the 18 and 20 patients there.

DR. OREN: Dr. Katz.

DR. KATZ: Just a followup. Could you put that slide back again, is that possible? The last one you showed about the Type 1 and Type 2 events.

DR. ZANINELLI: The retrieved dropout slide, the last one we showed?

DR. KATZ: Yes. I just want to make sure that I understand what it showed.

(Slide)

This is the number of -- there's a footnote at the bottom that says "12 Clozaril and 3 Zyprexa patients had Type 1 events after discontinuation". How does that jibe with the numbers that you have up on the chart? Maybe I'm just not understanding it. The second row on the chart seems to say that there were 20 Clozaril patients who had a Type 1 event.

DR. ZANINELLI: Right. Is that before discontinuation?

DR. KATZ: What I'm interested in is what happened during the retrieved dropout period.

DR. ZANINELLI: Jay Shu would be best able to answer that.

DR. SHU: Jay Shu, statistician for

Novartis. The 20 and 25 patients with Type 1 events, the 12 is actually out of that 20. Twelve patients that had an event after discontinuation.

DR. KATZ: And only after discontinuation, is that right?

DR. ZANINELLI: Right. So that was my mistake. Then these are the patients who had Type 1 events overall, and of those, 12 were after discontinuation in Clozaril and 1 in Zyprexa.

DR. KATZ: And that -- the 12 and the 3, that was the first time that they had a Type 1 event because, obviously, patients could have more than one Type 1 event.

DR. ZANINELLI: In all cases were first Type 1 events, yes.

DR. OREN: Dr. Wang.

DR. WANG: As long as we're dealing with analyses, in terms of the WLW approach, it certainly advantageous to use it. One of the assumptions, though, is that it's ideal for current events, true distinct events, and I was wondering if you could comment on the fact that some of these might be remeasures of the same event -- in other words, if someone has a decline in their score as well as has a Type 1 event, that could be the same thing.

DR. ZANINELLI: Right. Dr. Lin, would you like to comment on that?

DR. LIN: Hi. Danyu Lin, from University of North Carolina. The WLW method can be used to analyze various type of multivariable data. You could have a multiple event per person, and a multiple event could be the recurrence of the same of event, or it could be distinct events. And the correlation usually among different events, especially if you consider a distinct event.

In our case, the Type 2 event includes a Type 1 event. So, they obviously had to correlate it. And, statistically, actually, this is -- it's very simple. All we are doing is basically we fit two standard per person who had this model to each of two events, so I had the original estimates for the time of the first event and hazard ratio estimate for the time of second event which, in this case, are very similar -- .76 and .74. All we do is that we combine the two estimates. We just take an average of the two estimates. And because we take an average of two estimates for two highly correlated data, we know the correlation, but statistically that's what the method is for, it's to estimate the correlation empirically from the data, and correlate it just for the

variation. And so the correct variance is used in the denominator, and in the numerator you basically just average out the two estimates, and it give you just a normal statistic.

DR. WANG: Could I follow that up with another related question, and that is why you see a lack of efficacy when you look just at the blinded psychiatrist ratings -- you know, if you look at your hazard ratios, if you just do an analysis on Type 1 events, you have a ratio of .74. When you add in the Type 2 events, which the only new contribution is via the blinded psychiatrist ratings, the hazard ratio, if anything, gets a little bit worse, to .76.

DR. LIN: Can we show that slide? Can we show the number of events, the definition -- the one that we showed when we show the results of the study, when you show the composition of the Type 2 event.

(Slide)

Basically, it is that the difference between the two groups is most substantial in Type 1 event than the additional number of Type 2 events that's not a Type 1 event.

DR. WANG: The additional, when you add in the blinded psychiatrist ratings, it's not that it only adds a little, it actually detracts from the

benefit seen with Type 1.

DR. LIN: No, I'm talking about 18 out of 20, that difference is very small. Maybe I misunderstood your question.

DR. WANG: If you look at the regression co-efficient just for the psychiatrist ratings, it's actually in favor -- slightly in favor, and it's highly nonsignificant, but in favor of Zyprexa. I'm interested in your thoughts on why that might happen.

DR. ISLAM: As you can see, the Type 1 event separation, 102 and 141 patients. The Type 2, the CGI-SS contributed 18 and 20 to the Type 2. If you compare the 18 and 20, it's not much of a difference.

Now can I see Slide 37, please.

(Slide)

That's what it looks like in here because the CGI-SS didn't contribute much. So the co-efficient includes little, and that is the reason here.

DR. WANG: Any thoughts on why it didn't contribute? I mean, any thoughts on why the psychiatrist ratings had not contribution?

DR. KRISHNAN: Let me just briefly address that. I think it's really a question of how often were the ratings obtained, which were much more spread

out -- 4 weeks, 8 weeks, up to 12 weeks in the second part of the study. And the second reason for that is we actually looked at how these events happened, what type of precipitations of suicide. They actually don't correlate so much to the scaling that is done in the event-by-event thing. It probably correlates just to the time point closest to it. So, if you came in a week before and they did the scale, that correlates pretty well. But if you had come in 8 weeks before, it may not because the events seem to be more related to what's happening in the life of the individual leading to that particular trigger. And those scales do not capture the trigger factor.

So, although I think it was a nice addition, I don't think it actually added much value to the overall thing, and there are two reasons -- one, the frequency and, second, they were not time-relevant to the events because the events were different periodicity, if you want to call it, not connected to in the scale.

DR. OREN: Dr. Katz.

DR. KATZ: I have two questions related to the blind. There were various attempts, as you described them, to address the question of potential bias by the unblinded psychiatrists referring cases.

As I understand it,the Inginex staff could also refer cases, and presumably, of course, the Medical Monitor could identify cases that would be assessed in a blinded way by the Suicide Monitoring Board, but I'm just wondering what aspect of that -- the staff's, Inginex staff's referral or identification of additional cases was blinded. Was any of it blinded, or was that also unblinded?

DR. ZANINELLI: Inginex was not -- the Medical Monitor was not blinded, just performed the blinding.

DR. KATZ: Right, but it was also the Medical Monitor who could decide that there might be additional cases that could be sent to the SMB for blinded review, is that right?

DR. ZANINELLI: The Medical Monitor would essentially challenge the Principal Investigator if he found evidence for a potential Type 1 event, but it was ultimately the Principal Investigator who referred the case. It was blinded by the Inginex Monitor.

DR. KATZ: So there were no cases that the unblinded Medical Monitor for Inginex could identify independent of the cases identified by the unblinded investigator, they couldn't independently identify a potential case and then ship the blinded data to --

DR. ZANINELLI: They could because they were independent of the referrals reviewing in real-time, so to speak, the adverse event.

DR. KATZ: Right, that's my point, but they were doing that in an unblinded way as well, is that correct?

DR. ZANINELLI: Yes, unblinded.

DR. KATZ: That's really just the point I want to make. The other had to do with your attempt to go back and look at the 700 unreferred patients and identify cases. You described in some detail the steps that were taken to identify any additional cases, and somewhere along the line you said a particular step was blinded. I'm wondering if you could speak more explicitly about how you decided that some cases might have actually been Type 1 events. Was it basically an unblinded look at the case report forms and that sort of thing?

DR. ZANINELLI: Right. The program that was doing the match was unblinded to treatment. Ultimately, the Novartis staff -- there's a time issue here as well -- were not blinded necessarily, they could look into it if they wanted to. And we used the same criteria. Again, anything that -- any bit of evidence that was -- could be a potential Type 1 event

was considered.

DR. KATZ: Right, but those events were identified in an unblinded way, presumably. And then when you actually went and got those cases that were potentially Type 1 events, the review of that material was also unblinded.

DR. ZANINELLI: Was unblinded, yes.

DR. LAUGHREN: Just again a clarification. The material that was available to the Novartis reviewers in looking at the data from these roughly 300 cases that matched on adverse event terms, as I understood it, that's information only that was in the case report forms.

DR. ZANINELLI: The case report forms and -- James -- James Rawls, from Regulatory Affairs, who supervised the review.

MR. RAWLS: Good morning. James Rawls, from Regulatory Affairs. I helped to assist with the team that reviewed these events. There was a variety of information -- the same information that the SMB reviewed we had available, with the exception of the clinical history, but I think it should be pointed out that the majority of those events, since we picked up every term that could have been a suicide attempt or something related to suicide, the majority of those

that related to suicide attempts occurred prior to randomization. They were dealing with a baseline history information, and not events after randomization.

And then if you looked at -- we also found terms in terms of suicidal ideation that were picked up, but those terms, since those individuals were not hospitalized for the particular event, it was not forwarded to the SMB. However, that information, if it was a suicidal ideation, it was picked up as an adverse event in the I think it was CBR8, from Dr. Kane's presentation -- would you put it up, please?

(Slide)

This is where those reports of suicidal ideation would have been captured in terms of the patients in the Clozaril group and the number of patients in the Zyprexa group.

DR. LAUGHREN: I guess my question is, is it possible that this other information that somehow didn't get into the electronic database -- for example, nurses notes or a hospitalization at another site -- that somehow might not have found its way into the database that you were using to do the search.

MR. RAWLS: We reviewed all their comments or the comments that would have been captured at the

site. They would have been entered into comments database. We didn't have the actual -- I mean, the clinical history or the information at the particular site in terms of source documents, but that information was part of the case report form. So, I think we had the complete record for the particular patient.

DR. ZANINELLI: I think it's very important to emphasize this was not a purely electronic database comparison. Where the terms were matched in the database, you went to the hard copy. So, it was really a hard copy review which contained all the extraneous notes from staff investigators and anyone involved with the patient.

DR. OREN: Dr. Malone.

DR. MALONE: I think one of the concerns I have is if you have -- if you show that olanzapine is better than Clozaril, it could be that, for instance, olanzapine makes suicide worse, and it's hard to tell what that means about Clozaril. Is there any way to estimate what the, say, rate of hospitalization for schizophrenics is over a two-year period, from large databases, like Medicaid or Medicare databases?

DR. KANE: I think that's certainly a

reasonable question, but there's no evidence that that's the case. I think if you look at the rate of attempted suicides and rate of completed suicides in both the olanzapine-treated group and the Clozaril-treated group in this study, and compare it to data from, for example, the Kahn (phonetic) data that was referred to earlier, that the rates in both categories are extremely low. So, it would appear that there was an improvement that took place in both groups in that sense, although despite that, we're able to demonstrate a significant difference favoring Clozaril. So, there's no evidence when you compare these data to the data from other studies, that the patients in the Zyprexa-treated group were experiencing more events in any one of those categories.

DR. MELTZER: There no data that can really compare with this group. The annual rate of suicide attempts for the whole sample, even though only 80 percent had an event within the three years, was approximately 20 percent per year, and during the course of the study that rate was reduced dramatically in both groups. So there was no evidence that Zyprexa -- if you want to do that pre/post which has a lot of problems associated with it -- but clearly there was

no signal that Zyprexa made for increased suicidal behavior.

DR. OREN: Dr. Winoker.

DR. WINOKER: I'm going to have a few questions. The first two, I just want to have a chance to hear from the sponsor on a couple of issues that in the FDA review that was passed along to us were raised, that I don't think have so far been commented on.

One is the issue of the amendment that allowed subjects to be off-protocol for a period of time and then re-enter again, and in your analysis how that affected the overall.

DR. ZANINELLI: Do we have an analysis of the number of patients who left the study and came back, or an overview? I know there were relatively few.

(Slide)

DR. ISLAM: We have 158. This is our analysis excluding all data after the patient discontinued. So, if the patient discontinued like an RD or came back as an RD or something like that. So, we still have much more significant result.

DR. WINOKER: I'm not talking about the Retrieved Dropouts. I believe it was mentioned that

at a certain point there was an amendment that actually allowed subjects who had been enrolled and then for some reason were out of the protocol, to be resumed under original treatment modality and be included in the primary data analysis, if I'm right in understanding that.

DR. ISLAM: We do not have any separate analysis for this, we just considered that period of time that the patient didn't take drug.

DR. WINOKER: Do we have a sense of how many subjects would have been in that group?

DR. ZANINELLI: Twelve patients overall who left and came back, so I think it's like 8 in one group and 6 in the other -- or 4 in the other. I don't know which way it went, but it was a very small number of patients.

DR. WINOKER: There was another point that was raised -- and, again, just to hear the comment about the change in greater that occurred across two years, and whether that may have had an impact on the CGI-SS assessments.

DR. ZANINELLI: Okay. We did look at that. So the question refers to the fact that over the course of the two-year study, hot many patients in both groups had a change in blinded assessor.

(Slide)

So this analysis looks at the incidence of change in the blinded psychiatrists with regard to the worsening on the CGI-SS-BP. So, in the worsening, we find the score of 6 or 7. No impact was seen -- who did this one? Whose slide is this? I thought we did an analysis -- we'll have to come back to that one. I'm sure the analysis is in there somewhere, as well as the specific question.

DR. WINOKER: I'm coming back to the adjunctive treatment issue. For the antipsychotics, you showed the dose equivalents in terms of Haloperidol. I was curious about the -- well, two things -- the percentage of patients who got adjunctive antipsychotics in terms of typical and atypicals, and if you have any kind of at least qualitative feel for what led to adding an additional antipsychotic. I mean, obviously, on the face, it was for lack of efficacy, I would assume, but if there's any sense of what actually tended to drive adding -- because so many of the patients were on adjunctive antipsychotics.

DR. ZANINELLI: To answer the second question -- while you're looking for the analysis, I believe there was analysis of the first question. But

could we look at the curves for the concomitant medications, please, the mean dose over time.

(Slide)

So, in case of the antipsychotics here, this gives you a little bit of the idea. In both groups, the concomitant medication, which was probably the previous medication, was discontinued. At a relatively early point in the study, however, it bottomed-out for both groups, at a lower level for Clozaril than for Zyprexa. We take this to mean that the patients who were either going on to a new adjunct and staying there, or they are coming off a previous one and staying there, for whatever reason -- you can speculate on the reasons for that. John, do you want to say anything about this?

DR. KANE: I think part of this is a result of the fact that the clinicians treating these patients were given absolutely leeway to do anything that he or she felt was appropriate, and that was a very important aspect of the safety in this study. So, I'm sure there are a number of different clinical reasons that one could imagine. A portion of these patients were also considered to be treatment-resistant, 25 percent. So, you can envision in some cases the dose being increased for that reason, but It

think there were a variety of factors.

And I guess what I would emphasize is that despite this extremely liberal policy in bringing to bear whatever adjunctive treatment anyone wished, that we're still seeing the drug effect of interest.

DR. WINOKER: I think this question will be for Dr. Meltzer, and this is kind of indulging myself. I realize that the driving force in conducting this study was the retrospective analysis that suggested strongly that there was a reduction in suicide behavior in patients looked at, who had previously been treated with Clozaril in the retrospective database.

Apart from the empirical information, which I know is the driving factor here, is there any theoretical reason that intrigues you in terms of why there might be the kind of difference between Clozaril and another sort of cutting edge "atypical" antipsychotic that we should be seeing this kind of difference in efficacy on this measure?

DR. MELTZER: I think there are both qualitative and quantitative signals that could be explored, but it really would be very speculative. On a qualitative difference, there are significant receptor differences -- for example, in terms of 5HT6

and 7 antagonism with olanzapine having no blockade of a 5HT7 receptor and Clozaril blocking it, and they both were effective antagonists of the 5HT6.

My own personal bias is perhaps more toward the qualitative mechanism which looks at their relative abilities to enhance dopaminergic activity in the pre-frontal cortex versus the limbic system, although they both pull it in the same direction, the ability of Clozaril to enhance dopaminergic function in the cortex and the hippocampus is much more significant. And I think they are increasing evidence for a relationship of dopamine to depression, and my own personal -- again, very speculative -- but based on analysis that we did from the Cleveland sample and some preliminary things we're looking here, it's the depressive feelings, feelings of hopelessness, that seem to drive the suicide attempt, which I think, by the way, goes back to the previous question about the difference between the CGI ratings and the event.

What happens clinically, that I've seen, is the urge to deal with extremely distressing feelings can come up fairly rapidly and impulsively, and people act out and make an attempt. And it seems in some way that the Clozaril is preventing that from happening much more frequently than other drugs.

I would also add just one other thing, Andy, which is we still don't understand why Clozaril is so much more effective in treatment-resistant patients in the old sense. That remains an enigma. So much else has been figured out, and perhaps in some ways they're related, but I remain convinced that this is a separate signal.

DR. OREN: I don't want us to stop thinking about psychopharmacology, but for the next 15 minutes perhaps we can switch to considering the psychopharmacology of caffeine instead of clozapine. So, we will take a break now, and return in 15 minutes.

(Whereupon, a short recess was taken.)

DR. OREN: I know there are further questions from our panel, and Novartis also asked for a couple of minutes to address a couple of previous points. So, what we'll do now is I'm going to invite Novartis to take a couple of minutes to respond to some points that were made earlier, and then we will proceed to the presentation from the FDA. There will be plenty of time later for panelists to ask additional questions.

DR. ZANINELLI: There was one question from Dr. Winoker regarding the use of typical and

atypical medications, antipsychotics in the two treatment groups. I pulled this from the listings now.

About half of the patients in each treatment group had atypical or typical antipsychotics during some point during the study. The mean dose in the Clozaril group for atypical -- and these are dose equivalents, Haloperidol equivalents -- for typical was 2.14 mg, for atypical 1.37 mg. For the Zyprexa group, there was the mean dose of typical antipsychotics was 4.26 and of atypical 1.37, so no difference in the use of atypical antipsychotics and typical.

Then there was a question regarding the possible influence of the change in the blinded psychiatrists who rated the CGI-SS -- can I have the slide, please -- and I'll decipher the information on the slide by simplifying.

(Slide)

So all told, there were 13 cases in the Clozaril and 8 cases in the Zyprexa group where there was a change in the BP in a patient who experienced a Type 2 event. So Type 2 event, the main definition was a worsening, on the CGI-SS, a score of 6 or 7. Again, the 13 patients in Clozaril and 18 in Zyprexa

group who had a change in blinded psychiatrist.

The blinded psychiatrist change occurred after the Type 2 event, so after the original blinded psychiatrist had rated the patient, in 7 of the Clozaril cases and 5 of the Zyprexa cases, so more than half of them, or about half of them.

The change at the assessment of a Type 2 event occurred in 6 Clozaril patients and 3 Zyprexa patients after the change in blinded psychiatrist. These numbers are pretty small here, so I don't think they affected the analysis, ultimately.

DR. KRISHNAN: Completely addressing a couple of the questions that we asked, one question was what were the questions asked of patients at each visit -- vital signs, et cetera -- because the question -- there were two questions asked: How are you doing? And, second, did anything happen since the last visit -- which is required by the study design to be asked at each visit, trying to capture as much as you can if anything else had happened during -- and looking through the notes, there was one particular instance where somebody had mainly elicited it during that questioning, that an event had happened. And I can remember at least a couple of those instances from the notes that came through.

The second thing that I just briefly wanted to address again is the medication used. So, keep in mind, during that first phase, that's when most of the concomitant medication use is happening because that's when people are being tapered off and being restarted on this drug. So, that's the period when there is an overlap. So, if you look at the antipsychotic group, that's when you see most of the period, and you can see it rapidly dropping down as those drugs were removed. And I think that's important to keep in mind. It's not a question of using during the course at any high rate, it's mostly in that period of time.

The third one which I think you asked was the diagnostic issue of how the diagnoses were made, et cetera. One of the things you've got to keep in mind is most of these patients, when you read through the documentation -- at least for the ones that I reviewed for the thing -- these are patients being followed by the clinic, these are not advertised patients. These are not patients coming right out of the street. They are being followed by the clinic because these are high-risk patients, so they know these patients very well. And I think one of the reasons that you see a lot of the additional

documentation of co-morbidity, et cetera, comes from that pattern of usage. But there was no formal SCHD kind of interview to make the diagnosis. Thank you.

DR. OREN: Thank you. I'd now like to call on Dr. Khin, from the FDA.

DR. KHIN: As part of Division of Scientific Investigations, we've been involved when the application came in. We've done site inspections for routine data audit as part of the application, according to our Compliance Program.

In addition to this, Dr. Laughren and Dr. Katz, the team has requested that we get involved looking at the specific issues that I believe we've been discussing this morning.

(Slide)

One aspect that we were interested to look at is the Type 1 event. As it's defined, it's the occurrence of a significant suicide attempt, including completed suicide or hospitalization due to imminent suicide risk, including increased level of surveillance. It is as confirmed by the Suicide Monitoring Board.

(Slide)

What is the particular concern that we are going to look at, that was potential bias. As you all

know, the unblinded investigators at each site apparently had the final say whether or not a particular patient event would be referred to the Suicide Monitoring Board.

(Slide)

The purpose of our audit was we were going to look at a subset of clinical records from Clozaril group for whom events were not referred to the Suicide Monitoring Board in order to determine definitively whether or not potential events were ignored for subjects assigned to clozapine. In short, I'm going to refer during the talk as the "non-referrals". So, we are going to discuss mainly non-referrals, we are not going to discuss about referrals.

So, what we did was the Review Division has selected centers with high rates of non-referrals to the Suicide Monitoring Board among the clozapine-treated subjects.

(Slide)

To date, I have looked at two different centers, let's say Center A and Center B. Center A has 14 subjects enrolled for Clozaril group. Out of that 14 subjects, 12 subjects did not have any event referred to the SMB. For Site B, 10 out of 10 Clozaril subjects did not have referral.

On the other site, you might be interested in how about the olanzapine group. For Center A olanzapine group, we have 4 subjects had event out of 14 subjects, and for Center B, and then all the subjects on olanzapine group did not have any events referred.

So, what I did was this morning we were interested in looking at how the information got referred to the Suicide Monitoring Board, so first we are interested to look at the source document itself. So, both non-referral subjects, we went and looked at a source document at the site, which includes progress notes, hospital notes, including ER visits if there are any consultees on site involvement of in-patient hospitalization involvement, we were looking at those notes.

There is a little bit difference between the style among the centers, particularly Center B used like a worksheet style documentation. So, Center B will write for each subject whenever they come in every week or every two weeks, they have already printed out: Do you have any events? Did you go to any outpatient visit for medical reason, psychiatric reason? Are you going to treatment program? Do you have any hospitalization, et cetera.

In addition to looking at the source document, we also interviewed some unblinded and blinded psychiatrists at those sites, but because of the time lapse, some of the blinded psychiatrists and study coordinators have already left the study site.

Basically, out of those 12 subject non-referrals, only 4 subjects completed the study. Eight subjects were discontinued from the study. For the Center B, 5 subjects completed and 5 subjects discontinued during the study.

(Slide)

This is a busy slide, but it's just for a reminder for me. One thing that I want to point out is look at Center B. At week 4, the subject was discontinued, but when you look at the subject source records, the subject was hospitalized for exacerbation of psychotic symptoms. When I went and looked at the study source document, we also look at ER visit, nurses note, including medical student, the whole academic setting, whatever they have, together with the source document.

But in contrast, if you look at Center A, there are some patients that if you look at 1 subject at the bottom, there are some progress notes missing, and you will see 1 subject that there was no-show, and

they tried to contact the subject, and they sent certified mail and the mail was returned. So we see different scenarios of events going in both centers.

(Slide)

In summary, when I look at all the 22 subjects' records, there was no underreporting of Type 1 events. But one thing that I would like to bring to mind is that there is limitation to the inspections.

(Slide)

As we were talking this morning about how information was processed, the subjects were the ones who would report to the unblinded psychiatrist or the blinded psychiatrists during the visits whether they have any suicidal thoughts or events. So, if the subject did not reveal any events during the visits, we wouldn't see any notes.

The other point is the unblinded psychiatrists, even after the patients report any events, they have to use their clinical judgment whether to decide it's a suicide event or not. So, if the unblinded psychiatrist did not report any event, then I won't be able to find it.

And one point I would like to mention is it's limited time and resources. Even after reviewing all these source documents, we didn't follow up any

subjects during the inspection. And, also, the number of records that we looked at is approximately pretty small for Clozaril subjects, there were 368 non-referral patients, and we only looked at approximately 6 percent. And these are all U.S. sites only.

DR. OREN: Do members of the panel have any questions for Dr. Khin?

DR. MEHTA: Do you know if Novartis conducted their own internal audit? You conducted audit of about 6 percent of U.S. patients. They probably might have done it. So the total number of patient records which have been audited independently might be a much higher percent.

DR. KHIN: I think Novartis might be able to answer that question better, but according to my understanding, it is mainly looking at the database. So, what is reported in CRF, and they are looking through the database into the CRF, what is different with my inspection was we look at the source documents, so it's like going to the center and looking at the progress notes and hospitalization notes right at the center.

DR. MEHTA: I think the company audit will probably include the type of document that you're talking about, plus the clinical research associates

monitoring reports and things of that type. Am I wrong here?

DR. COX: Kevin Cox, from Inginex. Yes, our clinical research associates did 100 percent source documentation of everything that was in the CRF at the sites. In addition, they were asked to look at source notes to see if anything was missed, with particular focus on hospitalized patients who may have had increased surveillance.

DR. MEHTA: What percent of patients are audited? I'm talking about in terms of audit, not monitoring.

DR. KANE: I just wanted to put this in a sort of clinical perspective because I think it's important to recognize that this is a rather unique population and a rather unusual study.

The most frequent source of litigation against psychiatrists is suicidal behavior. You know, it's rare where we're engaged in a study where there's a tremendous incentive from the environment, if you will, to get it right. The notion that someone would be biased in terms of reporting or not reporting a suicidal event or suicidal ideation is very different in this kind of context. I just want to emphasize that. It would be hard to do justice to the level of

anxiety of the clinicians who participated in this study because my department was one of them.

You know, many of us are extremely uncomfortable treating a few individuals at this high a risk, and we know that in schizophrenia suicide can be very unpredictable and very lethal. So, I just want to convey a sense of the context because I know that understanding we're biased might enter into this is very important, but there's another element that's at-play in the treatment of these patients, and that's really the anxiety on the part of clinicians to make sure that they get it right, above and beyond anything to do with the research. And if something goes wrong in the context of a research study, it's even worse. So, I just want to kind of give you that perspective.

DR. OREN: Dr. Laughren.

DR. LAUGHREN: Just one brief follow-up comment. Ni, you might mention what your future plans are in terms of completing the sample.

DR. KHIN: For sampling size, we're thinking about we would go up to like approximately 10 percent.

DR. LAUGHREN: When you say you're thinking about that, does that mean that's going to happen?

DR. KHIN: We can't say.

(Laughter.)

MR. RAWLS: I just want to come back to Dr. Mehta's question regarding our audits. James Rawls, once again, from Regulatory Affairs.

We did conduct an audit at the highest enrolling centers after the study had been completed. It was a review to see that all events were reported, and we did not find any additional events, but that was at the highest enrolling centers in the U.S. and in Europe.

DR. OREN: Other questions for Dr. Khin?

(No response.)

At this point, I'd like to turn to the Open Public Hearing part of this agenda, and the first person is James McNulty, President of the National Alliance for the Mentally Ill.

MR. McNULTY: Mr. Chairman, distinguished members of the panel. My name is Jim McNulty and I am the President of the National Alliance for the Mentally Ill. With more than 220,000 members and 1,200 state and local affiliates, NAMI is the nation's largest grassroots organization dedicated to improving the lives of people with severe mental illnesses. I very much appreciate this opportunity to testify

before you today.

schizophrenia is a brain disorder that affects approximately two million Americans. schizophrenia is one of the most devastating and debilitating of all severe mental illnesses. The positive or "psychotic" symptoms of schizophrenia, including delusions and hallucinations, are excruciatingly painful and debilitating for those who experience them. Numerous studies have revealed that the majority of individuals with schizophrenia do not have access to even minimally adequate treatment. The consequences of lack of treatment or inadequate treatment for schizophrenia can be devastating -- homelessness, arrests, incarceration, or suicides.

The 1999 report of the U.S. Surgeon General revealed that mortality rates among persons with schizophrenia are significantly higher than that of the general population. The single largest contributor to this excess death rate is suicide. Studies reveal that 10 to 15 percent of all people with schizophrenia commit suicide. Many others attempt suicide or regularly experience suicidal thoughts. The human toll for individuals who suffer from schizophrenia and their family members is incalculable.

Just an aside, I received an e-mail this morning as a result of a anti-stigma e-mailing that we send out to our members on a regular basis -- this one for Halloween -- and, again, this family member sent me a story of how her nephew had committed suicide three years ago, a young man who was suffering from schizophrenia, and this is something -- she is a mental health professional, and yet nothing that she or her family were able to do was able to prevent this tragedy.

The tragedy of suicide is compounded even further because schizophrenia we know is very treatable today. New anti-psychotic medications, coupled with psychosocial rehabilitation services and supports, make recovery very possible for most people who suffer from this brain disorder. I personally know many people with schizophrenia who have recovered from the depths of despair and today are living independently, productively and with dignity in their communities.

Research has played a key role in facilitating the miracle of recovery for these individuals. Now, research is yielding even more promising information. The International Suicide Prevention Trial is a landmark study that confirms

that Clozaril, an atypical antipsychotic medication first approved in 1990, can significantly reduce the risk of suicidal behavior or suicide attempts among individuals suffering from schizophrenia or schizoaffective disorder.

For NAMI, news about any medication that reduces the risk of suicide or other tragic consequences of schizophrenia or schizoaffective disorder is welcomed. The costs of inadequate treatment of schizophrenia and other brain disorders are immense. The benefits of developing new treatments for these brain disorders are immeasurable. These benefits accrue not only to consumers, but to their families and to society as a whole.

The International Suicide Prevention Trial vividly illustrates the benefits of continuing research on medications after they are approved and on the market. Ongoing research is our best hope for unraveling the mysteries of brain disorders such as schizophrenia and restoring dignity and hope to those individuals who suffer from them. It is equally important to translate the promises of research into practice through rapid approval of medications shown through research to be effective. NAMI is very grateful to the FDA for its efforts over the years to

expedite the entry of new medications for the treatment of severe mental illnesses into the marketplace, after careful study of the safety and effectiveness of these medications.

Finally, I would like to take this opportunity to make one quick editorial comment. Budget deficits in most states and at the federal level threaten the continuing availability and accessibility of the most promising medications for the treatment of schizophrenia and other severe mental illnesses in the marketplace. While we appreciate the importance of balancing budgets, cost containment strategies that threaten access to potentially lifesaving medications for severe mental illnesses do more harm than good in the long run. The hope generated by important studies such as the International Suicide Prevention Trial will only be realized if we successfully forestall these misguided cost containment efforts.

Thank you for affording me this opportunity to testify. I look forward to your questions and comments.

DR. OREN: Any questions for Mr. McNulty from the panel?

(No response.)

Thank you, sir.

Our next registered member of the public is Dr. David Goldman. In contrast to what's listed on the formal agenda, I think he's appearing here in the capacity as a private citizen.

DR. GOLDMAN: That's correct, and thank you very much for taking this public comment. I'm David Goldman. I'm Chief of the Neurogenetics Lab in one of the NIH Institutes, but I'm here representing my family and not in any official capacity. To my knowledge, NIH has no stance on the issue of clozapine licensing or availability.

We welcome the results of the InterSePT trial, which does demonstrate, from what we've seen this morning, efficacy of this drug on suicide attempts. It's representative of the science-based approach which is so critical to the Division of Regulations, and it is also representative of the way that FDA and industry can work cooperatively in scientific partnership.

It's very important to keep in mind that there's a long way to go, however, when we look at the results of this trial and we see that still, after two years of treatment, that there's still 5 suicides out of approximately 500 individuals in the clozapine

treatment group.

The dominating clinical issue in clozapine remains the requirement for hematological monitoring in the administration of this drug and, indeed, that is the greatest barrier to the widespread application of clozapine in schizophrenia even though, as has been pointed out by John Kane and others, clozapine remains the most efficacious antipsychotic medication on the market and available.

That program of hematologic monitoring requiring a complete blood count every two weeks even in patients who have been treated long-term with clozapine is out of step with the science.

Neutropenia occurs early or rarely, and it is very rare in patients treated with clozapine for more than six months. In fact, the indication for hematologic monitoring is different in England where it's once every month, and in certain other countries there's no requirement for hematologic monitoring after six months. So, this ritual of bleeding -- my relative, who has schizophrenia, has actually been treated for about a decade, and has been bled some 350 times, is virtually medieval in its unnecessariness.

It's notable that in the InterSePT study, that despite the impulse to make the clozapine and

olanzapine groups as similar as possible, that the patients treated with olanzapine were, in fact, not bled weekly. And, of course, the effects of this weekly bleeding, I believe, are negative, but I suppose it's also possible that the findings with suicidality could have been colored in some way by the fact that the patients treated with Zyprexa did not receive this weekly venepuncture. I'll leave it to the panel of experts here and in clinical trials on schizophrenia to evaluate the results from the Zyprexa trial.

The only notable difference that I saw was a difference which I again believe just reflects the clinical efficacy of clozapine and emphasizes the underprescribed nature of clozapine, and that is that the olanzapine group was treated with far more ancillary medications than was the clozapine group. So the efficacy of clozapine achieved -- equal in this study to olanzapine, but achieved without the use of the ancillary medications to the same extent.

And so in conclusion, I hope that the FDA working with Novartis will extend their science-based approach to the regulation of clozapine to the most critical issue in the clinical use of clozapine, namely, the hematologic monitoring. Thank you.

DR. OREN: Thank you, Dr. Goldman.

Are there any questions from the Panel to Dr. Goldman?

(No response.)

Thank you.

DR. GOLDMAN: Thank you very much.

DR. OREN: Is there any member of the general public who wishes to make a statement in regard to the matters we're discussing today?

(No response.)

Seeing no further comments, we'll move to the next segment of the agenda, which is for the Panelists to ask questions of the FDA and to begin our discussion. We have a set of six issues that the FDA has requested our discussion and feedback, plus a formal vote. And I'd like to go through those question-by-question, but perhaps before we start that, I know Dr. Ryan may have some leftover questions from this morning.

DR. RYAN: I had a couple, I just didn't raise my hand quite soon enough. The first one I wanted to get clear is on the concomitant meds, Slide CBR-9. That's averaged across all subjects in the study, or all subjects who got a concomitant med in that class?

DR. ZANINELLI: That's averaged across all subjects who received concomitant medication.

DR. RYAN: My second question was just to make sure I understood the analysis correctly. On the WLW analysis, that takes into account the first Type 1 event that a subject experiences and the first Type 2 event that subject experiences, obviously understanding the nesting you were talking about before, but would not -- that analysis doesn't use the subsequent Type 1 or Type 2 events, is that correct?

DR. ZANINELLI: That is correct.

DR. RYAN: On Slide EF-198 that was showing the analysis if you truncated them when they dropped out of the study, is that easy to pull up? It was something around 198. Is that easy to pull up?

DR. ZANINELLI: 198?

DR. RYAN: I believe I have the number correct. It was the question on the people who left the study.

DR. ZANINELLI: Maybe it was 158.

DR. RYAN: 158 -- my apologies.

(Slide)

That was it, yes. On the Type 2 one down at the bottom, you have a p-value of .005, but the confidence interval goes to .99, is there a typo on

that?

DR. ZANINELLI: Um-hmm.

DR. RYAN: The confidence interval has a ratio that almost goes to 1, but you've got a p-value of .005, so that looks incorrect.

DR. ZANINELLI: We will check that.

DR. RYAN: The final one, and probably the only substantive one since I'd guessed right on the other things but wasn't sure, can you comment some more on the depression as a side-effect which also differed between the two treatment groups, as did the suicidality as a side-effect, and how that correlated with the actual suicide attempts because, obviously, as you talked about, your depression measures and your suicidal measures which didn't correlate with anything, but did depression as a side-effect -- the question was the side-effect was more frequent in the group that had also more suicide attempts. Did the two correlate?

DR. ZANINELLI: Dr. Krishnan?

DR. KRISHNAN: Just very briefly, if you model it for the purposes of effort-based analysis, which -- this is a very rich dataset, by the way, it allows you a lot of things you could do -- yes, there are a few mediating variables prior to the suicide

attempt, and the mediating variables appear to be drug abuse, alcohol abuse, as well as depression. Worsening of those things predicts events, both hospitalization as well as -- but it's epoch-based, it's just before. If you look at an epoch, it seems to predict it. Remember, that these are not done cross-sectionally, so you don't have event-to-event, you're really looking at epoch of the event.

The other interesting thing is negative symptoms also have an interesting interaction, but there are a lot of things that have to be explored with it, rather than making any definitive statements at this point.

DR. RYAN: Thanks.

DR. OREN: Dr. Rudorfer.

DR. RUDORFER: Just a follow-up question to that. Are there any data on the extent that patients in either group developed full major depressive episodes as opposed to just a score on the depressive symptom?

DR. ZANINELLI: No, that information wasn't collected, so reason for dropout did not include these as specific diagnosis if it was a psychiatric condition or not. So, we don't have that information.

DR. OREN: Dr. Cook.

DR. COOK: I'd like to -- in thinking about the Type 2 events, I wonder if you analyzed -- the analysis of adding the Type 2 defined events, or what's added when you go to Type 2, is so confounded by the Type 1 baseline. What I'd like to know is the analysis of worsening of suicidality is measured by CGI-SS-BP score of 6 or 7 in the two groups, and not having the Type 1s confounding that analysis.

DR. ZANINELLI: Comparing the 18 and 20.

DR. COOK: No, because -- what I want is the ones that would have been defined as Type 2 had they not -- irrespective of whether they were Type 1 or not. Does that make sense yet?

DR. ZANINELLI: But that would be those 18 and 20 --

DR. COOK: No, there are more than that. One would presume that of the ones hospitalized, many of them still had a worsening on the CGI-SS-BP. Does that make sense?

DR. ZANINELLI: So you're saying irrespective of whether it was a Type 1 and Type 2 event or not, whether -- if they had a worsening, so the analysis of that --

DR. COOK: Basically, in your Type 1s,

presumably there are many subjects that had they not met the criteria for Type 1, would have met the criteria for Type 2.

DR. ZANINELLI: Were the analysis based on first event, so it's a Type 1 or Type 2 event, do I understand?

DR. COOK: No. In a sense, you are only analyzing those that did not have a Type 1 and saying that they had a Type 2, I assume, because you don't have overlapping distributions there. So, what I'm getting at here is when you analyze the CGI-SS-BP score, basically you showed us a difference from baseline to 104 weeks. That's much different analysis than the survival analysis you did with Type 1 and Type 2, as you defined them.

So, I'm very interested in the discrepancy there, that troubles me. What I would like to know is what happened with the CGI-SS-BP score if you submitted just that to the same kind of survival analysis.

DR. ZANINELLI: I see. The analysis of the secondary variable.

DR. COOK: Well, that's not how it was defined in the material I got from the FDA. So you're saying that was secondary, what I got from the FDA is

that you had two primary endpoints, so this becomes very important. It's particularly important because it is the blinded rating, and that's important to me.

DR. ISLAM: Unfortunately, we do not have that prepared now, just for that CGI-SS -- time to worsening of CGI-SS 6 or 7. That's what I think you want.

DR. COOK: I mean, you have that for the ones that weren't Type 1.

DR. ISLAM: Right.

DR. COOK: So I don't understand why you don't have that for the ones that are Type 1.

DR. ISLAM: Because we define Type 2 as the correlation of CGI-SS in Type 1. That's why we present a Type 2 as combined.

DR. COOK: I can't imagine that that would be that hard to retrieve.

DR. ISLAM: It's not hard, we just do not have any slide prepared for that, that's what I'm saying. It's not hard at all.

DR. OREN: Dr. Katz.

DR. KATZ: I have one more question about the retrieved dropouts. You showed some information about those patients. Maybe you've already said this. When you retrieved them, did you only retrieve them at

Week 104, or did you evaluate them at what would have been their perspective study evaluation time point?

DR. ZANINELLI: So it was date of retrieval then ongoing and not just at the endpoint.

DR. KATZ: Right, it was adjusted at the end when they would have completed 104 weeks.

DR. ZANINELLI: The question is whether the retrieved dropouts, the date of retrieval was only at the end of their respective endpoint or during the study. So my understanding is also that at the -- periodically, data was retrieved from those patients that discontinued.

DR. KATZ: It was retrieved.

DR. ZANINELLI: It was retrieved.

DR. KATZ: At what would have been their study visits, had they continued.

DR. ZANINELLI: Yes.

DR. KATZ: And I notice that there were 12 clozapine patients who had a Type 1 event and 3 Zyprexa patients, if I remember the little footnote, out of, I think, 60 retrieved dropouts in each group, if that number was correct.

DR. ZANINELLI: Yes.

DR. KATZ: Do you know anything about the timing of those events in relation to when the drug

was discontinued, in each of those cases?

DR. ZANINELLI: The timing of the Type 1 events in the retrieved dropouts, do we have a distribution of that? No, not right now.

DR. KATZ: Is that something you could recreate, not necessarily by the end of the day, but --

DR. ZANINELLI: Yes.

DR. KATZ: Thanks.

DR. OREN: Any other questions from the Panel towards the sponsor or towards the FDA? Dr. Rudorfer.

DR. RUDORFER: I just want to clarify one point. As I understand it, other than the recommended doses, the PIs were not given any specific treatment manual or practice guidelines. During the course of the medical monitoring, was there any judgment made or correction made in terms of the clinical interventions being used -- for instance, whether concomitant medications seemed appropriate, or how they were used, or dosage?

DR. KRISHNAN: There were no strengths on those interventions deemed necessary by the Principal Investigator to maintain patient safety. So, hospitalization concomitant medication was done if the

Principal Investigator said it was necessary, and there was no interference from sponsor or from medical monitor with respect to these interventions.

DR. RUDORFER: If I could just make an observation because I don't think we should let the morning end without it. Concomitant medications, in my view, are potentially a two-way street here, and they don't always work out as planned. Antidepressants, which were used quite liberally, certainly can worsen psychosis.

We saw in some of the case material we received -- for instance, at least one case where a patient received Buproprion (phonetic). Now, we're not in a position to judge whether or not that was appropriate, but many people would consider that a high-risk intervention in a psychotic population.

Similarly, going back to some of my earlier concerns about the schizoaffective population, we don't know, for instance, if an antidepressant could have accelerated cycling or induced mania or mixed state in any of the patients, so the fact that some patients received more concomitant medications than others, on its face, I don't know that that's necessarily to those patients' advantage.

DR. KANE: You certainly raise an

important consideration. I think, really, the driving force in the design of this was to give the clinicians as much freedom to do anything that they felt appropriate. Now, of course, you could argue for practice guidelines and so forth, but I think we would have considerable debate as to what those guidelines should say in this context, and whether antidepressants are appropriate or inappropriate.

So, I think what we've seen here is a real-world attempt to allow the clinicians to treat these patients the way they saw fit. If we had not permitted that, I think it would have been extremely difficult to do this study, given the level of anxiety that the clinicians had. If we restricted their choices in any way, they would have felt extremely uncomfortable managing these patients.

I think it's difficult to -- you know, we could debate about the impact of antidepressants or not giving antidepressants or antipsychotics, but what we've seen here is within this kind of real-world framework, the differences are still apparent between the two drugs. The clinicians were doing their best to maximize the treatments that they had available, and despite that we're seeing a difference between Clozaril and Zyprexa, and I think that's very

powerful.

DR. KRISHNAN: Just to briefly address the same issue, it's not just antidepressants, but also the anticonvulsants and Lithium usage was more -- again, it goes to the issue that if you're looking at concomitant drugs and cycling, the pattern was not observed one group to the other. Just look at what all concomitant medications that were used. This is a real-world population that you're using whatever you can to keep them alive, essentially.

DR. OREN: Dr. Hamer.

DR. HAMER: Forgive me if this question has already been answered, but I don't think it has. I'm still curious about the use of olanzapine in the subjects randomized to clozapine, and the reverse. I think that you indicated earlier that most of that took place during the down-titration of whatever a previous medication was, and up-titration of whatever the randomized study medication was. Do you have any figures on how many patients during the course of the study, after down- and up-titration, were actually given the opposite drug as a concomitant medication?

DR. ZANINELLI: No, we don't at this time, but that would also include patients who -- the retrieved dropouts, for instance, who really

discontinued before participation were being followed up for endpoints -- may have been on both study medications as well. I know there were a couple of cases of that. We don't have a listing of the breakout of that.

DR. OREN: Dr. Hamer.

DR. HAMER: Let me ask a follow-up question. From your familiarity with the actual subjects and case reports, were there, in fact, subjects who were randomized to one of the two study medications during the study, and then the treating psychiatrist decided to prescribe exactly the other medication for clinical purposes?

DR. ZANINELLI: The database shows that two patients were randomized to Clozaril, but actually received Zyprexa.

DR. HAMER: As a concomitant medication or as a protocol violation?

DR. ZANINELLI: It's a protocol violation, so instead of the assigned drug.

DR. HAMER: Thank you.

DR. OREN: Okay. Members of the Panel are still welcome to ask questions of whoever will know the answer, as we go through our discussion, and I want to invite every member of the Panel to feel very

free and welcome to speak up and commenting on any of the questions that we go through.

So the first identified issue that the FDA wanted us specifically to provide some discussion and feedback on regards potential bias in referral of events to the Safety Monitoring Board. Dr. Katz.

DR. KATZ: I wonder if I could sort of broaden that question a little bit because I notice that one question that we have not explicitly put on the list has to do with the general issue of the unblinded nature of the accumulation of the primary data. Obviously, the primary outcomes were assessed on the basis of a blinded review of data that was recorded in an unblinded way, and Dr. Khin mentioned briefly and Dr. Khin addressed briefly, the question of the possibility that for whatever reason the data were recorded in such a way to minimize the number of events attributed to clozapine.

So, I would be interested in a broader discussion of the lack of blinding in the recording of the primary data which, again, could have had an effect in what was recorded in the first place, and the vigor, if you will, of how the unblinded Principal Investigators tried to gather data about, let's say, hospitalizations between visits, that sort of thing --

how aggressively they queried retrieved dropouts, that sort of thing, given the unblinded nature of the treatment assignment.

So, we're very interested in the specific answer to the question about potential bias in referrals, but also the larger question of the unblinded nature of the study.

DR. OREN: Dr. Wang.

DR. WANG: There's a third level that the bias could occur not only in the recording of the primary data and the referral to the SMB, but also there's the issue of the SMB itself, and there is one analysis that I had a question about.

It was in response to the FDA, a table was sent showing the proportion of cases that the SMB considered to be a Type 1 event, and then it showed a cross-tabulation that also showed what the blinded psychiatrist thought. And there was a significant across the diagonals -- in other words, there was about 4 percent where the SMB thought it was an event, the blinded psychiatrist did not, in the clozapine patients. But then it was about 12 percent in the Zyprexa patients. Again, 12 percent of the Zyprexa patients were felt to be Type 1 events based on the SMB but not by the blinded psychiatrist.

Could you explain to me -- maybe it's Dr. Krishnan -- why there's this statistically difference in the proportions.

DR. KRISHNAN: Let me just very briefly address what the reasons for the discrepancy could be. There are two possible explanations for this. First is the blinded psychiatrist evaluation of Type 1 event was just his own evaluation, not subject to any challenge. As I said earlier, one of the issues of classifying an event here required pulling together as much information as you can, and doing our own discussions of this, and it took a while to get us to work together to make that classification clear.

Second, there were only three of us making it for every event whereas the blinded psychiatrist just did it for a few events, and there were lots of blinded psychiatrists. So the potential for one blinded psychiatrist to do it differently from another one at another site was quite great.

On the other hand, you should turn it around and look at what is the concurrence that we have, and the concurrence, even if you look at it as 4 percent and 12 percent, the overwhelming majority is high concurrence between the blinded psychiatrists and the SMB Board as a whole.

DR. WANG: High concurrence is -- it's the differential that I'm wondering about.

DR. KRISHNAN: Yes, the differential is there, but you've got to also remember they are blind and we are blind. Whether they could have had a little more unblinding than us, the possibility is yes, because the blinded psychiatrist actually is seeing the patient when he does the ISST evaluations, et cetera. And potentially there is the possibility of unblinding by evaluating the patient, that actually occurred in a few instances where, if you notice, it says some of those patients, blinded psychiatrist data was not used because he became unblinded in the context of seeing the patient.

So, those are the two main key points why -- you've got to remember, the SMB was kept blind, and all that we reviewed were the records that were sent to us. But it's a good question, and why it differentiated between the two? Other than saying it was probably chance, I can't tell you another explanation for it.

DR. WANG: It was highly significant, it wasn't chance. Could I, as long as we're on this issue of bias, address the first issue of whether the referral to the SMB was potentially biased, and I

agree, the analysis that you presented is, on face value, reassuring. It says that if -- I think it was Slide 53. On the surface, it looks like -- if this bias is existing, it looks like it's small in magnitude.

But to feel reassured, I have two other questions regarding that, and that is -- if you show the slide, I can --

(Slide)

DR. KRISHNAN: It's just 1 point here, the concurrence, if you want to look at it, is 90.5 for the first events, the SMB and the blinded psychiatrists, and equal percent if you look at it as all events.

DR. WANG: That's not -- I'm looking for CES-53, if you have that.

(Slide)

The question is, in the 40 percent that -- in the second row, the number of cases with at least 1 search term matched, it looks like about 40 percent across both arms. Could you break that down by arm?

DR. ZANINELLI: For the Clozaril, of this number, it's 115 cases, and for Zyprexa, 164.

DR. WANG: And percents?

DR. ZANINELLI: Percent of the 490 or

percent of the --

DR. WANG: What percent of cases that weren't referred, these non-PEPs, what percent did your search match a term?

DR. ZANINELLI: Oh, 115 of the 701.

DR. WANG: If you take the 279 out of the 701, could you break that down by study arm? I'll tell you why I'm curious. Earlier you said that the review by the sponsor was potentially not blinded. So, in terms of this, this particular percent, it shouldn't be affected by any judgment of a nonblinded reviewer, so that's why I'm just curious if the percents were similar.

DR. ZANINELLI: Well, 279 breaks down to 115, and then -- for Clozaril, for Zyprexa to 164.

(Simultaneous discussion.)

DR. WANG: What percent of Zyprexa patients not referred.

DR. ZANINELLI: Do we know the breakdown of that? We can get that in the course of the session.

DR. WANG: Thank you.

DR. OREN: Dr. Ryan.

DR. RYAN: A quick followup. If you did the analysis based on the blinded psychiatrist

declaring Type 1 events rather than the blinded Board, it also comes out significant and slightly more significant, or did you do that analysis? Because the blinded psychiatrists declared more events in the Zyprexa -- that's for the greatest events that they declared, right?

DR. ZANINELLI: Do we have that? This is the cost analysis for the Type 1 event for the SMB, as seen during my presentation, for the BP alone, and then the cases where there was concordance between the SMB and BP. So the hazard ratio of .86 when the BP does their assessment, the p-value then drops to .236. Does that answer your question?

DR. WANG: Yes.

DR. OREN: I think the update is posing to us a broader question even beyond this specific study, just as far as the general study design, as far as the unblinded nature of the primary data analysis and referral to the Safety Monitoring Board. Do the Panelists have any comments on that?

(No response.)

Is this the kind of thing we'd like to see more of, see less of, improved?

DR. ORTIZ: I guess my initial reaction is that this particular group is such a complicated

clinically-challenging population. We're talking about people with schizophrenia who also have anxiety disorders, who have substance abuse disorders, who have mood disorders, and I think I agree with the sponsor that it would be detrimental to evaluate something like suicidality in this group, without allowing clinicians to use optical psychiatric medications for what they are seeing as needed.

DR. OREN: Dr. Katz.

DR. KATZ: I think that's a slightly different issue from the question of blinding because one could do that in a blinded study as well, I believe. Again, I believe the reason for the lack of blinding was that it was felt that you couldn't, as has been mentioned in several places, draw blood every week from someone who wasn't getting clozapine. So, that automatically would unblind it. So, I think that's what the unblinded design was related to, not the fact that physicians needed to maximally treat. I think you can maximally treat patients in the face of a blinded study.

DR. OREN: Dr. Malone.

DR. MALONE: The case reports were written by the unblinded psychiatrists, that's correct, isn't it? Couldn't you do a design where you had a parallel

thing done by the blinded psychiatrist, that he would write case reports and refer them to the Suicide Monitoring Board? At least you would have a measure of what the blinded psychiatrist thought should be referred versus what the unblinded did. It would be one way to have a blinded referral.

DR. OREN: Anyone else specifically on the blind?

(No response.)

I think there's no loss of sense that blinded studies are the strongest and the best, and balancing that with the real world. Dr. Cook.

DR. COOK: Well, I think there is a standard, and I can imagine this coming up before another committee to review a proposal at NIH, and it comes up in psychotherapy research all the time, for example, and the standard is blinded raters. And I don't know why we would change that. I can imagine many people thinking about various indications that would now become approvable on the basis of studies that are equally hard to do.

So, I have quite a bit of concern, given that there were blinded raters and given that there wasn't an effect seen, but that was a different analysis. I have a lot of concern that analysis of --

a survival analysis with only blinded rater data is not available to us.

DR. OREN: Again, continuing the broader view both with this study and with regard to other studies the FDA may be considering one of the issues is adequacy of the single randomized control trial to support suicidality claim. And maybe for the moment we can focus on the single randomized control trial part of that statement both with regard to this study and the broader question, given that the FDA standard is normally for two randomized control trials. We can focus on the suicidality perhaps a bit down the road in this discussion, but any comments on this? Dr. Ryan.

DR. RYAN: Yes. I've been reflecting -- in child psychopharm studies, you've got a similar issue of, you know, the hazard to people and what you inform them on, and I was wondering, as a family member of a potential participant in this study, if you had -- one trial that came out positive -- if you would seem to have an ethical obligation to tell people going into the second trial, that the first trial had come out positive. That's only one trial, it may or may not constitute evidence. But it's somewhat unclear to me, given the potential disastrous

outcome with suicide, that one could effectively recruit for a second study if ethically investigators are ones who insisted you inform them of a prior study that was deemed to be positive. So, I wonder if we don't have to take an approach like that simply to study these really overarching questions that are hard to recruit for and large, and yet it's hard to know how you'd do a second study, or how you would effectively recruit for a second study, or how you'd representatively recruit for it.

DR. OREN: Ms. Bronstein, you're our Consumer member of our Panel, any thoughts?

MS. BRONSTEIN: I really think it would be very difficult to suppress the information after you have some significant result, and I'm thinking in terms of your patient family members primarily, that really live on a day-to-day basis with this fear, and it would be very difficult not to address that.

DR. OREN: Dr. Winoker.

DR. WINOKER: I think we've also been told the single trial is more something that will be considered when there are additional evidence that would support the claim, and I think -- you know, we've had presentation of additional evidence, albeit retrospective, that certainly speaks to that.

I think this is focusing on an issue of significant public health importance for which the increasing scrutiny of human subjects research makes it extremely challenging to envision and conducting studies like this, with the standards being set ever-increasingly higher for protection of human subjects.

So, I think based on assessment of how these results are viewed, I would view that it would be difficult to still feel that a separate study in this population would be feasible.

DR. OREN: Dr. Hamer.

DR. HAMER: It would be simple to do two studies, just do them both at the same time. That way, you don't have the answer. Sponsors do that all the time.

DR. OREN: Dr. Katz.

DR. KATZ: The other issue, I think, when we're talking about whether or not that in this case a single study plus something called confirmatory evidence is sufficient, I think you have to take into consideration the meaning of the clinical outcome that was assessed here because, in fact, it didn't -- well, we don't know -- but there were very few events of actual completed suicide, so there was no effect on mortality, in that sense, or no differential effect

between the treatments. The effect was on something called "suicidality" as, obviously, defined as you've heard.

So the question is whether or not that endpoint -- which, of course, was a composite endpoint -- whether or not that endpoint is sufficiently known, for example, to be predictive of actual completed suicides to say, well, yes, this one study is sufficient because it's unethical, for example, to do another one because this outcome clearly, for example, is related to actual completed suicides. In this study, it wasn't.

So, I think when we think about is one study enough, I think we have to think about whether or not the outcome that was assessed and on which the effect was shown is an appropriate outcome for that sort of standard to be applied.

DR. OREN: Dr. Meltzer.

DR. MELTZER: In this study, the ratio of serious attempts to completed suicide was about 1 to 10. That is a lower ratio than the literature usually reports. It's usually closer to 1 to 5 in this population. For every 5 serious suicide attempts, one can expect usually in the next year or two at least one completed death in that population.

We did a para-analysis using what we saw in the study. If we had tried to do a study with the same kind of estimates of differences, we would have needed 20,000 patients in order to find a significant difference, with the same small number of deaths as the outcome.

So, I think there are applications for the ultimate mortality by reducing the number of serious suicide attempts.

DR. OREN: Dr. Kane.

DR. KANE: If I could just add to that, I think, in talking about suicide, obviously, that's the most dire outcome, but the effect of suicidal attempts and suicidal behavior is enormous. If you see these patients, if you talk to their families and you see what has happened to them as a result of failed suicide attempts, this is also a source of enormous morbidity, family burden, et cetera, et cetera. So, I feel very comfortable arguing that the prevention of suicidal behavior, the prevention of suicide attempts as a goal, in and of itself is absolutely critical. And it's clear, obviously, that people at highest risk for suicide are the people who have attempted suicide in the past, but I think we can certainly focus on the results in this trial based on suicidal behavior, not

on completed suicides.

DR. OREN: To go off-topic for a moment, I need to take the pulse of the committee with regard to how we proceed from here. We have officially on the schedule a possibility for a lunch break for an hour at this time, and I need to have a sense from the committee if that's something that we should take right now, as scheduled, or if people need some personal time, or if we should keep going and end the meeting at an earlier hour. Any thoughts? Another option would be to take a ten-minute break now and then to discuss further. Dr. Cook.

DR. COOK: I just vote for lunch.

(Laughter.)

DR. OREN: Lunch it is. We'll meet back here then in one hour.

(Whereupon, at 12:10 p.m., the luncheon recess was taken.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:10 p.m.)

DR. OREN: Okay. We have covered clozapine, caffeine, and the last hour proteins and carbohydrates, and now we're back to clozapine, and there are a couple of speakers from Novartis who have just asked for an additional moment to respond to some of the questions asked by the Panel earlier. We'll resume with them, and then we'll resume with our general discussion.

DR. KRISHNAN: The first issue is the blinded psychiatrist and the SMB, and just to give you an idea what the process differences were and who we were, the SMB, as I said, three of us rated everybody, looked at every event. The blinded psychiatrists, there were 68 of them, each site, very few events rated by any one of them.

We spent the first several months making decision points of how we were going to evaluate this, they didn't. There was no training set up for them to learn how they were going to make a decision. That was two critical differences between us and them.

The other thing to keep in mind is a blinded psychiatrist often did not get to rate the event in the same time frame. Sometimes there might

have been a delay before the time they rated it.

And the other piece that there was a greater propensity or potential for them to get unblinded because they were working in the same location, some of them did get unblinded, and they were also seeing the patients. Any of you who have worked with either clozapine or olanzapine patients, it's very difficult to keep the blind, especially in those who are psychotic in nature. Patients who are psychotic are going to say something, and that could always create an issue when the blinding -- whether they consciously or unconsciously do it, that's a factor. That is the reason why, up front, the decision was made that the SMB would be the one on which the final decisions were going to be made on whether it was a Type 1 event or not. So, that's the first piece.

And we also wanted to make sure the SMB was blinded to the experimental treatment, and also the location of the patient, and the packages that we received were anonymized and, therefore, there was no way of us knowing which patients were on clozapine and which were on olanzapine.

The allocation of actual treatments was random, as you know, and therefore any bias to

determine categorization by the SMB would have been random and could not have discriminated between the trial drugs.

The second piece that I wanted to very briefly state again is the rating scales, which I think has come up a couple of times. Two things to remember -- the rating scales were done -- the ISST, CGI-SS -- had designated time frames initially at four weeks and then started to spread out. Therefore, it did not have the same frequency at which events were happening or captured, and one of the things that if you actually look at the scale scores is the time for worsening on a CGI-SS is referring to the week before, and that may not have been a week when anything happened. The patient may actually have been doing better. And, therefore, that instrument does not work as well as the events that they are trying to capture. So, scale not measuring the same thing as an event, and the scale measures more on timed basis which were much less frequent than the events.

DR. OREN: Dr. Kane.

DR. KANE: John Kane, the Zucker Hillside Hospital. I wanted to get back to a question that had come up earlier also, which was the number of patients with a score of 6 or 7 on the CGI-SS-BP, so this is

the Type 2 event, if we could have that.

(Slide)

So we see that among the Clozaril-treated patients, there were 38; among the Zyprexa-treated patients, there were 42. And keep in mind that there were roughly 240 Type 1 events. So the Type 1 event proved to be a much more sensitive indicator of what was going on here, and for the reasons that Ranga just articulated, these assessments were done at fixed intervals, in many cases many, many weeks apart, so the real outcome of interest here, obviously, is the suicidal behavior that occurs at very unpredictable times during the course of followup.

I also just want to emphasize that the outcome measures, the amendments that took place to the protocol, were all done prior to any analyses and were agreed upon with the Agency. So this was a best attempt, I think, to bring a meaningful outcome measure to a very, very difficult population.

DR. ZANINELLI: I just have two brief responses to questions. One was Dr. Wang's question regarding the total number of non-referred cases, what the breakdown here was, 701. So, it was 368 patients in the Clozaril group, and 333 in the Zyprexa group.

And the next one was a slide here that Dr.

Ryan pointed out.

(Slide)

The confidence level was .99, that was incorrect, it is .90. Thank you.

DR. OREN: Okay. I want to turn now to the second issue that the FDA particularly raised about claim focusing on suicidality in schizophrenia or schizoaffective disorder. So, the first part -- Dr. Winoker, do you have a question with regard to that issue?

DR. WINOKER: Kind of as a continuation of the discussion that Dr. Katz had started before the lunch break, I was remembering back to an excellent presentation that Dr. Laughren had given at one of this committee's meetings about a year ago, I think, for the Alzheimer's discussion, and in that meeting Dr. Laughren presented a very nice overview of the fact that the Division now really was wanting to focus on specific and very recognized validated diagnostic entities for indications, and the trend was really to move away from more kind of symptom-based or not specific recognized disorder oriented indications, so I think you briefly touched on that point earlier this morning, as far as being open to this kind of indication. But it seems to me this is kind of the

mirror image of the question about how we feel about these behaviors as sort of surrogates for actual suicide, if you have any perspective on kind of the Division view on this type of indication.

DR. LAUGHREN: Well, I think they're sort of two separate issues. I mean, the one issue was whether or not you can focus on one particular aspect of a well-defined syndrome. And I use as an example ordinarily you wouldn't focus on one of many positive symptoms as the target for a claim. That we would consider, in a sense, a pseudospecific claim. But if you can show that a particular aspect of a disorder responds differently or doesn't respond to usual treatment and does respond to a particular treatment, that might be a legitimate target for a claim. So, it's not that we wouldn't accept focusing on a symptom, it's just that there has to be some justification for it. And if there's a differential effect of drugs on that symptom and it's an important symptom, then it would be a legitimate claim.

But the other question that you raised is whether or not the outcome, the suicidality outcome, in this trial is an acceptable surrogate for the outcome that everyone worries about, which is a completed suicide. That is, I think, a separate issue

that requires some discussion.

DR. OREN: Dr. Hamer.

DR. HAMER: I'm not sure, but I thought I heard someone say -- and it sounded reasonable to me -- that I don't think you need to think of attempted suicides, necessarily, as a surrogate for completed suicides, that there are enough serious consequences to attempted suicides of various sorts that it would be worthwhile addressing attempted suicides, whether or not you actually see a reduction in completed suicides.

DR. LAUGHREN: Yeah, I think that's a fair point and, again, it's something that ought to be part of the general discussion.

DR. OREN: Dr. Rudorfer.

DR. RUDORFER: I want to go back half a step in this discussion. Both of these compounds that we're talking about today are labeled for the treatment of schizophrenia, neither is labeled for the treatment of schizoaffective disorder, so that when we consider suicidality, we're considering that as maybe a secondary or another, an additional potential indication for Clozaril. On the other hand, there is no primary indication in terms of treatment of schizoaffective disorder.

So, I'm quite concerned about that because basic issues of efficacy and safety and dosing, as we've been alluding to, we have no data on in terms of the treatment of schizoaffective disorder. And I don't want to be redundant, but the field remains rather perplexed about what schizoaffective disorder is.

I'm reminded that when Clozaril was first approved under DSM3, there were no diagnostic criteria for schizoaffective disorder because the committee appointed by DSM3 could not agree on what the criteria should be. Every edition of DSM since has a different set of criteria, so they do exist for DSM4, but I don't believe they were properly followed in this study because the DSM4 states that a type should be -- not may be, but should be -- specified because the two types that are commonly recognized by the field may not both correspond as a subtype, if you will, or a relation of schizophrenia.

So, I have a problem with looking at a secondary indication in terms of a disorder, that is not a primary indication.

DR. OREN: Dr. Katz.

DR. KATZ: That's fair enough. I just want to sort of tease out the two -- at least two --

potential issues in what you said. One is whether or not schizoaffective disorder is well enough described and accepted as a diagnostic entity to even grant any sort of a claim for. And the related question is whether or not, if it is, the patients in this study who are called schizoaffective actually meet those criteria. So, that's one issue, the reliability of the diagnostic category.

The other issue is what the claim -- does this study support any sort of a claim in that population? It's quite possible that you could have a claim for suicidality or the reduction of suicidality in a particular diagnostic claim, without a claim that it treats the general symptoms of that claim. And that's what the sponsor has proposed -- it says "for the treatment of suicidality and schizoaffective disorder" -- it's not for the treatment of schizoaffective disorder. You could have such a claim, but it's unusual.

DR. RUDORFER: Right. And, again, for that we've seen no dose response data on that, or toxicity data related to this population specifically.

DR. LAUGHREN: Only what you have in this trial. Of course, it was not a fixed-dose study, so you don't have information on dose response.

But could I get back to your sort of elaborating on Rusty's points. Are you doubting the legitimacy of the diagnosis of schizoaffective disorder, as it is currently defined in DSM4?

DR. RUDORFER: No, but I'm questioning whether that was followed in this study that we're viewing. Again, there were no structured interviews done and, as Dr. Krishnan pointed out, the diagnosis is used somewhat loosely even in this country, let alone around the world, and I'm not sure -- and I made reference to the case that was called "schizomania" -- again, a term which we have not seen in the other materials from the sponsor. I'm just concerned that a large group -- maybe 40 percent of the patients we're talking about -- I'm not sure I really know what's wrong with them.

DR. OREN: Perhaps to help us focus in our discussion, let me ask the committee, and you can shoot me down if this isn't a good way to do it. In some ways, there are two questions that we're talking about here, one is suicidality as an outcome measure and how that should be defined and whether that's acceptable, and the second is the particular subject groups -- schizophrenia, schizoaffective disorder. Would it be worth talking about each separately?

So perhaps then let's stand on the suicidality, and we'll come back to the very important question of the population group. How does suicidality sound as a target measure, and obviously that will tie into labeling issues as well. Dr. Ortiz.

DR. ORTIZ: My concern with suicidality is that it's generally considered a symptom within a mood disorder and generally depression, and that using it in a new and different way is going to have implications for clinicians. And I think my biggest concern is not psychiatrists but, as we've seen with antidepressants, the majority of people using antidepressants are no longer psychiatrists, they are primary care and mid-level providers. And my concern would be how do they -- how would they understand a symptom of depression that's now used in a different context?

DR. OREN: Ms. Bronstein.

DR. RYAN: I might come down perhaps in a different position than what I sense Dr. Ortiz was trying to say, that it's certainly -- of the different aspects of the presentation, that was the one that certainly seemed to make a great deal of sense to me, the argument that this is a -- that suicidality is

separately something one wants to treat, whether or not -- presumably, it's a proxy for a completed suicide, but the argument on power calculations for a study to show a significant decrease in completed suicides, and the costs of such a study might well be prohibitive. And so it seemed like you have both that argument, but also the argument that there's a substantial societal gain to preventing suicide attempts, and that there's at least a rational basis in some prior data to suggest that this -- that some compounds may differentially treat that. So, I pretty much bought that part.

MS. BRONSTEIN: Treating suicidality in psychotic populations is really different than in other populations, and I know we're not on labeling yet, but I think as we're thinking about suicidality as a target to treat, I think it has to be really clear that this be for a psychotic population and not for a general population. And we don't have as many tools to treat psychotic patients as we do for non-psychotic patients. And I think the study is interesting in looking at its effectiveness for this population.

DR. OREN: Dr. Malone, did you have something to comment?

DR. MALONE: I was going to say something similar, that you would want to look at suicide perhaps within different disorders, or that there are different kinds of causes of suicide, so that, for instance, in adolescence, probably mostly those children are -- I mean, those adolescents are maybe taking substances and having impulsive acts, which would be different in someone who is psychotic having a suicide attempt, or at least the treatments would be different. So, if you had impulsive acts because you were on substances, you would stop the substances. But if you had impulsive acts related to psychosis, you might end up using an antipsychotic.

DR. OREN: Dr. Hamer.

DR. HAMER: Generally, this Division has historically been reluctant to approve medications for the treatment of particular symptoms, but you have at least started the slippery slope in terms of things like approval of medications for agitation in dementia. And, also, other Divisions -- I mean, there are clear precedence for approving things like medication for pain, or medication for fever, and the general -- my understanding of the general philosophy is that to do that it generally needs to be demonstrated that the medication is effective for pain

or for fever in the context of several different illnesses, and we don't have that situation here. This reads like treatment for "a" symptom in the context of "an illness".

DR. LAUGHREN: Just to clarify, that is exactly right. We in no sense view this as a nonspecific claim for suicidality. It's clearly in the context of these two specific illnesses.

DR. OREN: Dr. winoker.

DR. WINOKER: I would also endorse the view that treating suicidal behavior in the context of schizophrenia or schizoaffective disorder is a recognizable and meaningful clinical phenomenon. And with the previous clarification that we're not necessarily confined to talking about specific diagnoses, I do think these are meaningful targets to look at efficacy data to evaluate.

DR. OREN: Dr. Malone.

DR. MALONE: Earlier you had spoken about pseudospecificity, and I think, if I understood the data from Dr. Meltzer, the schizoaffective population seemed to have had suicidal ideation at least 90 percent of the time --

DR. MELTZER: Yes.

DR. MALONE: -- and the schizophrenic 60

percent of the time. I don't know how that ties to suicide being part of the syndrome and that to pull out suicide would be one of those pseudospecific phenomena.

DR. LAUGHREN: But, again, what it comes down to, in part, is what the data show. If you have a symptom that's part of a syndrome that responds differentially, then that might be a setting where you would be willing to focus on a particular symptom. The concern, in general, about pseudospecificity is that it's an artificial narrowing of the claim, that you have a drug that works for a variety of symptoms of an illness, but you choose, for whatever reasons, to focus only on a few of them when, in fact, it has an effect on all of them. But if you have a situation such as this where you have a particularly troublesome symptom that's part of an illness that does not respond to other treatments for that general condition, but does respond to this treatment, that would be a setting where there would be some legitimate reason for celebrating that finding. I think that's the difference.

DR. OREN: Dr. Cook.

DR. COOK: So,to follow that, I was somewhat convinced that it seemed to be treating

suicidality independent of treating psychosis, which would be an important distinction here. I don't know if we're going to address right now whether we thought there was evidence in schizoaffective disorder, we're going to defer that because that I wasn't convinced about.

DR. OREN: We'll defer that for the moment. If I could just say this to either Dr. Katz or Dr. Laughren, perhaps to restate what you've already clearly stated, but just for the record, the fact that an approvable letter has already been issued for this, that indicates that in the sense of the FDA, this condition or this state of suicidality is a, in the Agency's opinion, serious enough or a consequential enough state that going down the slope, if you will, is a step potentially worth taking.

DR. KATZ: Well, right, but again I would just reiterate that the fact that we have sent an approvable letter really, other perhaps than in that very narrow sense, shouldn't be taken to -- we'd really sort of like you to put that out of your minds, if you can, and just sort of come to an independent view or give to us an independent recommendation. But, yeah, the approvable letter is what it is. We think that it's certainly a possibility, as Tom is

saying.

DR. OREN: Dr. Winoker.

DR. WINOKER: I wanted to follow up a little bit also on Dr. Cook's comment. A small piece of the data presentation that we haven't focused on much, or talked about, is that, overall, as I recall the data, there were comparable improvements in overall PANSS ratings for both groups, about 25 points, as I recall, in each case. So, we do have, on the face of it, evidence for both treatments being comparably effective for general traditional symptoms that are usually looked at in the treatment of schizophrenia but, still, the evidence which we can talk about further about the suicide behaviors.

DR. COOK: The problem I just realized is that we have different analyses, so if we look at how the PANSS data were presented, that's the same analysis and presentation that showed no differential effect of clozapine. So, it's very similar to the CGI data. So, we would need the PANSS data analyzed as a survival analysis, to be able to see that, in fact, when people were suicidal, they weren't having a worsening of their psychotic symptoms -- unless I missed that particular analysis.

DR. OREN: Dr. Ortiz.

DR. ORTIZ: I have a concern about the word "emergent" suicidal behavior because I think it implies an acuity, plus I think it also is suggestive of an impulsive suicidality that is more common, I think, with substance abuse or maybe borderline personality disorder.

DR. OREN: Dr.Katz.

DR. KATZ: I think it's a fair point. I think we use the word "emergent" in the sense of something that emerges. Maybe it's a wrong usage. I don't think we necessarily meant an acute event of the sort you're talking about. I mean, that can be specifics of the wording, although we've asked you to address that, I think can be discussed, but we didn't intend to have it mean that.

DR. OREN: Dr. Hamer.

DR. HAMER: I also wondered about the use of the word "emergent", although I didn't wonder about it in its context of an emergency, but in exactly the context of emerging, and that was that since the subjects for this clinical trial were chosen, in some sense, to be rich in suicide potential or in suicidality, then I'm not sure we should be reading the data in this trial as including suicidality that emerged during the trial. I mean, it was there when

they started. They were chosen for possession of it.

DR. KATZ: A little more clarification. Originally, I believe, the sponsor proposed language along the lines for the treatment of suicidality, and we were trying to make a distinction that these patients weren't, at the time of enrollment into the study, acutely suicidal. As you point out, they had a history of suicidal behavior or ideation in the past, but at the time of their enrollment we were not treating an acutely suicidal episode. So, we tried to make a distinction between treating suicide, which was what was originally proposed, which we felt that the study didn't look at, and preventing that sort of behavior in the future, even in patients who had a history of it. That was really, I think, the idea.

DR. OREN: Dr. Laughren.

DR. LAUGHREN: We're open to suggestions about how to articulate the claim, and that was one of my major questions. And in other areas where we look at maintenance trials -- for example, we have used language such as "delaying the time to a suicidal event" -- that may be an alternative way of -- so that you're not suggesting that it's new behavior, rather, you're delaying the time to an event that might be expected in a particular population.

DR. OREN: Is there anyone who might want to propose any kind of language -- not yet referring to diagnosis, but referring to sort of the target symptom or target state, that we might achieve consensus. Dr. Katz.

DR. KATZ: Can I suggest that we sort of leave the details of the wording until we've decided that it ought to be approved for something?

(Laughter.)

DR. OREN: Fair enough. Dr. Malone.

DR. MALONE: I juts wanted to ask a question, really. If schizoaffective disorder had a 90 percent rate of emerging suicidality, or whatever you wanted to call it, would -- the if you label this drug for suicidality, would it be the drug of choice then for schizoaffective disorder so that a physician might be derelict for not using it in a patient who had schizoaffective disorder?

DR. KATZ: Well, I don't think we're in a position to say what the drug of choice is for anything, but we would hopefully construct an indication that accurately reflected the data. So, I think it speaks to Matt's point about what ought the claim to be, even though it hasn't been shown to work in the traditional sense. In schizoaffective patients

you might decide that it has been shown to work to prevent suicidality, or however we choose to say it. So, we would hopefully accurately describe what the data showed, and how it's used is a separate question.

DR. OREN: Let me ask you, is there any consensus that just as a general target, suicidality, or however it would be referred to, is a good target for a claim?

DR. RYAN: Two thumbs up for suicidality.

DR. OREN: All right. Not yet focusing on specific language, the other part then of that first question was applying it towards schizophrenia or schizoaffective disorder. So, shall we turn then to the diagnostic of which group or groups might be supported.

DR. RYAN: Let me see if I can state the problem, but it's unlikely to be more helpful to you in clarifying thoughts than mine have been.

It seems like they proposed an analysis across schizophrenia and schizoaffective disorder, without being powered for separate analyses, that they have the indication for schizophrenia and not for schizoaffective disorder. We will discuss probably in a more spirited fashion subsequently, but at least in the first interpretation we had an overall p-value for

the study on their proposed outcome measure, which they picked rational basis, they got the p-value on that one, and that the subgroup analysis is relatively uninformative, which is in the schizoaffective it's not different from the schizophrenia, but it's also not different from the control treatment because it's sort of intermediate and so you don't have a significant difference either way, but they knew they weren't powered for it going in, and that's where my thinking stops, but are we sort of agreed on that part, or that's what you're seeing, Dr. Katz, on what they've presented?

DR. KATZ: Yes, I think generally that's true, although I don't remember the number of the slide, but you had the slide up with the point estimate of the effect, the difference within the treatments, or the hazard ratio, whatever it was, and the confidence intervals, and the estimate of the effect in the schizoaffective patients was, I'll say -- that's it.

(Slide)

Thank you -- was less than, or larger if you want -- it was less compelling a finding that schizophrenia by itself doesn't overlap with one, that was significant by itself, whereas the schizoaffective

was not significant. Now, again, I don't believe it was powered to look at the -- I don't believe it was powered, anyway -- to look at the individual diagnoses, but that's the data. So, the question, besides Matt's question which was is it a real entity or was it adequately defined in this study and did they capture the right patients who should be called schizoaffective, but is there a differential response. We have what we have.

DR. OREN: Dr. Hamer.

DR. HAMER: With the exception of Clozaril and some other medications, in many, if not most, of the clinical trials that I've either run or participated in designing or in one way or another for antipsychotics, almost all of those trials took in patients who had both diagnoses of schizophrenia and schizoaffective disorder. I don't think that we're being asked to do anything unusual in that sense. This trial was designed to have both schizophrenia and schizoaffective disorder, however ill we may define it as entry criteria, and in that group as a whole it showed an effect for whatever that's worth. Now, I have my own difficulty with the blinding issue, but I'm not at all astonished to see that it showed the effect overall and failed to demonstrate it in any of

the subgroups, except schizophrenia which comprised most of the subjects anyway.

DR. OREN: Dr. Katz.

DR. KATZ: It's true that other studies have looked at both populations, but we've never granted a claim for schizoaffective, we've limited the inference to only the schizophrenia population. So this is different in that sense because we're being asked to expand the inference to both types.

DR. HAMER: So that means that we're pretty much treating schizoaffective off-label?

DR. LAUGHREN: Well, of course, you have to keep in mind that you would also be treating non-treatment-resistant schizophrenia off-label because the Clozaril only has a claim for treatment-resistent schizophrenias.

DR. OREN: Dr. Mehta.

DR. MEHTA: This protocol was discussed by the FDA and the sponsor four years ago. I guess the protocol said it very clearly, that these other two different diagnoses which were going to be used. One cannot use a post-trial argument that one of the subsets is not significant because if you look at the last slide, you can't recommend a drug for males or even females because none of them is significant

individually.

So, you can't change the rules of the game after you already agreed four or five years in advance, and that's a concern I had.

DR. OREN: Whatever the rules are, I think it's the duty of this committee as independent outside experts, one hopes to give our best opinion regardless of what took place previously.

DR. COOK: I would add, the question isn't whether this means the overall trial was positive or negative, which is probably what was decided years ago. I doubt years ago the idea would be this would support a new claim for schizoaffective disorder, it's two different issues.

DR. OREN: So, if there was to be some kind of claim referring specifically to schizophrenia and schizoaffective disorder, is there comfort or discomfort with a dual-diagnosis claim, or two-diagnosis claim?

Dr. Meltzer, I'll let Novartis answer, and then we'll come back just to the committee, but you can give the last word on behalf of Novartis.

DR. MELTZER: Well, I've seen a number of very large datasets from community mental health centers around the country, and the diagnosis of

schizoaffective disorder is about 25 percent of the sample. And I think it's very fortuitous, in a sense, that we didn't use a structured interview because I would bet, on average, the way the clinicians made their clinical diagnoses are comparable to the way it's done in America.

And what is happening is that when we completely rule out bipolar disorder by history and symptoms, you have this group of psychotic patients with a schizophrenic positive symptom/negative symptom type syndrome, and when, in addition to that, there is clearcut mood symptoms present, regardless of the temporal issue -- and that's where DSM4 came in and that's what most people don't understand that DSM4 diagnoses schizoaffective disorder in terms of a temporal relationship -- but the average clinician does, and this is why concomitant therapy is so prevalent today. Whenever they see depression, whenever they see mania, in addition to the schizophrenia picture, in the absence of reasons to call it bipolar disorder, they will diagnose it schizoaffective disorder.

And if they remember the RDC, the research diagnostic criteria, then we might call it schizoaffective manic or schizoaffective depressed --

in that finer RDC criteria it was beautifully laid out, and if DSM had stayed with it, we wouldn't be in this problem. But, clinically, I think it's very fascinating that in order to get this study -- or when sites were recruiting for this, one found about, what, 30 to 40 percent of the sample were considered schizoaffective, and the reason for that is just what I said, that's the population that's really at greatest risk for suicidality. And I would be concerned, really, if you did approve it just for schizophrenia, that it might be interpreted or might create some barriers to access to clozapine for the group that needs it perhaps the most -- that is, these people who the average clinician out there is calling, by his own empiric criteria, schizoaffective disorder.

DR. RUDORFER: I certainly agree that there's a major problem in the field in terms of identifying this disorder. However, I think we're faced with a dilemma that the inclusion criteria here with DSM4 definition, and I don't know how we could evaluate a claim where it's every clinician decides for his or herself.

According to DSM4, one needs a full mood syndrome, you need a full major depressive episode or a full manic episode, concurrent with criteria in (a)

for schizophrenia, for the diagnosis of schizoaffective disorder. Now, that means criterion (a) only calls for a month of psychotic symptoms. If people meet the full six-month criterion for schizophrenia, they should be called schizophrenia. If they are called schizoaffective by DSM4, it means they don't meet full criteria for schizophrenia. I mean, that's what we have to work with here.

DR. OREN: I'll recognize Dr. Leber, from the public.

DR. LEBER: This is a clarifying question I'll direct to Tom. In 1998, when this protocol was being planned, was it not the policy of the Division to make the claim for drugs used in the management of schizophrenia, antipsychotic rather than antischizophrenic and, if so, would that not explain the apparent dilemma that exists now?

DR. LAUGHREN: Yes, it's true. There has been a transition over the past four to five years. Prior to that time, all the antipsychotics did have a general claim, and it's since then that we've gradually shifted to focusing on schizophrenia.

DR. OREN: Dr. Kane.

DR. KANE: John Kane, Zucker Hillside Hospital. Just on this issue and keeping in mind the

nature of the patient population, if we think back to the demographic and treatment history characteristics of the sample included, these people had been ill for over ten years, and the average patient had made suicide attempts, was hospitalized for suicide.

I think we want to keep in mind the way that this drug is going to be helpful to patients who may need it. And I certainly understand the discussion here, and I think the point is well taken, that we've seen an evolution, but let's not lose sight of the population that really needs to be treated with this drug.

DR. OREN: Dr. Katz.

DR. KATZ: I think it is, of course, important to think about what is the population that might benefit from the drug or, in fact, might be treated with the drug, but we have to be concerned with what the data are and whether or not the population whom we're contemplating approving it actually was the population that was studied or is currently considered to be the population that we would indicate it for. So, we have to think about who it is going to be used in, but we really have to focus on what the data support.

DR. OREN: So, canvassing the committee,

is there any consensus on this diagnostic question? Dr. Cook.

DR. COOK: The only thing I'd like to state is we have a specific question, but often you're looking for more general direction. It seems to me that if this is schizophrenia or schizoaffective language on the basis of practicality, then that probably applies to every other schizophrenia indication, if most of them had put in similar sorts of populations. I don't think it's a particularly unique population, it's an appropriate population. Essentially, if you don't want this to be off-label for schizoaffective, that applies to the other antipsychotics. So, I just think it's a bigger policy decision than this specific study.

DR. LAUGHREN: Just one clarification. Again, if you recommended approving this claim, the claim is focused specifically on suicidality in these two populations, it would not be a general claim for either all schizophrenia or all schizoaffective disorder.

DR. COOK: I understand that about the specific language here, but if you extrapolate that logic, the same could be applied to the treatment of psychosis in schizophrenia and schizoaffective

disorder. I'm willing to say there's an independence here, and this is an interesting specific question, an important specific question, but as soon as you say this should be schizophrenia or schizoaffective disorder, the logic of extending that to treatment of positive symptoms in schizophrenia by antipsychotics would follow.

DR. OREN: Dr. Ryan.

DR. RYAN: Could I get a clarification from Dr. Laughren about the design of the study because it seems like you use the word "two populations", and yet that doesn't -- I'm having trouble making sense of that because when you approved it without power to test it in either one, it seems to me like it's possible you're thinking this is one population because if you're thinking about it as two populations and the study design leaves you in the quandary that we may or may not find ourselves in right now and -- you know, if you look at most of the other ways of saying whether is this one population we have trouble drawing the boundary versus two populations. So, what was the original thinking?

DR. LAUGHREN: Well, the focus is on suicidality. I mean, that's the primary focus of the study -- suicidality coming out of several different

populations. I mean, I don't know that I can be any clearer than that. And, again, I don't think this is so unusual.

DR. RYAN: But you didn't let them test it in bipolar disorder, say, or other things where it might be a completely splendid drug to treat the suicidality as well as the disorder.

DR. KATZ: Well, I think we're willing to grant a claim, assuming everything else is acceptable, for suicidality in schizophrenia and schizoaffective disorder. I think we would be willing to do that. The question has been raised that maybe these people didn't have schizoaffective disorder, as currently diagnosed, and therefore that would lead to misbranding, if you will, by saying these patients had schizoaffective disorder when, in fact, by common understanding they don't. So, that's one issue. The question is whether or not those patients really are labeled, if you will, appropriately in the context of the year 2002, or whatever year this is.

The other -- that's the main point, whether or not we really are dealing with the right population.

DR. OREN: Dr. Hamer.

DR. HAMER: Perhaps I'm wrong, but my

understanding of the way the diagnostic criteria were used here would imply that if these patients were mislabeled because they didn't meet criteria for a full-blown mood episode, then they probably met criteria -- the way that the criteria were used here, then they probably met criteria for schizophrenia. So, it's not like we have a mixture of schizophrenics and people who could be anything -- personality disorders, attention deficit disorder, whatever else -- it's either schizophrenia and schizoaffective disorder, or primarily schizophrenia. That's at least my impression of the way the diagnostic criteria were used.

DR. OREN: Dr. Ortiz.

DR. ORTIZ: Yes, I think I would agree with that. It sounds like the clinical information that we've gotten, that many of these people could have been schizophrenia and major depression, not necessarily schizoaffective.

DR. OREN: Dr. Rudorfer.

DR. RUDORFER: Or bipolar disorder with psychosis. I mean, I think the general issue -- one general issue I'm having problems with again is the fact that without the structured interview, we really don't know how the diagnostic criteria were used

because it sounds as if other than people being aware that there was a set of DSM4 criteria, we have no information on how the clinical data were applied to those criteria.

DR. OREN: Dr. Katz.

DR. KATZ: The other point when considering whether -- what populations it ought to be approved for, has to do with something that Dr. Mehta said, which was it wasn't powered to look at the individual subtypes, and there are many other demographic characteristics which we ordinarily wouldn't say, well, it doesn't work in men, or it works in women, that sort of thing. But you are allowed to look at the data as it was generated and, for example, if it turns out that the study was overall positive but all the action was in one particular subgroup and there was absolutely nothing going on in, let's say, the schizoaffective group, you could reasonably -- I mean, it's not immediately obvious what the best thing to do in that case was -- but you could reasonably say, well, yes, it was overall positive when we enrolled all these patients, but really it had no effect in one particular subtype. And, again, you saw the point estimate and the confidence intervals around the treatment effect for