U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE

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ORIGINAL

CLOZARIL AND SUICIDALITY

IN SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

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GRAND BALLROOM
HOLIDAY INN
2 MONTGOMERY VILLAGE AVENUE
GAITHERSBURG, MARYLAND

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MONDAY, NOVEMBER 4, 2002

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ATTENDEES:

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Other Participants:

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ATTENDEES: (Continued)

Other Participants:

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A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

(8:10 a.m.)

DR. OREN: Good morning. I'd like to call to order the meeting of the Psychopharmacological Drugs Advisory Committee of the Food and Drug Administration. My name is Dan Oren, and I'd like to welcome all the members of the panel and our guests, and we'll ask everyone on the panel, starting with Dr. Katz, to please go around and introduce themselves.

DR. KATZ: Russ Katz, Director of Neuropharm Drugs at the FDA.

DR. LAUGHREN: Tom Laughren, Neuropharm Drugs, FDA.

DR. COOK: Ed Cook, University of Chicago.

DR. WANG: Phil Wang, Harvard Medical School.

DR. HAMER: Bob Hamer, University of North Carolina.

DR. WINOKUR: Andrew Winokur, University of Connecticut Health Center.

DR. TITUS: Sandy Titus, FDA. I'm the Executive Secretary for Psychopharm.

DR. RUDORFER: Mat Rudorfer, National Institute of Mental Health.

DR. RYAN: Neal Ryan, University of

Pittsburgh.

MS. BRONSTEIN: Jean Bronstein, the public member.

DR. ORTIZ: Irene Ortiz, University of New Mexico.

DR. MALONE: Richard Malone, MCP Hahneman.

DR. MEHTA: Dilip Mehta, Industry Representative.

DR. TITUS: I'm going to read into the record the Conflict of Interest Statement for this meeting.

The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. All committee members and consultants have been screened for conflicts of interest with respect to the product at issue, competing product, and their sponsors. The reported financial interests have been evaluated and it has been determined that the interests reported by the participants present no potential for a conflict or the appearance of such at this meeting, with the following exceptions.

Richard Malone has been granted a limited waiver under 18 U.S.C. 208(b)(3) for his participation

as an advisor for a competitor. He receives less than $10,000. Under the provisions of the waiver, Dr. Malone will be allowed to participate in the discussions without voting.

Robert Hamer has been granted a waiver under 21 U.S.C. 355(n)(4) of the Food and Drug Administration Modernization Act for his ownership of stock in a competitor. The stock is valued from $5,001 to $25,000. Because 5 CFR 2640.202(a) de minimis exemption applies, Dr. Hamer does not require a waiver under 18 U.S.C. 208(b)(3).

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

We would like to note that Dr. Dilip Mehta is participating in this meeting as the non-voting guest industry representative.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any

current or previous financial involvement with any firm whose product they may wish to comment upon. Thank you.

DR. OREN: To begin our presentation this morning, I'd like to call on Dr. Katz, Director of the Neuropharmacological Drug Products Division at the FDA.

DR. KATZ: Thanks, Dan. I just really want to say welcome, thanks for coming. I think we've brought to you yet again another atypical, if I can use the word, issue. We're going to be asking you, as you know, to address the fundamental soundness of one particular study and, in addition, whether or not that study and whatever other information is available in toto support approval for the novel claim that the sponsor has proposed. So, I really just want to thank you in advance for your work, and I hope it's interesting.

There's one other point I want to make. As you know, we have issued to the sponsor an approvable letter for this application, which typically implies that with a few minor adjustments the application can be approved.

I would just urge you to not interpret that to mean that the definitive decision ultimately

about approvability/not approvability of the application has been made. We really are very interested to hear what you think about the data and whether or not they support either the proposed indication or some reasonably related indication.

So, with that, I'll turn it over to Tom Laughren, who will give you an overview of the issues we'd like you to consider. Thanks.

DR. LAUGHREN: Good morning. I'd also like to welcome everyone here to the meeting. The only topic for today is the supplement for Clozaril in the treatment of suicidality and schizophrenia and schizoaffective disorder.

(Slide)

I'd like to begin with giving a little bit of background to how we got to the InterSePT Study. As you're aware, the lifetime prevalence of suicide in patients with schizophrenia is roughly 10 percent, so it's a very big problem in this population.

Recently, we and other have done meta-analyses of clinical trials databases for the atypical antipsychotics. The reason for doing this meta-analyses was to try and determine if there was an excess risk of mortality from suicide in patients assigned to placebo as opposed to active drug. And as

you are probably aware, our meta-analyses and those of others have shown that these drugs, the atypicals, for the most part, are neutral with regard to suicide, suggesting that while these drugs have an effect on positive symptoms, there's no evidence, at least from the meta-analyses, that they have an impact on suicide.

So, given that background and an additional study that was done about five or six years ago that you'll hear more about, the ERI Study, which was basically a retrospective cohort study based on the Clozaril registry, in that study clozapine was greatly favored over other treatments with a risk ratio of 0.17, which is a very impressive outcome favoring clozapine. That, of course, was not a randomized study. But that was the start of our negotiations with the company to try and see if a prospective trial could be accomplished. And during those negotiations, we did reach agreement with the company that one adequate and well-controlled trial should be sufficient to support this new claim.

We also reached agreement on a two-year study comparing clozapine and olanzapine on the suicidality outcome, that is the InterSePT Study.

(Slide)

So, the study was done. The supplement was submitted in February of this year. The original claim that was sought in that supplement was for the use in the treatment of suicidality in patients with schizophrenia or schizoaffective disorder. And as you know, we issued an approvable letter for the supplement in August of this year.

(Slide)

Now, there are six issues other than the general question that we always ask you that we would like to have committee feedback on sometime during the course of the day. One issue is the potential for bias in the referral of events to the Suicide Monitoring Board. A second issue is simply the issue of adding a new claim focusing on suicidality in schizophrenia or schizoaffective disorder.

A third issue was the expansion of the Clozaril claim beyond the treatment resistant population for which it is currently limited. A fourth issue is the interpretation of the InterSePT Study with regard to olanzapine. A fifth issue is the adequacy of a single randomized controlled trial to support a new claim. And, finally, the adequacy of the suicidality outcome in the InterSePT Study. So I'm going to get into a little bit more detail about

each of these.

(Slide)

First of all, the question of bias. As you'll hear more about, Type 1 events are a critical component of the primary outcome for the study. Now, these events were confirmed in a blinded manner as being Type 1 events by a Suicide Monitoring Board. However, events that were to be considered by the Board were referred in an unblinded manner by psychiatrists at the sites.

The rate of confirmation of events that were referred was very high and essentially identical for both clozapine and olanzapine, 83 percent and 84 percent. So, there's a strong relationship between the number of events referred and the number confirmed. Therefore, it raises the question, since the events were referred in an unblinded manner, whether or not there might be bias in referring events.

(Slide)

So, we discussed this issue with the sponsor. They have some data that they think addresses it. FDA has also done its own independent audit to try and address this question, and Dr. Ni Khin, from the Division of Scientific Investigation,

is going to present her findings on their audit a little bit later in the morning. But, ultimately, we would like to have the committee's view on whether or not you think this issue of potential bias has been adequately addressed.

(Slide)

Next is the issue of a new claim that focuses on suicidality. Now, ordinarily, in the Psychopharm Group, we have not permitted sponsors to focus on what might be considered parts of a syndrome. For example, if a company wanted to get a claim for the treatment of hallucinations in schizophrenia, we would argue that that is pseudospecific, that of course the drug works for hallucinations, it also works for all the other positive symptoms.

So, one question that one might raise here is whether or not suicidality is just part of schizophrenia and shouldn't be teased out in some sense.

Now, obviously, we did issue an approvable letter, so the Division has taken a position on this that it is justifiable to separate this out, and our reasoning is that this is a serious event, and also there is a lack of evidence for effective treatments for this aspect of schizophrenia. But, again, this is

an issue that we need to have the committee's feedback on.

And in that regard, a major question for you is how should the claim be stated, if you feel that a claim is supported? Again, the company's initial proposal was to focus on the treatment of suicidality. This is the language that we proposed in the approvable letter: "Reducing the risk of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk for emergent suicidal behavior, based on history and recent clinical state".

So, again, part of the challenge to you is to help us try and articulate a claim, if you think a claim is supported.

(Slide)

Another issue is that if a new claim focused on suicidality were to be approved, this would clearly expand the use of clozapine beyond the treatment resistant population for which it is currently limited. Only about a fourth of patients in the InterSePT Study could be considered treatment resistant.

So, the question is do these data support -- and, of course, clozapine is not approved at all

for schizoaffective disorder. So the question is do the data support an expansion of the claim into this larger population?

(Slide)

Another question has to do with how the study should be interpreted with regard to the comparative drug olanzapine? One possible interpretation would be that this is evidence that clozapine is superior to olanzapine with regard to suicidality. Another possible interpretation is that olanzapine could be considered in some sense a representative member of the atypicals, and this is evidence that clozapine is superior to all atypical antipsychotics. Or one might do what we have done here, which is basically to take this as evidence that clozapine is effective for this particular clinical target. But, again, this is an issue mostly for labeling in how to describe the study in labeling, and how to describe the claim.

(Slide)

Another issue, of course, is this issue of whether or not one adequate and well-controlled trial is sufficient to support a claim. This, of course, is not the usual standard. Ordinarily, two adequate and well-controlled trials are needed to support a new

claim. There is, however, an alternative.

A single adequate and well-controlled trial along with confirmatory evidence is a standard that may be applied in certain situations. Now, the usual circumstance for applying this standard is if there is a single trial focused on mortality or irreversible morbidity, and replication is difficult for that reason.

A second possibility is that the single trial in question is so strongly positive -- either very small p-values or replication within that trial, because of positive findings at different centers, that there's a perception that there's no need to replicate it further.

So, the question, again, for the committee is is this standard appropriate for this particular situation?

(Slide)

And, finally, there is a question of the primary outcome in the InterSePT Study. Suicidality, as you'll hear more as the morning goes on, the were four events that fell under this definition of Type 1 events -- suicide, suicide attempt, hospitalization for suicidality, or need for increased surveillance for patients already hospitalized.

While clozapine was superior to olanzapine on this primary outcome, there was no actual effect demonstrated on completed suicides. The number was very small and it was roughly equal for both groups.

So, again, the question for the committee is in an absence of an actual finding on completed suicide, are these data sufficient to support a claim for suicidality.

(Slide)

The question that we need you to vote on is the usual one -- are the data sufficient to support a new claim? But, again, part of the challenge for you here this morning is to help us articulate the question, namely, if you think a claim should be supported, how should that claim be worded in labeling? And I'll stop there. Thank you.

DR. OREN: These are exceptionally interesting questions. To help us begin answering them today, I'd like to call on the Novartis presentations, beginning with Roy Dodsworth, Executive Director of Drug Regulatory Affairs at Novartis.

MR. DODSWORTH: Dr. Katz, Dr. Laughren, Dr. Oren, members of the committee, FDA staff, colleagues, guests, good morning. I'm Roy Dodsworth, from Novartis, and this morning I would like to guide

you through a journey of some ten years in the making, which culminates in our presentation to you this morning.

The journey relates to a rather unique clinical study that Novartis conducted in a high-risk population to assess the impact of Clozaril on reducing the risk of suicidal behavior, an important public health concern, and of particular significance to the psychiatric community.

Approximately 20 to 40 percent of schizophrenic patients will attempt suicide at least once during the course of their illness, and approximately 10 percent will ultimately die by suicide. This rate is probably even higher for schizoaffective patients.

(Slide)

Clozaril, known generically as clozapine, is an agent first developed during the 1960s and 1970s, and is generally considered to be the first atypical antipsychotic agent. It's a member of the dibenzo-diazopine class of drugs which work primarily on central dopaminogic and seratonogic receptors.

Clozaril was first approved in Austria in 1969, and was approved in the U.S. on September 26, 1989. It is currently approved in about 150 countries

around the globe, including Australia, Canada, and all members of the European Union.

The application that is subject of today's discussion was submitted to FDA on March 1st of this year, and was assigned a six-month priority review by the Division of Neuropharmacological Drug Products. It has since been submitted also in Australia and Canada, and will be submitted in the European Union later this month.

(Slide)

The current indication for Clozaril is for the treatment of severely ill schizophrenic patients who fail to respond adequately to other standard drug treatments for schizophrenia.

And the additional indication that we're seeking and which is the subject of your deliberations today is for reducing the risk of emergent suicidal behavior in patients with either schizophrenia or schizoaffective disorder who are judge to be at risk for suicide.

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This morning, we will present to you amongst all the information the results of InterSePT, the International Suicide Prevention Trial, a prospective, randomized comparison of Clozaril and

Zyprexa on their respective abilities to reduce the risk of suicide in a high-risk population of patients with either schizophrenia or schizoaffective disorder.

The study recruited patients generally excluded from other clinical trials, and encouraged investigators to do whatever was necessary to prevent suicide, maintain patient safety, and keep patients in the study.

Now, at the risk of repeating some of what Dr. Laughren said, we have had numerous discussions with FDA over the years, and this led ultimately to the design and execution of InterSePT Study.

(Slide)

In 1993, FDA asked us to assess the possible effect of Clozaril on mortality. This is the study by Walker and others conducted by a group at Boston University, which will be presented in greater detail in a few minutes by Dr. Meltzer.

From this assessment, we detected a possible signal that current Clozaril users seemed to have a reduced incidence of suicide and suicidal behavior, when compared to past users, based primarily on data from the Clozaril National Registry.

Following this finding, a report entitled "Mortality of People Using Clozapine" was published,

and this report formed the basis of a supplemental new drug application which the company submitted in 1995.

FDA subsequently issued a Not Approvable letter for this application primarily because it was a retrospective epidemiological analysis, but they expressed considerable interest in the outcome.

Given the significant nature of the suicide issue, FDA agreed with Novartis that a single prospective study which confirmed the reported observations and epidemiological signals would be sufficient for registering a new claim. Consequently, we embarked on a series of discussions with them, and this led ultimately to the design of the prospective study which we will present to you today.

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We've already submitted the final protocol for InterSePT Study to FDA in January of 1998, and initiated the study at some 67 centers in 11 different countries shortly thereafter. We completed it early last year, and along the path which led us here today, we participated in numerous discussions with FDA regarding the study, the statistical analyses, the results, and your review of our application. In fact, we submitted a draft report to FDA in December of last year, and filed a supplemental application requesting

a new indication on March 1st of this year.

Consistent with the industry goal for priority review drug, FDA rendered it approvable in a letter to us dated August 30, this year, but that letter also sought answers to several questions, many of which Dr. Laughren just outlined to you, and which have been provided to you in your briefing book.

We have since responded to all outstanding questions, and today FDA is seeking your guidance and counsel on several issues.

(Slide)

To that end, we have two objectives today. The first is to seek your agreement that reduction in risk for suicidal behavior in this population represents an important health issue that could clearly represent a new indication for a drug that is shown to possess such activity.

The second is to present the results of InterSePT, a prospective randomized controlled study designed to assess precisely that for Clozaril. It is our belief that the results of InterSePT, when taken together with the other published reports and available information, represents a significant body of evidence demonstrating that Clozaril does, in fact, reduce the risk of suicidal behavior in high-risk

populations, and that Clozaril should be so indicated.

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Therefore, let me please introduce our program to you today. Dr. Herbert Meltzer, from Vanderbilt University, will present an overview of suicidal behavior as a public health issue, along with some of the background data which led up to the design and execution of InterSePT. This will include a review of the epidemiological study carried out by Walker and others that evaluated Clozaril and suicide.

Dr. Rocco Zaninelli, Executive Director of Clinical Research and Development for Neuroscience at Novartis, will then present the InterSePT results themselves.

Dr. Ranga Krishnan, Chairman and Professor of Psychiatry and Behavioral Science at the Duke University Medical Center and Chairman of the independent Suicide Monitoring Board, will speak to the role of that board in the conduct of the study. The SMB made all primary endpoint decisions in a blinded fashion independent of the Principal Investigators in the study.

Finally, Dr. John Ken, Chairman of the Department of Psychiatry at the Zucker Hillside Hospital and Professor of Psychiatry, Neurology and

Neuroscience at the Albert Einstein College of Medicine, will summarize the benefit/risk assessment for Clozaril as an agent to reduce the risk of suicidal behavior in high-risk populations.

Allow me then, please, to introduce next on the agenda, Dr. Herbert Meltzer. Dr. Meltzer is Bixler Professor of Psychiatry and Pharmacology at Vanderbilt University of Nashville, and he will speak to suicide behavior as a public health issue, as a domain separate from psychosis, and the data that preceded and gave rise to InterSePT. Dr. Meltzer.

DR. MELTZER: Thank you very much, Mr. Dodsworth, and I'd like to thank Novartis and members of the committee and the FDA staff for the opportunity to speak to you today about this issue. It is particularly a personal pleasure since my role in research on the possible effect of Clozaril on suicidality led to InterSePT.

(Slide)

The presentation that I will give will discuss suicidal behavior in schizophrenia and schizoaffective disorder. The evidence of suicidal behavior is a separate domain of behavior from psychosis because that's a key part of the story to determine whether or not suicidality could be the

object of a specific therapeutic intervention and whether it could be a separate indication for Clozaril.

And, finally, I'll present the evidence which existed prior to InterSePT, which suggested that Clozaril reduces the risk of suicidal behavior in patients with schizophrenia and schizoaffective disorder, and led Novartis to accept my suggestion for a study which eventually became InterSePT, with the help of the FDA.

(Slide)

From the beginning of awareness of the concept of schizophrenia as a syndrome, there was evidence that suicidality, suicidal behavior, was a serious problem. Emil Kraepelin, in the textbook from 100 years ago which launched psychiatry, indicated his awareness of the potential for violence to self and others in what he called "dementia praecox" by the quote that you see there -- "Patients with dementia praecos often need hospitalization to prevent aggression against others and suicide".

Some 14 years later, Eugen Bleuler, who gave schizophrenia its current name, identified suicidal behavior as "the most serious of schizophrenic symptoms", reflecting that it must have

been very common in his era as it is now. And I think many of us remember that David Satcher, a few years ago, when he was Surgeon General, made the problem of suicide and mental illness in general one of the major focuses of his tenure.

(Slide)

Suicidal behavior should be thought of as a spectrum of behaviors. At one end of the spectrum are suicidal thoughts and suicidal plans which we must rely upon patients or their significant others to communicate and, unfortunately, they often do not do that.

At the other end of the spectrum are suicide attempts and completed behaviors, which are usually, but not always, apparent to observers. I think we are all aware that many suicide attempts and even completed suicides go unnoticed and unreported, in part because of the stigma associated with suicide.

There are numerous studies from all over the world, some of which are cited below, which report that 20 to 40 percent of patients with schizophrenia and schizoaffective disorder attempt suicide, and recent studies from Scandinavia indicate the rate is increasing in direct proportion to the decrease in the availability of hospitalization for schizophrenia, and

declining days per hospitalization.

As Dr. Laughren mentioned, approximately 10 percent -- the range in various studies is 4 to 13 percent -- of people with schizophrenia and schizoaffective disorder complete suicide. It remains the leading cause of death in schizophrenia up to age 35, and it persists thereafter even into later life.

According to Surgeon General Satcher's report in 2001, the annual number of suicides in the United States is 3600, and that's quite probably an underestimate because of the reluctance of medical examiners to identify suicide as the cause of death.

(Slide)

I will now discuss some of the evidence that suicidal behavior is a separate domain of psychopathology and does not follow strictly from psychosis.

(Slide)

There is considerable evidence that the control of positive symptoms alone does not provide optimal control of the risk for suicide. Dr. Laughren mentioned from the meta-analyses that Kahn, (phonetic) et. al. published, that even though the other atypical antipsychotics were very effective to control positive symptoms, they did not differ from placebo or typical

neuroleptics in the rate of suicide. And, indeed, every major review of the effect of typical neuroleptic drugs on the rate of suicide following introduction in the 1950s not only did not find any sign of a decrease in the rate of suicide, but there were a number of early indications that the rate actually increased and this was attributed to the more suicidal patients being specifically treated with typical neuroleptics.

In the study that I will review, the Meltzer Okayli study, that foresaw a similar but causally reduced suicide, we studied a large number of neuroleptic-resistant patients with persistent positive symptoms, and a smaller but still significant number of neuroleptic responsive who differed dramatically in the incidence or persistence of psychotic symptoms, and both the lifetime and current rates of suicidality in those two groups were indistinguishable.

(Slide)

I'd like to speak to the issue of suicidal behavior in schizoaffective disorder versus schizophrenia. These data from our Mental Health Clinical Research Center were patients who were diagnosed on the basis of structured interviews, and

I think it's fairly reliable, and they are very consistent with the rest of the literature comparing these two groups.

And you can see, looking at a lifetime never reporting suicidal -- part of the suicidal spectrum here, we had 40 percent of the group in schizophrenia, 10 percent of the schizoaffective -- very small number -- no difference in suicidal plans, but the attempt rate was, as would be expected, are consistent with most of the literature on schizophrenia are 40 percent, and up to 70 percent in the schizoaffective. And the literature again is very consistent that the means by which people with schizoaffective disorder attempt suicide is much more often violent and more likely to be lethal.

(Slide)

This slide provides additional data, looking now at psychopathology, on the relationship between lifetime suicidal behaviors and various types of psychopathology. The data are very similar when you look at current, and what we see here is that a very high correlation between a Hamilton-Depression Total score at the time of assessment, or the BPRS-Anxiety/Depression subscale, and the suicidal history of these individuals.

When we look at the current positive or negative symptoms and the more global measures of quality of life, this is the Heimler (phonetic) Carpenter scale, or the Global Assessment of Function Scale, you can see negligible correlations.

(Slide)

Now, the burden of suicidal behavior probably -- it's so important it needs to be mentioned, but I'm sure all of us are aware of it. It falls not only on individual patients, but also on their family and society.

Unsuccessful suicide attempts may lead to permanent physical impairment, as from a gunshot wound or an overdose which produces organ damage. It may also leave long-lasting psychological scars not only on the patient, but their families. Serious suicide attempts will undoubtedly disrupt the daily lives of patients and their families.

Obviously, this has big financial implications for the individual, for society which bears the burden of paying for the problems with schizophrenia. Palmer, et. al. estimated the average cost of a suicide attempt at $33,000 a year, mainly due to the cost of hospitalization. Indeed, today, hospitalization for suicide attempts or to prevent it

may be among the very most common reasons for hospitalization of schizophrenia.

(Slide)

I'd now like to briefly review the evidence that Clozaril reduces the risk of suicidal behavior.

(Slide)

I'm going to start with the mirror image study which Dr. Okayli, who was then a psychiatric resident, and I did at Case Western Reserve University. The impetus for that was my clinical observation that the number of times I was dealing with a problem of suicidal behavior in the patients I was treating with Clozaril was dramatically less than what I had come to expect in the same setting over a dozen years with similar types of patients.

The led us to do a very careful retrospective study of 88 consecutive patients, interviewing the patients again, their family members, and obtaining all available medical records as to the history of suicide in the two years before we began treating them with Clozaril. And we had prospective data. We had monthly ratings of suicidal behavior during the entire course of this study.

Patients were mainly treated

with Clozaril monotherapy. During this time, everybody was seen weekly. We did offer a psychosocial treatment program which would impact, of course, on the interpretation of the results.

(Slide)

This is the major result of that study. What we found was that the group as a whole -- 53 percent of them reported no suicidal behavior from that whole spectrum that I talked about in the two years before Clozaril, and that increased to 88 percent in the follow-up period.

Suicidal ideation, again, collected prospectively, did not change. Accident or unintended self-harm which were mainly due to command hallucination decreased dramatically. And the major finding was the number of low and high probability suicide attempts decreased dramatically. There were only 3 low probability attempts, all within the first few months of treatment with Clozaril, which you'll see an echo of that when you look at the Clozaril-Zyprexa comparison. It apparently takes some time before the optimal benefits of Clozaril are manifest.

And we published these data in the American Journal of Psychiatry along with some others which I'll mention in a moment, and it stimulated a

number of followups.

(Slide)

At the time we looked at the Clozaril National Registry which did have a report on completed suicides, and as of '94 -- the annual expected rate in the United States would be about 0.2, it was about 0.05 percent in '94, looking at the Clozaril National Registry. William Reid, the Commission on Mental Health in Texas, did a similar review in 1998, and found even a greater discrepancy from the expected rate.

Dr. Reid also compared the rate in all of Texas, from their records, for all mental health patients treated with Clozaril versus the ones not treated with Clozaril, and found almost an identical decrease in that subsample in terms of lower rates of completed suicide on Clozaril, and Rob Kulan's (phonetic) group at the Modsley (phonetic) looked at the U.K. Clozaril Registry, comparing it with a series of papers published in the 1990s from the United Kingdom on completed suicide and schizophrenia, and found again virtually the same reduction that everybody who has looked at this has found, and there have been a number of other subsequent replications of that.

(Slide)

Now I'd like to go into some detail which I know the committee was requested about this Walker study. The Walker study was an epidemiologic study connected by the Rothman (phonetic) group, a very respected group of epidemiologists, from Boston University.

(Slide)

The purpose of the study was actually to determine the mortality from all causes associated with the use of Clozaril, something that the FDA was very keen on because of the possible increased rate of pulmonary embolism of Clozaril.

The study examined mortality in all patients who had received Clozaril in the United States from its approval in 1989 until the end of '93. The main analysis in the paper and the data that I'll share with you was on the subgroup who were between the ages of 10 to 54, leaving out the group with Parkinson's Disease who were treated with Clozaril because of aldopapsychosis (phonetic) and who had a very separate mortality experience.

There were 67,072 current and former Clozaril users who constituted the sample, and they had a total exposure of 85,399 years.

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The group was divided into three groups. The first group were people who were currently still taking Clozaril, as indicated by the fact they had had a white count reported to the Registry within the last two weeks by the end of 1993.

Recent users had recently discontinued sometime between 15 and 106 days, and the third group were those that had discontinued even a longer period of time. So, everyone in the sample had received Clozaril at some time.

Of course, the mortality data that had been reported to Novartis during this period, but there were other data which could be obtained from the National Death Index and the Social Security Administration Death Master Files by cross-linking Social Security Numbers, initials, age, sex, race, et cetera.

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This is the key summary slide of that. The death due to suicide in the currently still taking Clozaril group was a rate of 39 per 100,000 person-years. The mortality due to suicide in the recent and past groups were 246 and 221 per 100,000. These are well within the range reported for the population of

people with schizophrenia as a whole. There is no signal in these data that having recently been on Clozaril, that the rate increased in relationship to the discontinuation. In fact, they did a special analysis, a very important part of that paper, in which they looked at the people who had been discontinued due to agranulocytosis, and they compared the rate in that group -- which wouldn't be biased by any possible stop in the medication because they were suicidal -- and that group did not differ from the rest of the group, indicating that the rest of the group was not particularly biased due to suicidal behavior as a reason for discontinuation.

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And when they looked -- again, the primary purpose was all causes of death -- there was a strong signal that Clozaril reduced the overall mortality, and that that overall mortality decrease was due to the lower rate of suicide. So, the current Clozaril users had a 54 percent lower risk of death from any cause than the past Clozaril users -- this is the 95 percent confidence limit -- does not overlap one, whereas the recent users were slightly elevated compared to the past users.

The suicide, as Dr. Laughren mentioned,

showed a hazard ratio of .17, a reduction of 83 percent, which is the exact same range that all the other studies that I've mentioned have always come up with. And we saw a slight increase, again, in the recent users.

Suicide accounted for 19 percent of all the deaths in the sample, mainly in the recent and the past users.

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So, these are the conclusions from Walker, et. al.m that Clozaril reduced the risk of completed suicide, that their findings were consistent with the previous finding, that the reduced suicide rate was the largest contributor to the lower overall mortality rate in the Clozaril current user group, and that the beneficial effects of Clozaril on suicide did not persist after it was discontinued.

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So, let me summarize with the key points that I hope I have made during this talk: that attempted suicide is a very important public health issue, occurring in at least 20 to 40 percent of patients with schizophrenia and schizoaffective disorder; attempted suicide is a major burden on patients, families, and society; that suicidal

behavior is a separate domain from psychosis -- antipsychotic drug does not necessarily mean antisuicide drug; extensive previous research suggests, but does not prove -- clearly, there are many problems with Okayli and others in terms of evidence-based medicine -- but they did suggest that Clozaril reduces suicidal behavior.

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And so the stage was set for InterSePT, which was designed by a number of people to provide a controlled, prospective test of the hypothesis that Clozaril reduces the risk of suicidal behavior, and Dr. Rocco Zaninelli, who is the Executive Director for Clinical Research and Development at Novartis, is going to present it. We think you'll see that it's an innovative design directed toward an extremely important public health problem in a very high-risk population. Thank you very much.

DR. ZANINELLI: Thank you, Dr. Meltzer. Good morning. Dr. Meltzer has discussed the scientific findings which led to the development of InterSePT. I will now present the detail of the design and the results of the study.

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My presentation today include a statement

of the objective of InterSePT, a discussion of the study design, a component of which is the independent Suicide Monitoring Board. Within that presentation, Dr. Krishnan will elaborate on the role of the Suicide Monitoring Board. I will then address the statistical methods and the efficacy and safety results of InterSePT. In response to a request from the FDA, I will also present a review of the process of referring cases to the SMB. Finally, I will draw some conclusions from the InterSePT results.

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The study title, which you have seen a couple of times already, is also a statement of the objective of InterSePT. InterSePT was a prospective, randomized, international, parallel-group study for comparison of Clozaril/Zyprexa in the reduction of suicidality in patients with schizophrenia or schizoaffective disorder who are at risk for suicide.

InterSePT was an open-label study, however, specific assessments were carried out by clinicians blinded to patient identifiers, patient treatment specifically.

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I will now describe the study design.

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The schematic you are about to see illustrates the study design of InterSePT. Patients were randomized to either Clozaril/Zyprexa for a duration of two years. The initial four weeks were the transition phase, during which patients discontinued their previous antipsychotic medications while beginning the assigned study medication.

Patients randomized to Clozaril started at 12 mg BID, patients randomized to Zyprexa at 5 mg once a day. The recommended dosage ranges were 200 to 900 mg per day for Clozaril, and 5 to 20 mg per day for Zyprexa. These ranges correspond to the dosage ranges for each of the medications in the 11 countries participating in InterSePT. There was no fixed dose for any length of time during the study.

For the first 26 weeks of the study, the patients received weekly intervals. This schedule corresponds to the necessity to monitor the white cell counts in the Clozaril patients. The visit frequency was the same in the Zyprexa group. So the frequency and duration of contacts in both groups with site staff was the same. Whereas the Clozaril patients blood drawn for the WBC counts at the contacts, the Zyprexa patients had vital signs taken.

After 26 weeks, the visit frequency for

both treatment groups became biweekly, again, corresponding to the required monitoring frequency for Clozaril patients.

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InterSePT included patients with schizophrenia or schizoaffective disorder recording the DSM4 criteria who were at high risk for suicide. Patients needed to satisfy at least one of the following criteria: A suicide attempt within the last three years; had hospitalization to prevent suicide in the last three years; moderate to severe suicidal ideation and depression within one week of the baseline assessment; or moderate to severe suicidal ideation and self-harm command hallucinations within one week of baseline assessment.

Many patients included in InterSePT met two or more of this criteria, thus confirming this was an at-risk population. The inclusion of a population at risk for suicide influenced other inclusion and exclusion criteria. For example, patients with a prior history of substance abuse or drug abuse were not excluded from the study. More importantly, in keeping with the medical mandate to prevent suicide and maintain patient safety, there were no constraints regarding the use of concomitant medication use during

the study.

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The choice of the comparison medication was deliberate. Preliminary to the design phase of InterSePT, the use of placebo in this patient population was considered unethical and medically inappropriate. Zyprexa was chosen because it is an atypical antipsychotic that is pharmacologically similar to Clozaril. A previous study by Tran, et. al. had demonstrated a lower rate of adverse events related to suicidal behavior among patients treated with Zyprexa compared to patients treated with Risperdal.

Zyprexa is effective in treating psychosis. It is generally well tolerated. Finally, it was available in all of the countries wanting to participate in InterSePT.

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The rational for the open-label design was based on the assumption that any attempt to blind the study would be compromised by at least two factors, one factor being the need to monitor white blood cell counts in the Clozaril patients, the other the clinical fact that Clozaril and Zyprexa have fairly distinct adverse event profiles, that it would be

difficult to blind the medications from experienced clinicians.

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The primary efficacy endpoint for InterSePT was a Type 1 or Type 2 event. I will define these types of events before describing the statistical methodology which was used to analyze the results.

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A Type 1 event was defined as a significant suicide attempt or hospitalization due to imminent suicide risk, including a increased level of surveillance in patients already hospitalized. The data concerning such events were assessed by the Principal Investigator at the site, and confirmed by the Suicide Monitoring Board.

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A suicide attempt itself was defined as actions committed by a patient either with willful intent or as a response to internal compulsions or disordered thinking that put him or herself at risk for death.

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A Type 2 event was defined as a worsening of suicidality as measured by a score of 6 or 7 on the

Clinical Global Impression of the Severity of Suicidality related by a Blinded Psychiatrist, or CGI-SS-BP. However, a level of 6 or 7 indicates a score of much worse or very much worse. This scale is a modified version of a Global Improvement Scale of Clinical Global Impression, which is a standard assessment in psychiatric research. The blinded psychiatrist performing the reading was at the site, but was not otherwise involved in the conduct of the study.

Type 2 events also included an implicit worsening of the severity of suicidality as indicated by the occurrence of a suicide attempt or hospitalization to prevent suicide. That is, every Type 1 event was also a Type 2 event. Every Type 1 event was therefore considered in two dimensions, the behavioral aspect -- the suicide attempt or hospitalization to prevent suicide, which was the Type 1 event -- but also in the implicit worsening which is associated with suicidal behavior.

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There are also a number of secondary efficacy assessments, the CGI-SS-BP, besides comprising a component of a primary endpoint, overall changes from baseline in a CGI-SS-BP were also

recorded as a measure of the clinician's impression of changes in the patient suicidality status.

The InterSePT Scale for Suicidal Thinking as rated by the Blinded Psychiatrist is a new scale which was especially developed for InterSePT. It is based on an adaptation of Scale for Suicidal Ideation. It has been validated for the InterSePT population.

Three scales were used to assess syndromal psychopathology, depression, and anxiety, respectively: The Positive and Negative Syndrome Scale, the PANSS, the standard measure in studies of schizophrenia and schizoaffective disorder; the Calgary Depression Scale, which was specifically developed to measure depression syndrome in schizophrenia; and the Covi Anxiety Scale, which is a standard measure of anxiety.

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A crucial aspect of InterSePT was the determination of Type 1 events for the independent Suicide Monitoring Board, concerning which Dr. Krishnan will speak to you in a few moments. I wish to describe in this schematic the overall process by which data flowed to the Monitoring Board.

Patients in this study were cared for at the site where all unblinded clinical assessments were

made. The blinded psychiatrist, as mentioned already, was also at the site. Information collected from the site during the study was forwarded to the Medical Monitor at the Inginex Pharmaceutical Services, the research organization responsible for conducting InterSePT. The Medical Monitor was a trained psychiatrist, whose main functions were to oversee the quality of data flowing to a database but, more particularly, to blind all information pertaining to suicide attempts, suicides, and hospitalizations to prevent suicides -- that is, potential Type 1 events.

The case information was then passed on to an Independent Suicide Monitoring Board which deliberated the case and made a determination of whether the data actually constituted a Type 1 event or not. The results of the SMB's deliberations were passed back to Medical Monitor. The data concerning these events were entered into the database.

Dr. Krishnan, who is Chairman of the Suicide Monitoring Board, will now present the details regarding the work of the SMB. Dr. Krishnan?

DR. KRISHNAN: Thank you, Doctor. It's nice to discuss the role of the SMB with the members of the Advisory Group.

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Let me very briefly tell you who we were and what we did. The SMB consisted of three individuals -- myself, Isaac Sakinofsky. He is Professor Emeritus at University of Toronto. His clinical work is on suicide in schizophrenia, and his clinical research is also focused in this area.

The third individual is Hannele Heila. Hannele Heila is an individual who conducted on of the largest psychological autopsy studies of suicide in the context of schizophrenia.

The three of us were not affiliated to any of the investigative sites. The membership remained constant throughout the trial, and each member participated in all the meetings and in all the decisionmaking for all the individual events.

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The primary role of the SMB was to evaluate all the relevant data to determine whether a Type 1 event occurred. So, we evaluated all deaths and determined if the cause was suicide; potential suicide attempts we evaluated to determine their potential lethality; and hospitalizations related to suicidal behavior were assessed to see if the hospitalization was due to imminent risk of suicide and not due to other reasons such as increased

psychosis, worsening of psychosis, et cetera.

Let me briefly give you an idea of the thought process that went into making some of these decisions. If you review the literature in the context of assessing suicide, it is clear that while it is possible to delineate historical and current risk factors for suicide in samples of patients, when you try extrapolating it to the individual, these data are suggestive but are not definitive. So, essentially they yield either too many false-positives or they fail to identify many of those who later turn out to be at risk for suicide.

The Suicide Monitoring Board, therefore, fell back on careful considered clinical judgment tested and tempered by teleconferences that had any conflicting opinions and drew reasoned consensus from the group, sometimes with the aid of additional information requested about the event and about the patient.

The key to evaluating the important behavioral phenomenon turned on assessing the seriousness of the suicidal intent and the driving force behind it. In this context, it is useful to distinguish between intent that is subjective -- in other words, not always that which is explicitly

stated by the individual, or objective intent which is implicit in the circumstances of the event. Objective intent is evaluated by evidence of preparation, choice of the method of attempting suicide, and by any steps taken to prevent the act being plotted by this.

The clinician and, in this case, the Suicide Monitoring Board, had to estimate the degree of trust that can be placed in a patient's statement of intent in both directions, i.e., that the patient will or will not kill him or herself. Patients are well known, for example, to threaten self-harm for the sake of some gain, such as admission to the hospital. On the other end, the seriously suicidal person is likely to deny or conceal intent, but suicide will not be prevented.

And, further, where an individual is in the midst of a psychotic episode, they do not always follow logical process. For instance, lethality of an attempt may not follow the degree of intent in either direction. This can account for the fact and the frequent finding that suicide victims were not perceived as at risk for suicide at their last clinical appointment. At the same time, buffering and mitigating factors also have to be considered, namely, where do they live? What is their willingness to

live? What is the circumstances in their life that at that point makes them either more likely or less likely to attempt suicide.

So, we had to consider all these factors and try to arrive at reasoned judgment as far as possible in making a decision whether they met criteria for one of those events by events that we discussed.

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What were the material that we utilized? There was a bunch of case report forms which is a suicide attempt form, the rescue intervention form, the Calgary Depression Scale, the InterSePT Scale, and we also looked at all the clinical reports from the charts and history of suicidal behavior. Remember, all these charts were carefully evaluated prior to our seeing them, to take out any information that is there about diverse experiences, any clue about what the drug was, et cetera, so everything which was connected to that was blacked out and sent to us. So, the information that we had was essentially anonymized as to which compound or which drug the individual was receiving.

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We reviewed 577 events, and we determined

483 to be Type 1 events, of which 111 were suicide attempts and 372 were hospitalizations to prevent suicide.

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In conclusion, I just wanted to emphasize a couple of things: Members were independent of any of the sites, that the review was blinded, and the classification of each event was on a pre-determined and pre-defined process, and the determination of Type 1 events were unanimous.

Let me just also briefly say one word. When we evaluated in the context of the Suicide Monitoring Board, what we actually got was stories of patients, and these stories were compelling. Here you are talking about a group of individuals who are generally excluded from most clinical trials. They were very, very ill. And the stories were striking. The number of attempts, the degree of co-morbidity with other problems, the lack of support systems very often in this group of patients, and the level and the chronicity of their illness during the time frame when they participated in the study and the time frame before they entered the study, and you can see to some extent from the type of events that occurred during the study and prior from the study, everything from

jumping off bridges, trying to hang themselves, overdoses, et cetera. And so one has to think of this in the numeric sense, in the statistical sense, I think it is also important to keep in mind the nature of this patient population that was evaluated and studied. Thank you.

DR. ZANINELLI: Thank you, Dr. Krishnan. I will now continue my presentation by turning to the statistical methods which were used to analyze the data from InterSePT.

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The primary efficacy analysis of InterSePT was a time-to-event analysis based on the approach of Wel, Lin and Weissfeld, the WLW method. This method is used to analyze time-to-multiple-event data. It allows the combination of different types of events into a single dataset, which was the case in InterSePT with the combination of Type 1 and Type 2 events. The WLW method provides an overall test of the difference between treatments. In the case of InterSePT, the difference between Clozaril and Zyprexa, with regard to the risk of experiencing a Type 1 or Type 2 event.

The WLW method was established as the primary efficacy analysis by protocol amendment. The regional InterSePT design designated only the Type 1

event as the primary endpoint, however, there was a concern there may be too few events of suicidal behavior in the course of a study in which the emphasis was on patient safety and the prevention of suicide. Therefore, the Type 2 event, which was reported to reflect more implicit suicidal behavior was introduced into the design.

The use of the WLW method was agreed to by the FDA during deliberations on the design of InterSePT.

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A number of supportive analyses were also conducted. The Cox proportional hazards analysis, which included in the model the factors of drug treatment, number of suicide attempts, current substance or alcohol abuse, country grouping, gender, and age.

Kaplan-Meier estimates of cumulative probabilities were also conducted. And, finally, analysis of clinical variables were carried out based on analysis of the last-observation-carried-forward dataset.

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The statistical assumptions behind the sample size calculation were as follows: the

randomization was set at 1-to-1; the log-rank test established alpha at 5 percent, with power at 80 percent. It was estimated that 45 percent of Clozaril patients of 55 percent of Zyprexa patients would have at least one Type 1 event during the two-year observation period. Therefore, a total 381 events would be necessary to distinguish a difference. With a frequency of 50 percent, at least 762 patients were needed for the study. And allowing for a 15 percent dropout rate, about 900 patients needed to be randomized to study medication.

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Finally, getting to the results of the study, I'll start off with the characteristics and disposition of the study population.

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InterSePT was conducted at 67 centers in 11 countries. The first patient was enrolled in March 1998, last patient visit took place in February 2001, the database was locked in June 2001.

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In total, 1,065 patients were screened, and most of those patients were actually randomized and started medication. The intend-to-treat population consisted of all randomized patients, 490

in each group. Approximately 98 percent of these patients actually received medication and, of these, about 61 percent completed the two-year observation period.

Of the 40 percent who discontinued the two-year observation period, 15 percent in the Clozaril group and 18 percent in the Zyprexa group, still contributed complete data to analysis at the primary endpoint, either by having a Type 1 or Type 2 event before or after discontinuation.

The study design included the stipulation that patients who dropped out would be, as much as possible, followed to their individual two-year endpoint to determine whether a Type 1 or Type 2 event occurred after discontinuation. These were so-called "retrieved dropouts".

The number of true dropouts -- that is, patients who had no event prior to discontinuation and were ultimately lost to followup -- was, therefore, 24 percent in the Clozaril group and 80 percent in the Zyprexa group. One of the conclusions of this is that about 80 percent of the patients in each group contributed complete data for the analysis of the primary endpoint.

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The distribution of age was similar across the two treatment groups. The mean age of onset of the disorder was about 24 years; median duration of illness, ten years. The percentage of males and females was similar across treatment groups. You can also see that the distribution of race was even in both groups.

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Looking now at diagnosis at baseline. This is about 60 percent of the patients were diagnosed with schizophrenia and 40 percent of the patients in each treatment group were schizoaffective disorder. Around 27 percent of the patients in both groups were classified as being treatment-resistant by history. This percentage was based on historical information from the patient's files, and not on the strict application of criteria for treatment resistance.

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Turning now to the psychometric scores. At baseline, we see that the severity of suicidal behavior at baseline as measured by the CGI-SS-BP was 2.2 in both groups. This corresponds to a rating of mild to moderate severity of suicidality. The mean number of lifetime suicide attempts, the mean number

of lifetime hospitalizations to prevent suicide was greater than 3 in both groups. These numbers underscore the fact that it is a high-risk population.

For both groups, the mean total score on the PANSS was above 80, indicating that although most of these patients were receiving antipsychotic medication before the trial, there was still a substantial degree of psychopathology present at baseline.

On the Calgary Depression Scale, a score of around 10 indicates mild to moderate levels of depressive symptomatology and, finally, Covi Anxiety score of around 4 indicates rather low level of anxiety.

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For those patients who discontinued the study, the most frequent reason for discontinuation was withdrawn consent, followed by discontinuation due to adverse events. For most of the reasons we see here, the proportion of patients that discontinued treatment was similar across the two groups. There were a few differences. Three patients in the Clozaril group, none in the Zyprexa group, discontinued because of abnormal lab values or procedure results, while 6 patients in the Zyprexa

group and none in the Clozaril group discontinued due to unsatisfactory effect on the suicide risk.

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With regards to study medication, the mean dosage for Clozaril during was 274 mg, if it was Zyprexa, 17 mg, so overall during the study. For Clozaril, the mean dosage beginning in month 4, that is following the titration period that's customary for Clozaril, the mean dosage is about 225 mg per day.

The dosage for Clozaril patients ranged from 13 to 725 mg per day, from which we can deduce that no Clozaril was dosed at the ceiling of the recommended range. For Zyprexa, the actual dosing range was 3 to 41 mg, with about 18 percent of the patients receiving doses in excess of 20 mg per day.

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I will now present the results of the analysis at the primary endpoint, which was again the time to first Type 1 or Type 2 event.

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These bar-graphs represent the distribution of Type 1 events -- that is, suicide attempts and hospitalizations to prevent suicide in the two treatment groups.

Overall, 102 patients in the Clozaril and

141 patients in the Zyprexa group had a Type 1 event. The suicide attempts and hospitalizations to prevent suicide, you see there are 34 suicide attempts in the Clozaril group, 55 in the Zyprexa group; hospitalizations, 82 in the Clozaril group, 107 in the Zyprexa group. These numbers, 34 of each, don't add up to 102 because there were patients who had a suicide attempt and a hospitalization in both groups.

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This slide shows the distribution of patients in the treatment groups and the number of Type 1 events they had. You see that most patients in each of the treatment groups had only one event -- this is the number of patients. But there were not a few patients who had more than one Type 1 even during the course of the study. In each of these cases, there were more patients in the Zyprexa group than in the Clozaril group.

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This slide shows the distribution of Type 2 events across the treatment groups. We'll review the definition of Type 2 again. Type 2 events encompass a worsening of suicidality on the CGI-SS-BP as well as a worsening implied by the occurrence of Type 1 events, suicide attempts or hospitalizations to

prevent suicide.

So, with that in mind, look at this. The Clozaril group, there were 120 patients who had a Type 2 event, in contrast to 161 in the Zyprexa group. However, 102 of these events were actually the Type 2 events we saw two slides previously in the Clozaril group. These 141 we also saw two slides previously, that is, the preponderance of the material making up the Type 2 event was actually the Type 1 event. This result needs to be kept in mind when you consider the further results in the analyses I'm about to present.

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The results of the primary efficacy analysis using the WLW method indicates a significant difference between the groups in favor of Clozaril, the p-value being .031. The results of the supporting Cox Proportional Hazard analysis show ratios of .74 and .76 for Type 1 and Type 2 events, respectively, a ratio of greater than 1 would be in favor of Zyprexa or a ratio of less than 1 in favor of Clozaril. The differences for both types of events were statistically significant. You see here the p-values, .021 and .026 for Type 1 and Type 2 events, respectively. The mean result here that for the Clozaril group relative to the Zyprexa group there was

a reduction of risk of 26 percent in the Clozaril group relative to the Zyprexa group, reduction of risk for suicide attempt or hospitalization to prevent suicide.

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Look now at the Kaplan-Meier plots, you can observe the cumulative probabilities of a Type 1 event were 24 percent in the Clozaril group and 32 percent in the Zyprexa group. The probability estimate is fairly constant for Clozaril of about 22 to 24 percent from about month 12. Confirming results of the Cox analysis, this represents for the Clozaril group a 25 percent reduction in the probability to have a Type 1 event.

What this means clinically can perhaps best be shown from the time point at which the Clozaril patients have a 24 percent probability, which is around 12 months or so. This indicates that the acuity benefit accruing to the Clozaril patients is amplified during the second year of the study.

The Kaplan-Meier plot for Type 2 events is very similar, which is not surprising considering that the data involved in this analysis are driven by the preponderance of the Type 1 events, as I mentioned before.

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To assist the robustness of the Clozaril treatment effect, a Cox Proportional Hazard Analysis was carried out for each of several diagnostic and demographic subgroups, so that's for the schizophrenia and schizoaffective diagnostic subgroups, treatment-resistant and treatment-nonresistant, look at geographic distinctions for North America and the rest of the world -- gender, race and age grouping.

For the subgroup, the hazard ratio was less than 1, confirming the reduction in risk in the Clozaril group relative to the Zyprexa group for a suicide attempt or hospitalization to prevent suicide. Remember, less than 1 is in favor of Clozaril.

Also note that the hazard ratio of the individual subgroups are very close together, thus demonstrating a high degree of internal consistency.

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Now I'd like to review the changes in the secondary clinical assessments which were carried out during InterSePT.

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Looking first at the change from baseline in the severity of suicidality as rated by the blinded psychiatrists on the CGI-SS-BP, you see that they were

equal or very similar proportions of patients form the treatment groups, each change category at the end of study, that explains a bit -- these are the change categories, so the CGI-SS-BP is a change from baseline scale. So, relative to baseline, in this case, about 25 percent of the patients in each group were rated very much improved; about 30 percent of the patients in each group had no change relative to baseline; about 5 percent of the patients overall in each group had some degree of worsening in suicidal status, as rated by the blinded psychiatrist at the site.

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Here are the other secondary measures. You see for the ISST-BP, much the same result as for the CGI-SS-BP. Relative to baseline in both treatment groups, there's a reduction in the score from the baseline of 7.4 by about 5 points at the end of the study. This considerable reduction is essentially the same in both treatment groups. This pattern of response also holds true for the psychopathology variables. On the PANSS-T, CDS and Covi, there are very similar reductions in the groups relative to baseline, and these are mostly indistinguishable.

Here are some of the results we've seen sos far. For Clozaril patients relative to Zyprexa

patients, there was a significant reduction in the risk of experiencing suicidal behavior, Type 1 or Type 2 event. However, from the results we see here this difference appears not to be related to differential improvement in measures of psychopathology or measures of suicidality as rated by the blinded psychiatrist.

There are perhaps a number of reasons for this finding. One might be the fact that the assessments of psychopathology, especially the CGI-SS-BP and the ISST-BP, occurred at only a few discrete time points separated by intervals of eight weeks, while the patient's suicidal behavior is obviously not tied to these time points. Thus, these assessments ultimately may not contribute to the assessment of drug effects.

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There was an intrinsic of Clozaril on suicidal behavior. I don't want to speculate on this now, but if that is the case, it would be important to address the possibility that such a drug effect may be confounded by the greater use of concomitant psychotropic medication in the Clozaril group. Remember, there was no constraint on the use of psychotropic medications.

To look at this possibility, or to examine

this possibility, we looked at the use of concomitant psychotropic medication in the two groups during the study. Specifically, the concomitant psychotropic medications in the four classes -- antipsychotics, antidepressants, sedatives/anxiolytics, and mood stabilizers, we used equivalents to get these drugs into a common denominator -- Haloperidol equivalents for antipsychotics; fluoxetine equivalents for antidepressants; diazepam equivalents for sedatives/anxiolytics; and carbomazepine equivalents for mood stabilizers. For each of the four classes, as we see here, there's a significant difference between the groups with respect to the mean dose of these classes of medication. In each case, the mean dose of each of these medication classes is significantly greater in the Zyprexa group. This result would appear to discount the possibility that the effect of Clozaril on the risk of suicidal behavior is due to a greater use of adjunct psychotropic medication.

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To move on to discuss the safety aspects of the study.

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As could be expected in a two-year study,

90 percent of the patients in each group had at least one adverse event report. About half of the patients in each group also had at least one report serious adverse event. However, there were no cases of agranulocytosis, myocarditis or cardiomyopathy in the Clozaril group. There was 1 case of cardiomyopathy in the Zyprexa group.

On the following slides, I will present the adverse events of interest for Clozaril adverse events separately, then consider the psychiatric and neurologic adverse events and deaths for the two groups together.

(Slide)

Looking at the Clozaril adverse events of interest, we see that the incidence of salivary hypersecretion, white blood cell decrease, constipation, weakness, postural hypertension, and convulsions is greater in the Clozaril than the Zyprexa group.

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On the other hand, looking at the Zyprexa adverse events of interest -- weight increase, dry mouth, asthma, laceration, epistaxis -- are greater in the Zyprexa group. The incidence of diabetes mellitus NOS, not otherwise specified, is about the same in the

two groups. The reports of laceration we see here were not related to suicidal intent.

(Slide)

This slide summarizes the frequencies of psychiatric and neurologic adverse events in the two groups. The blue field are those events where the occurrence or the frequencies of events are higher in the Zyprexa group -- that's depression, suicide ideation, suicide attempt -- again, as adverse event reports -- drug abuse, tension, mood disorder, insomnia, akathisia are greater in the Zyprexa. In the yellow text area, we see that somnolence, dizziness, dysarthria and syncope are greater in the Clozaril group.

(Slide)

There were 22 deaths during the study, of which 10 were suicides. During the two-year observation period, there were 5 suicides in the Clozaril and 3 in the Zyprexa group. In each group there was 1 suicide -- that's the number in parentheses -- that occurred after the two-year observation period, but within the 30-day safety followup period. Considering the high-risk population of InterSePT, the number of suicides was very low. The difference in the number of suicides attributed to

the groups is not statistically significant.

The other deaths that occurred during the study were associated mostly with cardiovascular or oncologic events. With regard to the single fatal motor vehicle accident we see, there was no evidence to indicate that this was the result of suicidal intent.

(Slide)

In the final part of my presentation, I'll address one of the questions raised by the FDA during their review of InterSePT results. This question concerns the process of referring case material from the unblinded Principal Investigator to the blinded Suicide Monitoring Board.

(Slide)

Now, the situation involved in this question is perhaps best explained if we take another look at the flow chart describing the movement of unblinded data to the blinded Suicide Monitoring Board, as I mentioned before. The information was collected at the site by the Principal Investigator, information concerning potential Type 1 events, potential suicide events or hospitalization to prevent suicide. This information was collected in a nonblinded fashion. The Principal Investigator was

aware of all the assessments going on, was in many cases the actual treating physician for the patient. This information was passed on to the Medical Monitor who blinded it and passed it on to the SMB.

Because the PI is aware of the patient's treatment, there is obvious potential bias here. During the study itself there were a number of checks in place to identify potential Type 1 events that may have been missed by the PI. In particular, the Medical Monitor reviewed adverse event and serious adverse event reports; all hospitalizations, medical and psychiatric; and reports of self-harm, and actually anything vaguely associated with self-harm.

If there was any evidence in this body of data to indicate that the PI may have missed a potential Type 1 event, the Medical Monitor contacted the site and queried the investigator. At the same time this was going on, on a regular basis the field monitors reviewed the source documents for all unreported cases of suicidal events, and in those cases where there was no referral to the SMB, they made sure that there was no evidence there for potential Type 1 event.

In response to the FDA's recent request, Novartis conducted a retrospective review of the

referral process, which I will now describe.

In our review of the process of referring Type 1 events from the Principal Investigator to the SMB -- potential Type 1 events, excuse me -- we made the assumption to refer the bias when we ruled the case not referred to the SMB. Nonreferral of potential Type 1 information occurred in 701 of the 980 patients who were enrolled in InterSePT. The search term dictionary or glossary, to use the technical term, were then developed, which was based on terms from the reports clearly corresponds between the investigative sites, the Medical Monitor and the Monitors, in comments from the site staff entered into the case report forms which comprise the documentation for each case.

There were more than 300 terms in the search dictionary, covering not only explicit suicidal behavior, but also events not necessarily related to suicidal behavior, such as drunkenness or abrasion.

The next step in the search term dictionary was applying to each of the 701 cases, looking for matches -- the search dictionary was programmed to look for matches in each of the 701 cases. The search program was blinded to patient treatment.

The case report forms from those cases where terms were matched were then reviewed by Novartis. For example, if the term "abrasion" which was in the search dictionary, popped anywhere in a patient's case report form, the entire documentation from that patient was then reviewed by Novartis clinical staff. The review covered several -- well, three questions were asked: Whether the term was potentially related to suicidal behavior or was related to potential suicidal behavior? If so, were the PI queried regarding occurrence of suicidal behavior? And if the PI was queried, what was his or her response? We then graded this review to establish whether potential cases of suicidal behavior were not referred to the SMB for a blinded and independent assessment.

(Slide)

Now, the results of our review, so summarized here. There were matches of at least one dictionary in 279 out of the 701 cases -- that is, again, the 701 cases represent those patients for whom no there was no potential Type 1 event which had been referred prior to the SMB. In 279 of the 701 cases, there was at least one search-term match -- again,

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these cases were we able to determine that there was evidence indicating that there may have been a Type 1 event, evidence for potential Type 1 events here.

We feel that the results of this review that, although the Investigators were unblinded to patient data, they acted without bias in referring case material to the SMB.

(Slide)

To move now on to conclusions from InterSePT. During InterSePT, treatment with Clozaril compared with Zyprexa was associated with a 26 percent reduction of risk for a suicide attempt or a hospitalization to prevent suicide.

For all subgroups examined, there was a high degree of consistency in the reduction of risk for suicidal behavior in the Clozaril group compared to the Zyprexa group.

(Slide)

The reduction in risk in the Clozaril group appears not to be attributable to a greater effect on psychotic or depressive symptoms, or to a greater use of concomitant psychotropic medications. Adverse event profiles for both study drugs were generally consistent with previous experience and current product labeling. Finally, the open-label

design was not associated with biased assessments by the Principal Investigators.

(Slide)

The overall conclusion, the results of InterSePT show that Clozaril is effective and safe in reducing the risk of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are at risk for suicide.

I'd like to introduce Dr. Kane, who will present the risk/benefit assessment for Clozaril in the treatment for reducing the risk for suicidal behavior.

DR. KANE: Thanks very much. I'm very pleased to have been part of this project which I think is important not only because of the significance of the results, but also because it demonstrates that studies can be conducted in high-risk populations in a way that is both safe and scientifically informative, as well as clinically meaningful.

(Slide)

As clinicians, we need to assess the benefit and risks of treatment interventions. When considering the benefits and risks regarding the use of Clozaril in the treatment of suicidal behavior, one

needs to consider both the risks of treatment intervention and the benefits of reducing suicidal behavior. But in this assessment, one must also consider the risk of not treating these patients.

(Slide)

As you know, Clozaril was first approved in 1969 for the treatment of schizophrenia. After 33 years of use, it is recognized as the most effective agent in the management of treatment-resistant and partially-responsive patients. Despite numerous efforts, no other second-generation drug has been able to match Clozaril's consistent efficacy in this population.

In addition, over the years, other properties and clinical uses of Clozaril have drawn increasing interest and attention. Some of these include reduction in substance abuse, smoking, movement disorders, aggression and violence and, importantly, suicidal behavior.

Many of these observations came from uncontrolled or small trials or epidemiologic studies. The pivotal study that we're discussing today obviously represents an extremely well-designed and well-controlled trial attempting to look at the issue of suicidal behavior.

(Slide)

The burden of suicidal behavior is very clear. Left untreated, it's associated with increases in morbidity and mortality; hospitalizations both psychiatric and medical; emergency room visits; interventions to prevent suicide attempts such as the use of concomitant medications and increased surveillance. The family burden is enormous, and anyone who has worked with families in this context can appreciate the tremendous strain and sense of anxiety that this creates. The societal costs, as you heard earlier today, are also substantial.

(Slide)

Well, the InterSePT study clearly provides a new basis for understanding potential benefits and potential risks of Clozaril utilization. It was a well-designed study that was consistent, with very valuable input from the Food and Drug Administration. It utilized prospectively defined and objectively rated endpoints that were assessed by, as you've heard, a blinded Suicide Monitoring Board.

The study compared two atypical antipsychotics over a period of two years, which allowed for a long-term perspective on the efficacy and safety outcomes. Very importantly, procedures

were designed to maximize patient safety and, as we've seen, the overall rate of completed suicides in this study was remarkably low.

(Slide)

Now, as you've seen in Dr. Zaninelli's presentation, there were a number of statistical methods brought to bear in the analyses. Clearly, from my perspective, the most impressive thing is that there was consistency across a variety of ways of looking at this, demonstrating the superiority of Clozaril in this high-risk population.

Now, these two analyses demonstrate the statistical superiority of Clozaril over Zyprexa in reducing suicide attempts or hospitalizations to prevent suicide.

(Slide)

Here, we're looking at the Kaplan-Meier estimates of the cumulative probabilities of suicide attempts or hospitalizations to prevent suicides. Again, this analysis demonstrates significant superiority for Clozaril over Zyprexa.

(Slide)

Now, the previous slides involve the key statistical comparisons. From a clinical standpoint, it's also very impressive to see the consistency of

clinically meaningful differences across measures of suicide attempts and hospitalizations, and we see that on the left-hand side of the slide.

It's also important to note, these are items you saw in Dr. Zaninelli's presentation from the adverse events reports, and I think from a clinical perspective it's very valuable to look at the adverse event reports as another source of information. When clinicians are treating patients, they are not usually filling out rating scales, but they are responding to reports from the patient of what might be considered adverse events.

Here we see that depression as an adverse event occurred significantly more frequently in the Zyprexa-treated patients. Suicidal ideation reported as an adverse event also significantly more frequent in the Zyprexa-treated patients. So, this, I think, just is another way of getting a sort of clinical sense of how these differences emerged and how many different ways.

(Slide)

In addition, these differences were apparent despite the fact that as you saw previously, Clozaril-treated patients received significantly less concomitant medication in ever psychotropic drug

category. Dr. Zaninelli had presented the mean daily dose of concomitant psychotropic medication, and shown significant differences in each drug category. Here, we're looking at mean daily dose displayed over time for each category of adjunctive medication -- antipsychotic, sedative/anxiolytic, antidepressant, and mood stabilizer.

So, the superiority of Clozaril in the array of measures that have been discussed was apparent despite the fact that the Zyprexa-treated patients received consistently more adjunctive medication.

(Slide)

Well, to place the current use of Clozaril in the context of the benefit-to-risk ratio, it's important to consider where we are in our understanding and management of some of the serious adverse effects that can occur with Clozaril, the first being agranulocytosis. The current estimated incidence in the U.S. is 0.3 percent during the first year of treatment, and then it goes down considerably after that. There is clearly a well-established risk management system which has contributed to the very low levels of morbidity and mortality currently associated with agranulocytosis.

More recent concern has arisen around the risk of myocarditis. The current incidence in the U.S. is estimated to be 5 per 100,000 patient-years.

Seizures or convulsions are another adverse effect that is associated with Clozaril, and the current incidence estimates in the U.S. package insert is 3 percent.

Weight gain and disturbances in glucose regulation are also adverse effects associated with Clozaril and some other second-generation antipsychotic drugs.

(Slide)

The averse events associated with Clozaril in InterSePT were generally consistent with previous clinical experience. There were, in fact, no cases of agranulocytosis, myocarditis, or cardiomyopathy in the patients treated with Clozaril. Convulsions occurred in 2.5 percent of patients, that's 12 individuals out of 479 patients, and that's very consistent with prior experience as well as the package labeling.

(Slide)

So, Clozaril proved to be superior to Zyprexa in reducing both the overall number of suicide attempts and the overall number of hospitalizations to prevent suicide. What we see, in fact, is a very

impressive 26 percent reduction in the risk of suicide attempts or hospitalizations to prevent suicide for Clozaril relative to Zyprexa. And, of course, this has tremendous implications. This clearly leads to the potential for lower health care costs through a reduction in hospitalizations and less frequent use of concomitant psychotropic medication, as well as decreased surveillance necessary to attempt to prevent suicide.

(Slide)

Well, to really put this in perspective, let's translate the InterSePT data into the so-called number needed to treat analysis. So, when we do this, Clozaril has a two-year number needed to treat of 13 patients. Now, what does this mean?

If 13 at-risk patients were treated with Clozaril instead of Zyprexa, we would prevent 1 suicide attempt or 1 hospitalization to prevent suicide.

(Slide)

Now, fundamentally, as clinicians, we need to assess the benefits and risks of treating patients, as well as the risks of not treating patients. When assessing the benefits and risks of using Clozaril to treat suicidal behavior, we need to look at the most

significant risks, agranulocytosis and myocarditis, versus the benefits, and that is the reduction in suicide attempts or hospitalizations to prevent suicide.

Here, we see that based on our current estimates for agranulocytosis and myocarditis, that for every 1,000 patients treated for two years, approximately 3.5 would experience agranulocytosis, fewer than 1 would experience myocarditis. This compares with a dramatic reduction in suicidal behavior with Clozaril treatment because we find that for the same 1,000 patients treated for two years, 77 would be prevented from a suicide attempt or hospitalization to prevent suicide.

(Slide)

As we've heard, suicidal behavior in patients with schizophrenia or schizoaffective disorder is a serious public health problem and represents an important unmet medical need. The analysis of the safety and efficacy results from InterSePT taken together with the published literature demonstrate that the beneficial effect of Clozaril in reducing suicidal behavior clearly outweighs the associated risks.

These data are very impressive and

clinically valuable. I believe that they should serve as the basis to extend the indication for Clozaril. As always clinical judgment is critical in deciding for which patients to recommend this treatment, but I would emphasize how important it is to give our patients and their physicians this option. Thanks very much.

DR. OREN: At this point, I'd like to invite members of the committee with questions for the Novartis to offer them.

DR. ZANINELLI: I will be the moderator for Q and A here.

DR. OREN: Dr. Winoker.

DR. WINOKER: I've got a few questions, should I just run through those?

DR. OREN: Sure.

DR. WINOKER: The first is, with respect to the dosing guidelines that you've mentioned, you also mentioned that 18 percent of the patients on olanzapine were at doses above the recommended upper dose. So, I was just interested in whether the recommendations were just recommendations but Investigators were perfectly free to use their judgment, or they were really expected to stay within the 5 to 20 -- and this actually represented people

going outside of what you had intended with the study design.

DR. ZANINELLI: Right. As I tried to make clear, the dose recommendations were in line with the prescribing information occurring at that time, 1997. Most of the clinicians in the audience will know the Zyprexa tends to be dosed outside, above that recommended range. But as the sponsor of the study, we were not able to go outside the labeling, so to speak. But it was to be expected that for both groups, actually, there would be dosing outside the range. It just happened more in the Zyprexa group.

DR. WINOKER: As it turned out, the dosing range for olanzapine actually conformed to current practice and that's very nice, but I guess what I'm trying to clarify is this would not have been considered a violation of the expectations of the study in terms of Investigators not following specific instructions.

DR. ZANINELLI: Not at all, it was not a protocol violation.

DR. WINOKER: And I had a second question about the use of adjunctive medications, particularly the antipsychotics. You did a very nice job of summarizing how that broke out across the different

categories.

We saw in one of the information packets that we got that there were a few instances of patients assigned in the protocol to Clozaril, who ended up receiving olanzapine as well, and conversely. That appeared to be a limited number, but I just wanted to understand how that might have affected data analysis and if you did any further assessments to make sure that there weren't -- that clearly could have represented -- confounded interpretations.

DR. ZANINELLI: Right, that's true. Because, as I tried to explain, in the study design there were no constraints on the use of concomitant psychotropic medications, including using the other study drug to treat patients who were assigned to Clozaril or Zyprexa.

(Slide)

And as you see here in this summary, 69 patients who were assigned to Clozaril received olanzapine at some point during the study. This could have been during the transition phase where they're coming off olanzapine and coming on to Zyprexa, but there was possibly a period in individual cases where they were getting both drugs. And 17 Zyprexa patients also had clozapine as a concomitant medication.

Again, it could part of the function of the transition phase.

If we exclude these patients from the analysis, the results of the WLW analysis actually are a little bit more robust, at .021.

DR. WINOKER: Thank you. The next question I had is, there were four initial inclusion criteria for identifying high-risk individuals, and I wondered if you conducted any type of analysis -- I'm sure you did, so if you could share a little bit of that with us in terms of how subjects distributed across the two treatment groups in terms of representation for one or more than one of the criteria. I'm asking that because two of them represented historical information that could have gone back up to three years, and the other two were more -- you know, very current -- within the past week.

DR. ZANINELLI: Right. We do have the one slide showing the number of events across the two groups. So, we showed you the mean, but we could actually break that down to 1 to more than 5 events. Could we get that information? Maybe John Kane could answer to that as well.

While we're pulling up some relevant data,

I think it would be important to point out that about 80 percent of the patients participating had at least 1 hospitalization or 1 suicide attempt, as a qualification for the study. So, the overwhelming majority met those two criteria.

(Slide)

DR. ZANINELLI: No, this is not what I meant. At baseline, the distribution of suicide attempt and hospitalization to prevent suicides by the categories 1, 2, 3, greater than 3 -- I don't know if you have that or not.

In any case, we look at the past history of suicide behavior, drilling down into the numbers, they are essentially the same for both treatment groups. So, although the mean of greater than 3 in each group, there were no more patients having greater than 5 in the Zyprexa or Clozaril groups than the other group. Here, this is the one.

(Slide)

So, just looking at lifetime attempts, again, the number of patients who had no attempts was relatively low, and then we broke it down to 1, 2 to 3, 4 to 5, and greater than 5. And, again, we see that regarding the past history, there were similar numbers of patients in both groups having 1 or

specific numbers of events. This is also true for hospitalizations.

DR. WINOKER: Thank you. And the last question I had, in discussing the issue of referrals of the Type 1 events to the Suicide Monitoring Board, what type of training or instruction were provided to the Investigators at the different sites in terms of how to approach identifying what rose to a level of the case that should be brought forth?

DR. ZANINELLI: Okay. In general, the information had to be collected in a potential endpoint package, which consisted of a series of forms. I think Dr. Kevin Cox is here, he could perhaps prescribe the -- he was the Medical Monitor for the U.S. -- perhaps describe what sort of information, or how the PIs were prepped, and what sort of information was in the potential endpoint package.

DR. COX: I'm Kevin Cox, from Inginex Pharmaceutical Services. I was the Medical Monitor for North America. At the Investigator meeting, Investigators were told that we wanted to look at any event that was related to suicide, that included a hospitalization or a potential attempt.

The packet that was included -- I think

Dr. Krishnan pointed out -- there was a suicide attempt form for any patient who had a potential attempt. There was an imminent risk of suicide requiring hospitalization form, which included all the reasons why they felt that hospitalization was related to suicide. There was some of the scales, the InterSePT scale for suicidal thinking, the Calgary scale, and then there was the hospital reports.

DR. ZANINELLI: I hope that answers the question.

DR. WINOKER: Thank you.

DR. OREN: Dr. Rudorfer.

DR. RUDORFER: We were told about the visit schedule in terms of the weekly for six months and then biweekly. Were those the clinical visits as well as the --

DR. ZANINELLI: Not necessarily, no. For instance, you mean the assessment visits for CGI-SS-BP and ISST?

DR. RUDORFER: Yes.

DR. ZANINELLI: No, they were not. Those were at eight-week intervals, actually. There was a baseline, I think, at week 4, and after that at eight-week intervals. So those did not correspond with the clinical assessments. However, they did correspond

with assessments of adverse events, or if an adverse event report came in during that one-week interval or two-week intervals, they went into the database. Dr. Kane spoke to that. So, actually, there were more assessments than adverse events regarding suicidality than there were assessments of suicidality status.

DR. RUDORFER: If I could return to the concomitant medication issue for a moment, Dr. Meltzer, before, presented his 1995 study with clozapine monotherapy, and I wonder if there are data in the InterSePT study in terms of clozapine monotherapy versus olanzapine monotherapy, at least in terms of antipsychotic monotherapy.

DR. ZANINELLI: So the question is were there patients who had only Clozaril or only Zyprexa alone?

DR. RUDORFER: Yes.

DR. ZANINELLI: To my knowledge, during the whole course of the study, there was no patient who was on either study drug for any length of time, solely on that study drug without a concomitant medication.

DR. RUDORFER: Okay. How about where the concomitant medication were only non-antipsychotics?

DR. ZANINELLI: Do we have the

availability of information due to patients taking study drug plus just one class of medication with -- I don't think we have that analysis up to now, no. It was actually very few patients who would not take -- the mean number of drugs was about three for the Zyprexa group and 2.5 on the Clozaril group. So there were very few patients who were not taking at least one or two concomitant medications at any point in the study.

DR. RUDORFER: I still have the floor. Can I ask another question?

DR. OREN: Yes.

DR. RUDORFER: I want to go back to the issue of diagnosis. We've heard DSM4. How were the data gathered? Was there a structured interview, or how was the diagnosis made?

DR. ZANINELLI: The SCHD (phonetic) or mini-SCHD (phonetic) were not carried out, so there was no documented structured interview, but the protocol did stipulate the application of DSM4 criteria for these two diagnoses.

DR. RUDORFER: Now, DSM4 indicates that a type of schizoaffective disorder should be specified, either bipolar or depressive. And I wonder if that information was gathered?

DR. ZANINELLI: I don't think -- that was not gathered, no. That was not gathered. That was only schizoaffective disorder, present or not.

DR. RUDORFER: Okay. May I refer to a case in our material? A patient report that I noted, a patient in the Zyprexa group received a diagnosis called "schizomanic relapse" -- I can refer to the exact case, but I wondered what that --

DR. ZANINELLI: I assume that's a European case. Dr. Krishnan perhaps can give the details on that.

DR. KRISHNAN: Just to briefly address this, I think it's very clear that a diagnosis of schizoaffective probably depends on which country we were getting the patients from, and it probably again reflects the fact that that diagnosis is a hard one to make even under the best of circumstances. So while we use the term "schizophrenia/schizoaffective", it's more important to think of this as people who have psychotic behavior looking like schizophrenia, which is consistent, in addition to some degree of affective disorder. And if you look at the case, it's not the CRFs but the way people write notes, and you get translations of the notes which was done, you would find people with all sorts of different additional

labels, probably reflecting the country of origin.

DR. RUDORFER: My concern is that -- and my understanding the reason why DSM4 calls for the subtype differentiation is that there may be differences in the clinical course of the subtypes, that the bipolar subtype may look more like mood disorder as opposed to more like schizophrenia. So I was concerned that a patient called "schizomania" might be closer to a mood disorder patient.

DR. KRISHNAN: you read the notes, most of them are schizophrenia with or without significant affective disorder, and having had a chance to look through the history of at least the people who came into this, these are not bipolar patients, these were patients you would -- when you try to label them, schizophrenia remains like the core context, and then on top of it you have drug abuse, alcohol abuse, everything you name. This is the patients you can use a lot of labels, that's important to keep in mind. You see them in the emergency rooms. This is the kind of patient, you do an interview, and if you go through a checklist, you can add on additional labels with the core construct of schizophrenia.

DR. RUDORFER: Thank you.

DR. MELTZER: I think there are some data

which speak to having more confidence in the differentiation between the two groups, namely, that if you look on the history of number of hospitalizations for suicide and number of suicide attempts, the group diagnosed as schizoaffective had significantly more than the group diagnosed as schizophrenia. Then during the study, the group diagnosis schizoaffective disorder went on to have more Type 1 and 2 events of more severity, and that is consistent with the literature for schizoaffective disorder. Had it been just sort of a random term applied, I don't think you would have seen that.

DR. OREN: Just to follow up on that specific point, there was one bit of data presented, I think in your Slide 39, showing the relative efficacy of Clozaril versus olanzapine for schizoaffective disorder. That particular subgroup was perhaps the least impressive of all the different subgroups on that slide. Do you have any additional data teasing out the difference between responses between the schizoaffective and schizophrenic groups?

DR. ZANINELLI: Do we have --

(Slide)

Following from that last slide -- the number of percent of Type 1 and Type 2 events by the

diagnosis subgroup -- so, schizophrenia, schizoaffective disorder for Clozaril and Zyprexa -- we see here the ends for the respective diagnoses and the Kaplan-Meier estimates. So, for both diagnoses, in the Clozaril group, the probability of having a Type 1 or Type 2 event is less than it is in the Zyprexa group. It's somewhat higher in the schizoaffective group, but it's still comparable.

DR. OREN: Dr. Ortiz?

DR. ORTIZ: I would be interested in hearing a little bit more and some elaboration on why a structured interview was not used.

DR. ZANINELLI: Dr. Meltzer will probably be best because he was one of the designers of the study.

DR. MELTZER: There was considerable discussion and desire to do that. It was felt that the three hours or so that it would take to do it, given the context of the study, was not something that various of the sites were prepared to do.

DR. OREN: Dr. Katz.

DR. KATZ: I have a few questions -- four, actually. The visits, as you say, were between four and eight weeks apart, although I know they were seen more frequently for blood draws or vital signs. What

was the procedure for ensuring that all events of interest were actually captured? For example, it might have been possible the patient would have been hospitalized for a suicide attempt at some distant hospital not related to the study site. What exactly were the PIs instructed to look for or ask for in that sense?

DR. ZANINELLI: That -- and, again, it's accurate to say that many of these hospitalizations occurred in the interval and not necessarily at the site where the patient was being treated during the study, but the information did flow into the adverse event and serious adverse event forms, and that was the main source of information.

DR. KATZ: What I'm asking is what was the process by which you ensured that that happened? How was that that information from a distant site flowed, as you say, to the adverse event forms?

DR. ZANINELLI: Perhaps Kevin again, the Medical Monitor for the study.

DR. COX: At each visit, patients were asked how they were doing, has anything happened since their last visit. So, it was pretty much reliant on patient report. In addition, sites were instructed to gather information from collaborative sources wherever

they could.

DR. KATZ: Maybe just one other question, and I have several I could ask later. There were a number of, as you call them, "retrieved dropouts". Could you possibly present some data on the events, Type 1 and Type 2 events, that occurred during that period of time after the patients were discontinued from study group?

DR. ZANINELLI: Okay. We have a number of analyses looking at retrieved dropouts.

(Slide)

Okay. Again, the definition of "retrieved dropout". Again, a stipulation of the study protocol was that if a patient discontinued the study before the end of their personal two-year observation period, every attempt should have been made to follow-up that patient at least with respect to the occurrence of a Type 1 or Type 2 event.

So, how many patients were there that were retrieved dropouts? There were about 60 in each group. And this looks at of those patients, about two-thirds of them, 60 percent, had no Type 1 event after dropout, and about 30 to 40 percent had a Type 1 event. So, this was a useful method of accruing data to the analysis of the primary endpoint. Again,

it was not possible in all cases to get this information. Patients were lost to followup or changed clinics or whatever.

DR. OREN: Dr. Hamer.

DR. HAMER: I have a possibly related question. For the survival analyses, for a Type 1 event, did you actually capture data to the actual day that it occurred, or was it rounded to the week of the nearest visit or something like that?

DR. ZANINELLI: It was actual date.

DR. HAMER: What about Type 2 events?

DR. ZANINELLI: Also --

DR. HAMER: I mean, I understand that most of the Type 2 events were actually Type 1 events, but some of them were reports of increased suicidal ideation, and I wonder how you would capture those to the days on which they actually occurred.

DR. ZANINELLI: Okay. Dr. Zahur Islam is the Chief Statistician for the project, and probably can give the best information on that.

DR. ISLAM: A Type 2 event is a combination of Type 1 and worsening of CGI-SS-BP to a scale of 5 and 6. CGI-SS is measured at the scheduled visit, so part of the Type 2 events were from the scheduled visit, and it affected, as you have seen, on