talking about a subset of patients.

DR. GOODMAN: I agree with that.

DR. TEMPLE: But B as monotherapy, that could be broadly based or it could be only in people who fail or don't tolerate other therapies. It's a lot of ways to write it.

DR. LAUGHREN: You could have a third question that deals with the issue of monotherapy, for example.

DR. GOODMAN: I like that. So we can move -- 2 would just be, has Seroquel XR been shown to be acceptably safe as a treatment of major depressive disorder as an adjunct? No different parts; just that one. And then 3 would be --

DR. TEMPLE: But if you want to capture it, you need to say -- like we did yesterday, you need to say broadly approval or something to capture what you might not agree with, so that you can agree with

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something different later. You could also say "for some definable population" right in here, then that wouldn't be broad.

DR. GOODMAN: Well, I'm going along with the notion that Dr. Pine raised, is that, by virtue of suggesting as an adjunct, it's presupposing it's more narrowly used. So I'd be comfortable just keeping that -- separating number 2, and then our new number 3 would have either "broadly" or "more narrowly".

DR. PINE: But again, so there's no ambiguity at all, when talking about an adjunct, just say it could be acceptably safe in patients, whatever you want to say, that have failed or a select group of patients, just so it's transparent to anybody who's not here that we're talking about an adjunct in a select group of patients, however you want to word it.

DR. GOODMAN: I'm fine with that.

Yvette, can you -- I don't know if we've made it -- who's got control of the slide right now?

DR. TEMPLE: Then, would you put that up in

the lead-in sentence, has Seroquel XR been shown to be acceptably safe in a select group of patients as a

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treatment for, and then go on?

DR. GOODMAN: Correct.

Dr Pine, you want to try --

DR. JENKINS: Dr. Goodman, can I go back to the point I made earlier. I think when you start rewriting the question to apply second line or be explicit about second line, it presupposes that the Committee has voted no to first line. So why can't you vote on first-line therapy first, and if you vote yes or no -- if you vote yes, I guess you're done. If you vote no, then you can vote on second line.

DR. GOODMAN: Right. That's fine. That's fine, sir.

DR. JENKINS: I think there's a bias introduced when or one or two committee members suggest let's rewrite the question to a second-line status, but --

DR. GOODMAN: That's why I took it out. You influenced me, and I removed the second line for that very reason.

DR. PINE: But then you've got to take out "adjunct".

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DR. GOODMAN: You separate out the adjunct as a separate question, and then number 3 would be without second line.

And then, if we say no, then we could add a question.

DR. JENKINS: And again, I'm going back to what the sponsor has requested. The third slide the sponsor presented shows what they're requesting, which they refer to as kind of an all-comers indication. That's what they requested from us. We need to hear from you do you think it's acceptably safe for that indication. If yes, as I said, I guess you're done. If no, then you think it should be okay for a second-line indication.

DR. GOODMAN: So we're going to make some typing changes. Don't anybody leave, but there will be a pause in discussion. I don't think we want anymore input at this moment.

DR. TEMPLE: Just to be sure we understand John, he's saying the second question, what would be the new second question, would simply refer to major depressive disorder and generalized anxiety disorder

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without saying adjuvant or any of those things. It would just be the broad use. That's first line.

Right? That's what you meant.

DR. JENKINS: That's what the sponsor is requesting, so that's what I would make the second question. And then, I'd go forward from there if the Committee doesn't believe that it's acceptable.

DR. GOODMAN: All right. So what you're

saying is retain the original second question, and then see what the answer is.

DR. JENKINS: Yes.

DR. GOODMAN: I'm fine with that, too.

(Dr. Pine departs from the hearing)

DR. GOODMAN: Request for a five-minute break. But again, please don't stray far.

(Whereupon, a recess was taken at 2:55 p.m.)

DR. GOODMAN: Okay. I think we're ready.

Let me show the panel what we came up with, and, hopefully, you will find it acceptable.

We've answered number 1; we're on to number 2.

Has Seroquel XR been shown to be acceptably safe as an adjunctive treatment for major depressive

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disorder?

Number 3. Has Seroquel XR been shown to be acceptably safe as a treatment for MDD as a monotherapy or GAD as a monotherapy? That implies a more broad use; number 3 implies more broad.

Number 4. If the answers are nay to number 3, has Seroquel XR been shown to be acceptably safe in certain instances as a treatment for MDD as a monotherapy and GAD as a monotherapy?

So 4 would be conditional and number 3 would be broad.

Hopefully, that's okay, because I think it's the best we're going to come up with. And it retains the best of the original questions.

MS. LAWRENCE: Are we voting 3A and then 3B or A and B --

DR. GOODMAN: Yes. The A's and B's are separate.

Dr. Temple?

DR. TEMPLE: So 3 is about the broad use for just everybody.

Are we understanding it right?

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DR. GOODMAN: That is right.

DR. TEMPLE: Fine.

DR. GOODMAN: Does everybody understand that? We're talking broad for number 3, and 4 would be qualified.

Let's activate the voting system. We're going to vote first for number 2.

Has Seroquel XR been shown to be acceptably safe as an adjunctive treatment for major depressive disorder?

UNIDENTIFIED SPEAKER: What about Dr. Pine?

DR. GOODMAN: Dr. Pine has left.

(Pause)

DR. GOODMAN: Okay. The vote is 6 yes, 3 no, zero abstentions.

Could we start with you, Dr. Malone?

DR. MALONE: Richard Malone. I voted yes. I do have to say I was kind of on the fence, but I voted yes.

MS. LAWRENCE: Margy Lawrence. I voted no because I'm still not pleased with the studies.
DR. HARRINGTON: Robert Harrington. I also voted no for a variety of reasons, but mostly concerning the short-term exposure in the clinical trials that we saw just doesn't seem to me to be adequate for therapies that will be taken chronically. I just don't think that the long-term risks have been adequately characterized.
DR. KELSEY: Sherry Kelsey. I think my votes are inconsistent, but this is correct. I do believe that given the risks and benefits, yes is my vote.
MS. GRIFFITH: Gail Griffith. I voted yes. The patient community in this instance is very conflicted, as we saw from Dr. Greenhill's presentation, juxtaposed to what we received in the written statements from a number of the communities. But, again, I think we are hoping that this might be a treatment resorted to as a treatment of last resort.
DR. GOODMAN: Wayne Goodman. I voted yes. In addition to the data presented, there's other precedent for using adjunctive antipsychotics for cases that have not responded adequately to an antidepressant alone.
DR. GREENWAY: Frank Greenway. I voted yes. I think that this represents sort of a second-line therapy, so I felt that that was appropriate.
DR. NEATON: Jim Neaton. I voted no because this is based on 946 patients and two six-weeks studies, and we have uncertain risks over the long term.
DR. ROBINSON: I'm Delbert Robinson. I voted yes. I think, one, because, obviously, an adjuvant implies that somebody has failed.
DR. GOODMAN: You may want to speak up a little bit. Just speak up a little.
DR. ROBINSON: Okay. I voted yes because, one, obviously an adjuvant is for somebody who has failed a prior trial. And, yes, I'm comfortable about some of the levels the evidence about the side effects in this population long term, but we do have at least some consistent data about its use in other populations long term. So in terms of balancing the risk-benefit, I think they would be acceptable in sort of an adjuvant situation.
DR. GOODMAN: It sounds different. I'll stay with it.
We're turning our attention to number 3A.
Has Seroquel XR been shown to be acceptably safe as a treatment for major depressive disorder as a monotherapy? And here, we're talking about use broadly in major depressive disorder.
Could you activate the voting system?
Mine is not on. We're waiting. Oh, mine is on now.

Everybody active?
DR. WAPLES: Please, everybody, press one more time.
DR. GOODMAN: Do you have the totals, first?
The vote is no yeses, 9 noes, no abstentions.
Dr. Malone, would you start?
DR. MALONE: Richard Malone. I voted no. I think the long-term risks of the antipsychotics are greater than I would like to see for metabolic syndrome and risk of dyskinesia for a monotherapy treatment.
MS. LAWRENCE: Margy Lawrence. I voted no for very personal reasons, because my son died last summer having schizophrenia with sudden cardiac death, and Seroquel was part of his cocktail. So I'm voting no.
DR. HARRINGTON: Robert Harrington. I voted

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no. I was impressed at the discussion around how large the potential patient population to be treated was, the broad use that these drugs might see, and what I felt was the insufficient evidence regarding long-term chronic safety.
DR. KELSEY: Sherry Kelsey. I voted no because of the risk-benefit in this large population. It was not favorable.
MS. GRIFFITH: Gail Griffith. I voted no out of patient concerns.
DR. GOODMAN: Wayne Goodman. I voted no. I saw no clear advantage demonstrated in efficacy. There are side effects that we discussed with some unknown risks and consequences. Also, unintended consequences. I was concerned about the wide-scale use of the medication in various settings.
DR. GREENWAY: Frank Greenway. I voted no because I think that there are safer alternatives for primary therapy.
DR. NEATON: Jim Neaton. I voted no because the benefit from efficacy is pretty modest when you balance that against the kind of known risk and the

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potential risk.
DR. ROBINSON: I'm Delbert Robinson. I voted no. This is an area where there are a lot of other first-line treatments, and I didn't think that the safety profile warranted being among them.
DR. GOODMAN: Okay. We now turn to voting on --
They're rebooting the system, but our regular mics are dead.
We turn to Question 3B.
Has Seroquel XR been shown to be acceptably safe as a treatment for GAD as a monotherapy?
DR. WAPLES: Please wait a minute. We're resetting the systems. Hold on for one minute, please.
(Pause)
DR. GOODMAN: The voting results are as follows: no yeses, 9 noes, no abstentions. And we can start with Dr. Robinson this time.

DR. ROBINSON: Yes. Delbert Robinson. I voted no. In a very similar way in terms of for MDD, I didn't think that the side effect profile warranted it being a first-line agent.

DR. NEATON: Jim Neaton. I voted no for the same reasons stated before.

DR. GREENWAY: Frank Greenway. I voted no because I think there are safer first-line agents.

DR. GOODMAN: Wayne Goodman. I voted no for similar reasons. I think the bar needs to be higher for this medication, given the concerns we have.

MS. GRIFFITH: Gail Griffith. I voted no to be consistent.

DR. KELSEY: Sherry Kelsey. I voted no for the reasons stated.

DR. HARRINGTON: Robert Harrington. I voted no for the same reasons I gave for MDD.

MS. LAWRENCE: Margy Lawrence. I voted no for my same prior reasons.

DR. MALONE: Richard Malone. I voted no. Again, I think the long-term risks of dyskinesias and metabolic side effects are fairly well documented, and I don't think they're acceptable for this use.

DR. GOODMAN: Thank you.

Can we get the next question up? This should be our last question; number 4A.

Has Seroquel XR been shown to be acceptably safe in certain instances -- you can read that as instances, cases, subpopulations, some defined group -- as a treatment for major depressive disorder as a monotherapy?

Before you vote, Dr. Temple has his hand up.

DR. TEMPLE: Well, I just want to hark back to a couple of things. As everybody knows, we do not have the study where they randomize back to the drug that failed and the new drug. So you don't have that, but there have been situations where we and advisory committees have thought there's enough reason to hope anyway, so it should be approved. That's one thing.

The other thing is, not discussed much, there are people who don't tolerate certain side effects on some of the SSRIs, sexual dysfunction and stuff like that. So you need to think about that as a possible group where you're less interested in randomizing back because you know these drugs don't have those same effects.

Just a couple of little contextual things.

DR. GOODMAN: So, it's another way of saying this also could be as a second-line treatment, not a first-line treatment.

DR. TEMPLE: Yes, although --

DR. GOODMAN: Where exactly it is in the cascade of treatment choices is to be determined.

DR. TEMPLE: Right.

DR. GOODMAN: Are we ready to vote?
Go ahead and cast your votes; 4A.
Has it been tallied?
Press again. Be consistent; we're checking.
(Pause)
DR. GOODMAN: Once again cast your vote.
MS. REESE: We're going to have to take a manual vote because we have to reset the machine.
DR. GOODMAN: Is that permissible?
MS. REESE: It is.
DR. GOODMAN: Why don't you reset it? Let's be consistent in how we do this, if we can. We'll give you two minutes and that's it.
(Pause)
DR. GOODMAN: Any update from the engine room?
We're ready. So a reminder, we're voting on

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4A.
Has Seroquel XR been shown to be acceptably safe in certain instances as a treatment for major depressive disorder as a monotherapy?
DR. WAPLES: We thank everyone for your patience, and for the record, Dr. Pine's early departure after Question 1C needs to be noted into the record.
DR. GOODMAN: Okay. The votes are 4 yes, 4 no, 1 abstention.
Could we start with Dr. Malone?
DR. MALONE: This is Richard Malone, and I voted no. I think the one use is the adjunctive treatment, and I think antipsychotics have been useful for psychotic depression, but given the data, I don't want to talk about any monotherapy right now.
MS. LAWRENCE: Margy Lawrence. I voted no.
DR. HARRINGTON: Robert Harrington. I voted no. Dr. Temple may well be right, that we can identify subsets for which there's a favorable risk-benefit, but we didn't see data specifically addressing that question. So I have an open mind. I'd be willing to

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look at more data, but right now, I would vote no.
DR. KELSEY: Sherry Kelsey. I voted yes because I think there should be options for patients who fail or have side effects on other medications.
MS. GRIFFITH: Gail Griffith, and I voted yes. Again, I think that the patient community is asking for as many treatments in their toolbox as possible, and I'm hopeful that you can identify specific instances.
DR. GOODMAN: Wayne Goodman. I abstained. I think there were insufficient data to render an answer, a decision. I, obviously, wavered a bit on this. And major depression, I agree that it's good to have additional options, but I'd like to see additional data.
DR. GREENWAY: Frank Greenway. I voted yes. I think there should be options as a second-line for patients with these problems who don't otherwise

respond.
DR. NEATON: Jim Neaton. I voted no. I view this as a question about a subgroup for which the risk-benefit balance was there, and I didn't see it.
DR. ROBINSON: I'm Delbert Robinson, and I

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voted yes, because part of the thing I was thinking about, I took this question to mean would there ever be a subgroup of patients that it would be appropriate for. And I think we know from a lot of the Star*D programs, et cetera, that there are a lot of patients who don't respond with major depression now. And if they really have gone through the sequence of the algorithm, how you would balance off the cardiovascular effects of like tricyclic antidepressants versus quetiapine or what is the relative risk benefit of going on to ECT versus getting adjuvant quetiapine.
Those were the sort of cases I was thinking of. And I think the real problem is we don't have a good way of saying, okay, how many things must you have failed because we don't have any trials looking at this. Do you need to fail an SSRI and a tricyclic, et cetera. And I think that's a huge difficulty for you guys. But I voted for it in the sense that, yes, you could envision at the end that, obviously, quetiapine's risk-benefit would be -- you could argue about ECT, those sorts of issues.
DR. GOODMAN: We will now be voting on 4B, has

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Seroquel XR been shown to be acceptably safe in certain instances as a treatment for generalized anxiety disorder as a monotherapy?
(Pause)
DR. GOODMAN: The vote is 2 yes, 6 no, 1 abstention.
Dr. Robinson, maybe we can start with you.
DR. ROBINSON: On this one, I voted no, but, honestly, I was much more conflicted about. And the reason why I voted no on this one versus the MDD is that normally with GAD, you don't go to -- people respond usually in GAD much better, most people, with benzodiazepine or various standard antidepressants, get better. And you usually are not thinking about the really aggressive treatments that you have to often do for people with, really, refractory MDD.
I mean, the case could be made, well, somebody has failed a good trial of benzodiazepine and has failed a trial of a standard sort of tricyclic, or SSRI. Then, yeah, I could see saying, oh, well, instead of not giving them any options for therapy, of course, give them quetiapine. But those are such an

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unusual group of patients that that's why I sort of didn't include -- that's why I sort of changed the vote between the two classes of disorders.
DR. NEATON: Jim Neaton. Pretty much the same reason as last time, and theoretically a good question,

I guess. But the studies really weren't designed to address this question, so we didn't see the data.

DR. GREENWAY: Frank Greenway. I voted yes. I felt that there should be the availability of something with a different mechanism for those people who don't respond to anything else. We heard earlier about the risk of suicide and the tremendous amount of quality of life problems that these people experience.

DR. GOODMAN: Wayne Goodman. I abstained. I was much closer to voting no on this one than I was in the case of major depressive disorder. Not as clear that we need the alternatives as much as we do for cases of depression that haven't responded to usual treatment. So I would like to see additional data, and right now, I don't see that there's a clear advantage for this medication, and the disadvantages are in the area of questions about safety or side effects; not

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side effects, but more safety.

MS. GRIFFITH: Gail Griffith, and I voted no. I think that anytime when we consider major depressive disorder, we're looking at risk for suicide, which general anxiety disorder doesn't necessarily carry the same comparable risks. So I voted no. I felt that it wasn't as strong a case.

DR. KELSEY: Sherry Kelsey. I voted yes in order to have increased options for the patients.

DR. HARRINGTON: Robert Harrington. I voted no for similar reasons that I stated for MDD.

MS. LAWRENCE: Margy Lawrence. I voted no.

DR. MALONE: Richard Malone. I voted no for the same reasons as in depression.

DR. GOODMAN: Dr. Temple?

DR. TEMPLE: I'm just curious about one part, mostly on the depression matter, in particular, the people who didn't think there was any case.

What about somebody -- or didn't think there was enough data. You know from what I said before, I think finding out that a drug works and people have failed none of the therapy can be done in a rigorous

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design, I don't want to see those studies. But there are people who don't want to take a drug because they don't like the side effects. Sexual dysfunction on SSRIs is in the neighborhood of 50 percent. You know, I'm not a woman, so I can't understand it fully, but I understand many of them don't like that.

Suppose that was very important and they thought they might want to use an alternative? No sympathy for that? I mean, you don't need to do a study. The SSRIs cause sexual depression; these drugs don't. Is side effects something? How do people feel about that?

DR. GOODMAN: Gail Griffith, and then Dr. Malone.

MS. GRIFFITH: I think that the risk profile of the medication -- actually, I take these

medications, so I have debated all of the issues with respect to the side effects. But looking at that, I'm very concerned about the risk for sudden cardiac death. I mean, the bulk of the serious potential side effects would probably balance out my interest in mitigating the sexual dysfunction, some of the other side effects

as well.

DR. TEMPLE: But even if they could --

DR. GOODMAN: Your mic is dead.

DR. TEMPLE: It's going to be hard to have this conversation.

But the thought there -- I mean, I take it, from what people said, that if somebody did do a study showing that in failures on other therapy, this drug worked, and they did the right kind of study, people would be happy with that because you have to treat depression. But it's, in some sense, equally true that if you can't tolerate the other drugs, you're not getting your depression treated. But I didn't hear -- I heard some sympathy for the idea that that might be a reason, but not others. And I'm curious about, Bob and Richard, what was your thought there. If you can't tolerate the available drugs, and these drugs work, is it a lack of data or what? Because we might have to deal with that. We need to understand.

DR. MALONE: I think I was concerned about the lack of data. And I guess always in the back of my mind is that these drugs are available, and physicians

use them in special circumstances. Right now they're used off label for many circumstances.

DR. TEMPLE: Yes, we don't like that, though.

DR. MALONE: No, but it would be good to have data showing these things, too.

DR. TEMPLE: Well, that's what I'm asking. Do you need data on the intolerance part? I definitely, totally agree, as you heard I said, you need data on does this work and people who fail on other therapy. I love those trials. We're hoping we'll see some sometime. But you don't really need that if they can't tolerate the other drug, do you, or do you? Maybe you think you do.

DR. MALONE: Oh, I think you do. I would be interested in it, yes.

DR. TEMPLE: Well, these drugs don't cause that kind of sexual dysfunction. I don't think that would be a question, but maybe it would.

DR. MALONE: So is that the one circumstance?

DR. TEMPLE: Well, I'm not a user of these drugs. You've got to tell me what side effects make people want to stop, but that's the one I know about

because it's not adequately described in labeling.

DR. GOODMAN: But it sounds like that study could be performed.

Dr. Harrington?

DR. HARRINGTON: I had a consistent no vote, Bob, on the safety issues. And I too was a bit influenced by the fact that the drug is already available on the market, but I wanted to -- my vote was really to express caution about broadening the marketing to include this much broader group of patients. And so, my no vote really carried with it the plea for the company to do more studies because I do think that there are a host of things that they could ask, really trying to quantify some of the clinical outcomes that we heard about this morning, really trying to quantify the benefits over other commonly available drugs, as we've heard throughout the day. And I like your study a lot of people who have failed in other drugs.

So my no vote was acknowledging that the drug was available. You might not like to hear that, but as clinicians, we all know that. And we're not denying

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the doctors who really believe that they have a role for this drug, but we're sending a note of caution that more work needs to be done. So that's what my vote reflected.

DR. GOODMAN: I think that's very well said.

We're in overtime, largely because of technical difficulties, not because of the performance of the Chair, just to point that out. Let's put that in the record.

Is there anything else you need from us, either Dr. Temple or Dr. Laughren?

DR. LAUGHREN: No. I just want to thank the Committee for two days of very hard work and some very challenging questions, which you helped us to formulate. So thank you very much.

(Whereupon, at 3:39 p.m., the meeting was concluded.)

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CERTIFICATE OF REPORTER

I, JANET EVANS-WATKINS, do hereby certify the the foregoing proceedings were taken by me and thereafter reduced under my direction to typewritten form; that this transcript is a true record of the proceedings; that I am neither counsel for, related to, nor employed by any of the parties to this action; and, further, that I am not a relative or employee hereto, nor financially or otherwise interested in the outcome of the action,

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