the two subtypes. So, one could ask the question whether or not, even though these patients were, for example, accurately diagnosed and accurately labeled and the prospective analysis included all patients and it was overall positive, when you look at it there's nothing going on in one particular subset. I'm not arguing that position, but I'm saying that one could look at the data in that way.

DR. OREN: Do we feel the data for the schizoaffective population is strong enough for such a claim on the basis of what's been presented? I'm not hearing any disagreement on the schizophrenia side of the question. Dr. Hamer.

DR. HAMER: Well, looking at that slide which you've kindly flashed a couple of times, with all the effect sizes for all the various subgroups --

DR. OREN: Would you mind putting that slide up again, No. 39?

(Slide)

DR. HAMER: As I look at that pattern of confidence intervals and I see them -- all the point estimates hanging around there on the low side of 1 -- it seems to me that if we were going to deny schizoaffective disorder which was a relatively smaller subgroup, then we might want to deny a variety

of other of these claims, too -- like whites, it doesn't seem to work too well in whites, or elderly people over 44 -- I guess I'm in that category --

(Laughter.)

So, I have a hard time singling out schizoaffective disorder and saying, yeah, it doesn't work in that subgroup.

DR. OREN: Any other comments on that?

(No response.)

Okay. We're also asked to talk about expanding -- I'm sorry. Dr. Katz.

DR. KATZ: I'm just not sure what the sense of the group is on this question about whether or not schizoaffective ought to be included in any potential indication.

DR. OREN: It's sounding to me like there is -- maybe by virtue of silence, so I'll ask people to speak up -- but it's sounding to me like the group is, on the whole, supportive of such -- no? Would it be worth -- should we go around and just invite people to comment? You can pass, as well. Dr. Mehta.

DR. MEHTA: I would include both indications as part of the protocol.

DR. OREN: Dr. Malone.

DR. MALONE: I'm not on the vote --

DR. OREN: This is just discussion.

DR. MALONE: I don't know. I think it a bit strange to have a disorder indicated for suicide, but it's not already primarily indicated for the main treatment. So, for instance, Clozaril has schizophrenia as an indication, but --

DR. LAUGHREN: Can I just clarify, it does not have a broad claim for schizophrenia, it has a claim for treatment-resistant schizophrenia, which is -- you know, it's a fraction of that population. So, we would be moving into both areas, not just into schizoaffective. We'd be moving into suicidality in garden-variety schizophrenics as opposed to treatment-resistant. So, it's really two new populations.

DR. MALONE: And this is apart from whether there is evidence to say that it actually does treat suicidality? But apart from that, I don't really see any big problem with including schizoaffective if they were part of the study population. If you think it worked in the study population, I don't think you would take schizoaffective out of the study population.

DR. OREN: Do you think it worked in the group?

DR. MALONE: Well, see, the way the study

was designed, you just have two active comparatives, and I'm still not convinced that just having the two active comparatives shows that the one drug, just because it looks better than the other, is shown to be an effective treatment for suicidality. So, that's why I say if you assume that, I wouldn't have a problem with including schizoaffective.

DR. OREN: We're talking prevention rather than treatment.

DR. KATZ: Yeah. You know, in some sense, we're doing this backwards because we're trying to figure out in which population the finding has occurred, when we haven't really signed off on the fact that there's a finding in the first place. So, I think part of this we can do sort of backwards. We're trying to figure out who the patients were, that sort of thing, I think you can do that independent of what the results were actually, to some extent, so I think it's probably okay. But I don't think we've yet fully discussed the question about whether or not, with all the potential problems -- blinding and everything else -- the study is really a bona fide positive study.

So, I think if we could just figure out which patients a particular claim would include,

before we figure out whether the claim is valid yet, is doable. I don't think we're yet at the question of does it work.

DR. OREN: Dr. Laughren.

DR. LAUGHREN: Let me try and clarify what I think two separate concerns of the committee are. One is when you look at the data for the schizophrenic patients as opposed the schizoaffective patients, you see a somewhat different effect size. This is a common subgroup problem that we deal with all the time. So, I think that's one issue, is how you evaluate those data.

But a separate issue the one that Matt brought up, and that is the question of whether or not, in thinking about schizoaffective, the patients in this particular trial were accurately diagnosed. There seems to be an acceptance of the current criteria for schizoaffective illness, the question that seems to be on the table is whether or not, in this particular study, they were accurately captured.

DR. OREN: Dr. Wang.

DR. WANG: I think in terms of clozapine looking like it's effective in the schizoaffective population -- I mean, the point estimate looks like it's trying to be, and it's probably under-powered.

I think my concern would be since we're not seeing data on its treatment of psychosis in that population, maybe some kind of sub-analysis just to show that PANSS scores weren't horrible specifically the schizoaffective population.

If the treatment of psychosis was basically the same as it was in the schizophrenia population, that would reassure me because that speaks to this expansion of use not only to treat suicidality, but also psychosis in schizoaffective population.

DR. OREN: Does Novartis have any data on that specific question?

DR. ZANINELLI: Not at the moment, no.

DR. OREN: Okay. Dr. Ortiz.

DR. ORTIZ: Do you want us to check in on this? I think Dr. Laughren brought up what my main concern is, that there were not consistent criteria used for the diagnosis of schizoaffective disorder, and on top of that we have international confusion as to what schizoaffective disorder is. So, therefore, I would not be in support of the schizoaffective label.

DR. OREN: Ms. Bronstein.

MS. BRONSTEIN: I'm going to pass on this.

I see it as a diagnostic question, and I don't feel qualified.

DR. OREN: Dr. Ryan.

DR. RYAN: Sure, I'm near equipoise, but not at it on balance. I'd suggest not including the schizoaffective labeling because of the issues that Dr. Rudorfer brought up and that Dr. Laughren elucidated, that it's substantially likely that a number of those were schizophrenia, and there may have been a very small number of schizoaffective people that it was tested in, making it just hard to get a separate estimate.

DR. OREN: Dr. Rudorfer.

DR. RUDORFER: Well, I'd just like to emphasize one additional point -- that is, it is very possible, as I understand the current evidence, that a subtype of schizoaffective disorder is closer to mood disorder, specifically to bipolar disorder.

Clozaril may or may not have the same effect there as in the subtype of schizoaffective disorder, it's more like schizophrenia. My overall concern is that we simply don't know because we don't have those data, we don't have the subtype analysis.

And if I could add one other caveat, throughout we've made references to the fact that

suicidality often is, in fact, a component of mood disorder. We heard that we don't have data on whether people had, say, frank depressive episodes in the context of this two-year study, but people were being treated with concurrent medications along the way, so I have a lot of trouble still teasing out a lot of pieces of this puzzle. For instance, could a person that developed a secondary depression along the way, maybe with suicidality as part of that, and they are treated with -- even the Clozaril people, we were told, were often treated with other medications -- and they are treated with something else for that secondary mood disorder, the suicidality improves and they go on and, for all we know, the Clozaril or the Zyprexa had nothing to do with change in the suicidality status. I think there are simply too many variables at play.

DR. OREN: Dr. Winoker.

DR. WINOKER: We were told this morning, if I recall, that the diagnoses were made using DSM4 criteria, and I think the main problem that has us hung up now is the lack of use of structured clinical interview as a basis to obtain data to apply diagnosis.

I don't know whether the sponsor has any

additional comments that they'd be in a position to make in terms of the extent to which the fidelity of diagnoses based on the quality of clinical information was obtained, that baseline evaluations would support the diagnoses.

If we could feel confident based on understanding the relationship between the information from baseline clinical evaluation and the assessment of diagnostic interview, we might be more comfortable coming to the kind of position that you're asking for.

DR. OREN: Dr. Krishnan, do you want to address this point?

DR. KRISHNAN: Yes, just very briefly. I think Matt's point is could this be bipolar disorder. If it was, then we clearly would have missed it if we had not read through every chart that we had seen. Of the 400-some patients, 577 events, we saw the charts. We reviewed those charts. They are not bipolar disorder.

There's another piece of evidence which I think points it out. Look at the AA experience. If it's a bipolar population, would you not expect hypomania (phonetic). That was not an event profile that came up.

So, this, from my opinion, is not bipolar

disorder. Whether it's schizophrenia and how much you extend it to schizoaffective is another question that I can't answer, but it's not that. If you look at the mood event rate, the depression event rate is different, but not mania, no hypomania. So even if you take this through 8 mood disorder patients, that doesn't again suggest that the majority of this population, or even a significant proportion of this population, is bipolar disorder. I hope that helps. Thank you.

DR. RYAN: Were they schizoaffective, though, when you reviewed them?

DR. KRISHNAN: In the broad category, yes, mostly schizoaffective depressed. I don't recall except one or two where there was any schizoaffective mania features in it. When you read through the case histories, remember, even if it is not a diagnostic interview -- and I actually think in long-term patients, case histories are more important. In many ways, the psychotic patient coming in trying to get a SCHD interview is not the most reliable thing. What is often more reliable is if you have the full background information to take a look at, and I think that's what we had in this case. Thank you.

DR. OREN: Dr. Meltzer.

DR. MELTZER: I happen to have the DSM criteria for schizoaffective disorder on my laptop, from a lecture I gave about six months ago, looking at the relationship between the three disorders, and I'll spare you the lecture, unless you want to know my bottom line on it, but it's very interesting to look at the criteria as they really are written.

Lead criteria, as Matt said, they have to meet criteria for major depression, mania, or mixed-episode concurrent with the Class A criteria for schizophrenia, namely, delusions, prominent hallucinations, incoherence, and catatonic behavior.

Now, the next one is the kicker. The next one says, "Delusions or hallucinations for two weeks, without prominent mood symptoms". And this is what nobody pays attention to. So, I'd be very surprised if that were in the thinking that led to the clinical diagnoses.

What is prominent is the next criterion -- "Mood symptoms prominent for substantial period of time psychosis is present". That is what the clinician operations on. That is the operational definition for him. When they see the Criteria A for schizophrenia and mood symptoms are prominent, they call them schizoaffective. And because of the link

that I showed you between depression ratings and suicidality, a lot of the very people that are going to have the kind of histories that went into this are going to be diagnosed by the community psychiatrist -- not your GPs -- as schizoaffective, and I think you need to take that into consideration when you make your final decision. I mean, I'd have to say it's probably true that, according to DSM4 criteria, that independent period of psychosis with no mood symptoms, we can't really say that there was that prominent a group of DSM4 schizoaffectives.

What the world, on an operational basis, calls schizoaffective disorder, they were studied, and they showed a differential effect of the two drugs.

DR. OREN: Dr. Winoker, do you want to add anything else?

DR. WINOKER: Those were helpful, but I'm not sure I got an exact response to my question, which was, in the absence of using a structured clinical interview, were other steps taken to verify the diagnosis, for example, by reviewing the initial clinical history and seeing that there was an appropriate support for the diagnosis through the specific intake history that was obtained.

DR. COX: There was a diagnostic worksheet

which was basically a checklist straight out of DSM that they had to check off, but there was not formal interview, but they did have to check off and the PI had to sign off on the diagnosis using the checklist, and it was basically just DSM4 criteria.

DR. WINOKER: So the checklist was geared to identifying the presence of symptoms that led them to establishing the diagnosis?

DR. COX: That's correct.

DR. OREN: Dr. Hamer.

DR. HAMER: The lack of a structured clinical interview doesn't bother me very much. Rarely have I seen my colleagues use structured clinical interviews in their ordinary day-to-day clinical practice. So, the people who are going to be using this medication in their patients won't, by and large, be making diagnoses with structured clinical interviews.

Except for my continued discomfort with the blinding issue, I'm comfortable in the claim for the schizophrenia and schizoaffective disorder for suicidality, generally.

DR. OREN: I'm curious whether your discomfort is outweighed by your support for the claim, or not?

DR. HAMER: You know, I don't know. I honestly believe -- and I've come to this belief during the course of this meeting as opposed to based on the material in the briefing books that I red beforehand.

I've increasingly come to believe that it would have been possible to have designed this as a virtually double-blind trial where the only people who were unblinded was the psychiatrist who actually prescribed the medication, that some psychiatrist had to know what the medication was the patient was on, and the technician in the lab who either stuck or didn't stick the patient with the needle, that everyone else in the entire study could have been blinded, the patient goes into the lab, either gets stuck or doesn't get stuck, and then the patient just has to get told "Tell your doctor whether you got stuck or not".

So, the fact that this wasn't designed this way weakens the strength of the evidence, although it's hard to see how it could have introduced the systematic bias, but then again we usually like blinding whether we can see how lack of it would introduce a systematic bias anyway. So, that's my discomfort.

My discomfort is more based on the regret that this study was not designed in a much more blinded manner.

DR. OREN: Dr. Wang, do you want to comment?

DR. WANG: Yes, just on the schizoaffective issue. Again, it would be nice if there were some reassuring data just either from InterSePT or another RCT, just to suggest that clozapine is effective for psychosis in schizoaffective disorder because the last thing you want to be doing is treating someone's suicidality and then potentially give them an ineffective antipsychotic. If there is that data -- and maybe there is -- then I would feel comfortable expanding the indication to also then include suicidality.

DR. MELTZER: There are those data, published data, from a paper by Joe Calabrese and myself, of treatment-resistant bipolar disorder and schizoaffective disorder, structured interviews, DSM3 or 4 criteria -- I'm not quite sure, probably 4 -- and the drug is more effective in bipolar disorder -- strikingly effective in these treatment-resistant disorders -- but it was also effective in the schizoaffective disorders. That's in treatment-

resistant schizoaffective, and I've analyzed my own data on schizoaffective versus schizophrenia, and in that population the effect on psychosis and mood symptoms is greater in schizoaffective disorder than schizophrenia. That's also published.

DR. OREN: Dr. Cook.

DR. COOK: I also have concerns about the blinding, but on the question of schizophrenia or schizoaffective, I'm very much in the middle, slightly to it's okay. It's almost as much an abstention as anything.

DR. OREN: Personally, I think the schizoaffective disorder is a second level of leaping. I think claims need to mean something, and certainly I think it's much stronger, the claim focusing on suicidality in schizophrenia, and I would be quite comfortable with that claim. To go beyond it, I'm glad it's on somebody else's shoulders to make that additional decision.

Let's move on. On the subject of leaping, as has been brought up, one aspect of this is expansion of the Clozaril beyond treatment-resistant schizophrenia, specifically to schizophrenia in general, and perhaps beyond that. How do -- do people want to offer any comments just in general on the

expansion of the claim? Dr. Wang?

DR. WANG: It seems like there's two ways you could expand it. One is to expand it to all patients who are at high-risk of suicidality, regardless of whether they're treatment-resistant or not. And then a second way to expand it is just to patients who are treatment-sensitive, whether or not they're at high risk for suicide. I mean, there are two sort of separate ways to expand it. The first depends on what the --

DR. RYAN: My apologies. I didn't understand the second point at all.

DR. WANG: You could also expand it just to treatment-sensitive patients, capture everybody. In other words, not designate necessarily for high risk. And there's a reason why I'm bringing this up. The first one, if you remember what I said, it seems supported by at least the back-of-the-envelop calculation that Dr. Kane showed where if you sort of weigh the risks and the benefits of potentially expanding into this high-risk population of treatment-sensitive and treatment-resistant, it looks like it's in favor, maybe an order of magnitude in favor, of clozapine. In other words, the risks that you add for agranulocytosis are relatively minimal, and same for

cardiomyopathy.

The second question is much trickier. It's not an obvious win for the sponsor. It would take a decision analysis of some sort. The reason why I'm raising this is because it's hard to identify patients at high risk for suicidality. And so in the real world, the real practicing clinician, it's going to be a mixture of the two. They will not necessarily be able to identify their patients who are at high risk for suicide both because there are very few predictors -- even from the InterSePT study, there are only two significant ones -- and the relationship is so weak -- again, from the InterSePT trial, the point estimates for the other co-variates -- even for prior attempts, it was about a 3 percent increase per attempt. So, in reality, the clinician in the real world will end up having to apply clozapine to a larger than just high-risk population. So, that's why I'm raising these two potential scenarios as ways to expand the indication. I hope I didn't lose everyone there.

DR. OREN: Dr. Ryan.

DR. RYAN: I'll try. I think I understand what you're saying, but I'm not sure, so let me go through it again and see if I can repeat it, or at

least explain my confusion.

You could, in theory, say apply the algorithm that was applied in this study to select your patients. Given that, you prevent somebody's suicide attempt on an 87 per 1,000, by treating with the Clozaril rather than a different compound -- and we'll talk later which different compounds.

Obviously, you could say that one could neither apply that reliably, or people will generalize too much and sprinkle it higgely-piggely on people, but it seems like they gave a number in here which is fair enough -- you know, it's your best estimate so far, 87 per 1,000 people that you treat with Clozaril rather than something else, but prevent one or moire suicide attempts, and they gave some dollar value to be imputed value of preventing a suicide attempt.

DR. WANG: Just to clarify, in this material, the question that was put to us is could you expand the indication to treatment-sensitive and treatment-resistant patients who are at high risk for suicide, and that's what I was calling point one, the scenario one. And to answer that question exactly as Dr. Kane did, you weigh the risks versus the benefits. And at least if you do that back-of-the-envelop calculation, which didn't take into account

potentially greater efficacy of clozapine, that sort of thing, it looks like a pretty clear win for clozapine.

I'm just saying there's another way in which the indication might, in the real world, de facto, get expanded, and that is you may not be able to target patients who are at high risk for suicide, you may end up having it be given to a broader population that is essentially a treatment-sensitive and treatment-resistant population maybe not necessarily at high risk for suicide.

DR. COOK: In your logic, the one thing that -- I wasn't worried about the second -- is the fact that there's not a correlation -- there aren't predictors -- may have been because they were good at selecting the specific groups. They didn't study the larger group you're talking about, and I think it would be important in labeling to make that clear, what the trial was about. It wasn't the overall population -- that's your concern -- is to highlight for people that this was a selected group of patients.

DR. OREN: Dr. Katz.

DR. KATZ: We asked the question in a certain way, but I think it is fair to ask whether or not the claim that we are contemplating is in any

sense practical. We can always fashion a claim that conforms point-by-point to the study that was done, but if it turns out that that's clinically meaningless or misleading or along those lines, we'd like to hear it. I don't know if people think it is, but that would be an important thing for people to talk about.

DR. OREN: Dr. Winoker.

DR. WINOKER: This study was conducted with a majority of patients who were viewed as -- who were entered because of suicidal behavior that got them in, the majority of whom were not treatment-refractory, so the data that we're looking at was based to a large extent on people that from a clinical perspective showed suicidal behavior at risk, but didn't fit into the treatment-refractory subset. If, at the end of the day, we end up as a group feeling convinced by the data for differential significant beneficial effects for Clozaril for suicidal behavior potential in this population, I think that logically extends the indication beyond the treatment-refractory group because we don't currently have specific treatments to recommend, and we have apparently a situation where a comparative antipsychotic drug that was effective in general for symptoms of psychosis showed less beneficial effects for suicidal behavior

specifically.

DR. OREN: Dr. Katz, could you clarify what kind of a label or what kind of a claim might be made that would be impractical?

DR. KATZ: Well, for example, we defined -- the protocol defined treatment, you know, high risk for suicide in a certain operational way, and these patients presumably met those criteria. But if it turns out, as Dr. Wang points out, that that's a diagnosis that, for all intents and purposes, can't be made practically on a clinical basis by the average practicing psychiatrist, that would put us in a tough spot, but we'd like to know. If that really is true, we'd like to know. I'm certainly not saying it is true, but it's been brought up, and it's not an unreasonable point to raise.

DR. MELTZER: Can I please speak to that issue because there really is enormous literature on that. I've reviewed it a number of times, contributed to it, and it's really in high agreement, enormous agreement, the risk factors for suicide and schizophrenia. And the proof of it is that how many events we had in this study. We used those criteria to design this study, and the No. 1 criteria is having made a previous suicide attempt. That probably

accounts for 50 percent of the variants.

Then you get into substance abuse -- male, first decade of illness, family history of suicide, depression, hopelessness -- what isn't a predictor is control of positive symptoms, which is why the other extension that you postulated would not be in the patient's best interest at all.

So, is it possible for the average clinician? Absolutely, to determine who is at high risk. Now, can they miss a lot of people? Absolutely, the people who -- and a good example is, in fact, what happens in the FDA database where low risk of suicide is supposedly one of the criteria for entry into the study, yet in the literature that was reviewed by the FDA and by Kahn, the rate of suicide in that group was no less than what is average for the population. So, you can't very well rule out or identify the low-risk patient, but you can certainly identify the high-risk patient, which is what the basis of the claim is.

DR. OREN: Dr. Malone.

DR. MALONE: You know, I think if you look at the number of patients screened for the study overall versus the number enrolled, a very high percent -- 80 or 90 percent of the people screened

were enrolled in the study -- so I guess when you're screening, you're trying to rule out people who don't meet your protocol. So, if that high of a rate of screening to enroll occurred, I would think a similar rate would look -- you would see a similar rate when you had a commission that's trying to judge whether this patient indeed meets criteria for anything you write, especially if you're writing something about at high risk for suicide.

DR. OREN: Dr. Laughren.

DR. LAUGHREN: I think the company can probably speak to that. The question is what was the source of patients referred for screening. I'm assuming it was not just a random sample of the population of patients.

DR. KANE: I would make two points. The fact that the screening rate was so high means that the subject were prescreened, and clearly there are such patients out there, which is one of the things we've been emphasizing, and the sites were able to identify them reasonably well. But these were not just random patients taken from clinics or hospitals, these are patients who were identified as potentially eligible for the study by the clinicians who knew them.

DR. ZANINELLI: Just to emphasize that point, remember that the design phase before the study start was about a year, and potential sites were lining up patients for the study start. So these were preselected, as Dr. Kane said.

DR. OREN: Dr. Malone.

DR. MALONE: Just a comment. When we do a study in aggression, we prescreen everybody for them to come in because we don't want to go through a whole interview. And only people in the study are prescreening, yet our enrollment rate based on just them meeting the criteria for the study still falls around 50 percent after a first screening that we've done before we bring them in for more detailed screening.

DR. KANE: John Kane, Zucker Hillside Hospital. You have to keep in mind that this was events that in many ways affected this trial. We took patients who were substance abusers. We took patients who had co-morbid conditions. We took patients who required concomitant medication. The average clinical trial is much more exclusive and, in fact, excludes people with risk of suicide. So, I think that, coupled with the fact that, as Dr. Zaninelli said, there was a lot of advanced warning, people were eager

to participate with the anxiety that I mentioned, but they certainly felt that this was an important opportunity, and they had many patients that they felt would be eligible.

DR. OREN: Dr. Malone.

DR. MALONE: Just to followup, usually when we're excluding people out, it's only because they don't meet symptom criteria, not because they have other exclusionary diagnoses. So, usually they, on the phone, seem to meet a certain criteria for aggression to get in the study, but when you bring them in, it's really the aggression criteria they don't meet -- the specific symptoms, not that they're excluded for other reasons.

DR. OREN: Do you have a direct answer --

DR. COX: I don't have a direct answer to that question, but I just wanted to add, one of the reasons that the enrollment rate was so high is that we responded with a randomization number within 30 minutes of the site's request because we considered these patients to be in a critical state, or potentially. So, there was only a 30-minute time period. So these patients were generally screened and randomized in a very short period of time. So there wasn't a lot of time for patients to change their

mind.

DR. OREN: Other comments from the Panel specifically on expansion beyond the claim for treatment-resistant schizophrenia? Dr. Laughren.

DR. LAUGHREN: Can I raise sort of a related question to expansion of the claim? My question has to do with once a patient is designated as a high-risk patient -- perhaps a treatment-sensitive patient, but a high-risk patient for suicide -- how long does that status prevail? My question is, supposing you have such a patient, you treat them with Clozaril, they are improved, they are stable for some number of years. Do they stay on Clozaril forever, or is there some point at which -- again, this is a patient who is not treatment-resistant, they are just high-risk -- is there some point at which they revert to a non-high risk status and can go back on something else, or once that decision is made are they on Clozaril for life?

DR. MELTZER: That's a terrific question, and there are no hard data to answer it. I can give you a number of anecdotes that the answer for some people is for life. I have seen people have a phenomenal response to Clozaril in terms of people with multiple suicide attempts, and go into long

periods of remission that no one ever expected they would on Clozaril. Clozaril is stopped for one reason or another, and the suicidality comes right back.

Now, I can also imagine -- and that's anecdotal data, but I can share them wiht you if you want -- but I can also imagine that there are certain constructs here that are relevant, like the issue of hopelessness which stems from social and work function -- that is, people really work out some of the fundamental problems they've had. And we heard from the NAMI person who spoke, there really are a number of major recoveries, that as people recover, some of them, the urge to take their lives might diminish sufficiently, they could be transferred to some other medication. But those are going to be some real problems out there. There's no real simple answer. So, it might well be -- I mean, I'm speaking now as a clinician, I would be very loathe to take somebody of the kind that I just mentioned to you, with recurrent suicidality, got on clozapine, did well, and never recommended they stop it because there was something else that seemed to appeal to them for some other reason.

DR. KANE: John Kane, Zucker Hillside Hospital. If I could add to that, the database that's

most informative in that regard is the Walker database, where the three groups that were examined included patients who had been on clozapine and patients who came off clozapine. So, that would suggest that discontinuing clozapine in a high-risk population does increase the risk of suicidal behavior.

DR. OREN: Anything else on this?

(No response.)

Just a little bit off the top, but we've been focusing on clozapine, but the study obviously studied olanzapine, and we've been asked to make some comments on the interpretation of the InterSePT study with regard to olanzapine. I think, Dr. Malone, you made a comment about that before. I don't know if you want to say anymore.

DR. MALONE: No. I think I said that it looked like Clozaril worked better than olanzapine in the study, but I don't know that you can say anything else.

DR. OREN: Dr. Katz.

DR. KATZ: At this point, I think I would sort of argue that we ought to attack the primary question because before we start getting into how we're going to describe it in relation to olanzapine,

I think we really have to figure out whether or not we think this trial, as conducted, with the results that we've seen, can actually be considered sufficient for approval. And I think when we address that -- when you address that question, I think we also really do have to finally take on the question of whether or not a single perspective control trial meets the current criteria for approval on the basis of a single trial and what's called confirmatory evidence. There's no real -- I mean, just to give you a context for that, as Tom pointed out, in '97 the law was changed to say that that can be a standard for substantial evidence of effectiveness -- single trial and confirmatory evidence. But Congress, in its wisdom, didn't see fit to define when that standard ought to be applied, or what confirmatory evidence means.

The Agency has constructed a guidance or a document which talks about the circumstances in which a single trial and confirmatory evidence might be acceptable, and Tom pointed out some of that in his opening remarks. It's typically a case where -- although there's nothing hard and fast -- but, typically, it's a case where the study shows an effect on mortality or some irreversible morbidity and really can't be repeated on ethical grounds. Typically, such

a study would show, as Tom pointed out, internal replication across individual sites, or show, in effect, in multiple different subgroups, severe patients, mild patients, moderate patients. It might have a very low p-value, suggesting that it wasn't positive by chance alone, it was very unlikely -- more unlikely than the typical standard we ordinarily apply -- to be positive by chance alone.

So, those are sorts of the types of things that we would consider, or typically a thought that would apply in this case. So, I think the committee has to think about whether or not a single trial of this sort that we have in front of us, where there are questions about blinding, about the outcome, about the robustness of the finding -- the overall p-value is .031, I think, or .03 -- so when that's all put together, does that constitute the sort of evidence to which we can apply the one study plus confirmatory evidence standard. I'll stop there.

DR. OREN: The question is, does this one study show something -- we haven't necessarily agreed what that something is, but putting that aside, what do people think, does the study show something sufficient that the FDA can stand on in approving a claim? Dr. Malone.

DR. MALONE: As I understand it, it's one well-controlled study and, to me, if you have a lot of questions about a study, you might argue that it's not a well-controlled, or that there's some problem with it, and that you wouldn't want to go on the basis of that one study.

There is some confirmatory evidence, but I think you would still want the one study to be fairly strong, irregardless of the confirmatory evidence. I really have a lot of doubts about this study both from the blinding, the design of only having two active components, to think that it definitely shows that it has an effect on suicide, apart from showing that Clozaril is better than olanzapine for this indication.

DR. OREN: Dr. Katz.

DR. KATZ: I just want to sort of -- you seem to conclude that it shows that it's superior to olanzapine. Are your questions related to the fact that the unblinded nature of the data accrual make you question the reliability of that difference, and the fact that you're not sure whether or not Zyprexa patients -- I'm trying to understand your reasoning, it's very important to us.

DR. MALONE: I think it's everything put

together, that if you wanted to have confirmatory data and one well-controlled study, you'd want that study to be fairly definitive. And I think with questions about blinding and still in my mind with questions about not having a no-treatment group or -- I don't know how you would do that, maybe a community-control -- but without having that in the study, it's not a strong enough study to stand on its own as one single study. I'm not sure if I answered it.

DR. OREN: Dr. Ryan.

DR. RYAN: I think I come down in a somewhat different position, so let me sort of be long-winded about it. It seems like that the FDA and industry together made a plan for the study which was substantially carried out as planned, that there's a lot of decisions that went into a complex and ground-breaking study like this that one could make second-guesses on but none that I'm strongly urged to make a bad second-guess on, and certainly none of the decisions where you say, "Well, they snuck one over", and they weighed it in a way that's really going to be helpful to them. I mean, you know, the question of which blind rater to use, I would have made the decision the same way. I was personally convinced by the evidence that that was much better than a whole

bunch of separate blind psychiatrists.

The question of whether you could have really done it blind or not is an interesting question, you know, that people with more expertise in schizophrenia than I have suggested would be very hard to do blind. Perhaps we can say we do have a blind, but they seem to make a substantial argument that way.

So, I individually, separately, would say that this study was positive and done well and what they'd agreed to. And so for me, separately, the only one you're left with is the p-value that is certainly, you know, 1 chance in 33, so it's under the 1 chance in 20 that we arbitrarily say is significant, and yet not a .001 or something, not the numbing homerun that's separate, positively each separate site, and so then you're left with a very solid p-value, but not a .001. You may never be able to pat over a study so you get a .001 with a base rate on the phenomena here. And the separate question of how strong the other evidence is.

I actually would weigh on the whole enchilada of saying that the other evidence with one study, in my understanding of what you're saying, is enough, but certainly separately it seemed to be a well-designed, well carried out study where we could

make second-guesses, but not certainly ones that disturb me a bit.

DR. OREN: Dr. Cook.

DR. COOK: I realize there are problems with the Walker study, but this seemed to have been designed as a replication of a relatively solid piece of epidemiological work, so I do think the confirmatory evidence is not only there, but it preceded. And I sort of go along with what Neal is saying, essentially a shot was called. It was a reasonable shot, there was consultation with you, decision seemed reasonable, and that's the best you can do. There's clearly not a "well, the original call was negative, so we went back and found something that was positive" sort of thing.

DR. OREN: Dr. Winoker.

DR. WINOKER: I'm also of the mind to think that the previous "confirmatory" data is significant so that a study that we judge to be supportive would not be convincing here. Again, I'm mindful that this is a both very clinically important and challenging problem and a very difficult one to design and conduct a clinical trial in this era of increasing challenge, with all of the concern about protection of human subjects. I think that's just the

constantly evolving factor to address important clinical problems.

The main issue that I can see or understand -- and maybe some of our colleagues can sort of expand on this, or present some different perspectives in terms of the lack of blinding, which certainly make us all fell more comfortable -- relates to the question of under-referral of the Type 1 events in the subjects on Clozaril, and while I don't think we can have absolutely satisfactory clarification of that, I found myself reasonably persuaded that pretty legitimate efforts to investigate that and look systematically at sources of under-referral did not really support that. So I found myself being reasonably comforted or assured against the concerns about the lack of blinding and otherwise feeling persuaded that the data favoring Clozaril for suicidal behaviors, which I think are tangible and clinically meaningful events -- and, again, in the face of the overall evidence that olanzapine was producing clinically significant effects along other sort of standard criteria, plus I didn't see any evidence that that population was being undertreated, there was the question about whether they were almost on excessive adjunctive treatments, but they were certainly getting

aggressive treatment apparently to manage their clinical situation. So, I came out on the side of being persuaded by the evidence.

DR. OREN: Dr. Rudorfer.

DR. RUDORFER: I'm afraid I'm going to have to stay up the negative terrain. I was, on the whole, disappointed by this study. Aside from the blinding issue -- which, again, I think that if this were to be the single definitive trial, I think that should be a requirement. I find the concomitant medication treatment overwhelmingly troubling -- that is, we are not even able to see a subset of this population comparing the two active treatments head-to-head. We see comparisons of clozapine plus some other things versus Zyprexa plus a lot of other things, and those other things may have been beneficial, they may have been detrimental, I'm not sure we've fully resolved the dosing issue. It seemed that the clinicians in the Zyprexa group were forced to go beyond the protocol -- and I'm not sure that they all did. I mean, we saw -- we actually have the data on the patient deaths and, as I read the case reports, all of the patients in the Zyprexa group who died received no more than 20 mg a day of Zyprexa, so I'm concerned there that clinicians -- some clinicians

may have been reluctant to exceed that. And, again, the bottom line for me is that I would like to see, even in a subset of patients, a head-to-head comparison because I think that's what the study purports to be. So, I'm afraid I just don't find this evidence persuasive.

DR. OREN: Anyone else want to comment? Dr. Ortiz.

DR. ORTIZ: I guess since this is kind of a check-in, I think the way Dr. Winoker put it in terms of -- I think I am persuaded that suicidal behaviors were decreased and suicide was prevented in the study. I think I'm not as concerned about the blindedness because of the incredible co-morbidity and complicatedness of these patients, and I suppose a study could be designed that is able to do that, but I'm not sure about the safety and ethics of doing something like that.

I am still a little concerned about the implications from -- though I think Dr. Hamer has suggested that we've already got indications for symptoms in other medications, so suicidality isn't adding anything new in this -- though, for me, the concern is it's more -- it's associated with mood disorder. And then the treatment-resistance, I guess

that doesn't bother me as much as schizoaffective, which I'm still not convinced is well substantiated. But I guess just the question of suicidality in this particular population or this study, for me, the data is persuasive.

DR. OREN: On the specific subject of is a single randomized trial good enough, I keep getting pulled in each direction. One of the points I'm still wrestling with -- I don't know if the company has any thoughts on it -- the baseline level of suicide attempts or suicidality in the Clozaril group was higher than in the Zyprexa group -- I think it was about 3.7 incidence in each of those categories for the Clozaril group, and about 3.2 in the Zyprexa group. Could any of what we are seeing with the relative efficacy of Clozaril be a regression to the mean? If there were two studies up, I wouldn't be asking that question.

DR. RYAN: I was just mumbling that they didn't include that in the thing, so wouldn't that work against them rather than for them?

DR. OREN: If they were a sicker group, it would work against them. If just by the way time captured they, they were a totally equivalent group, that might work to their advantage.

DR. RYAN: How?

DR. OREN: By virtue that at the end of the study there would be a greater likelihood that all would have had a similar total number. If both drugs had no effect by the end of the study period, it's possible that the levels would have been the same in both groups, even if statistically one happened to be higher than the other at the beginning. Dr. Zaninelli.

DR. ZANINELLI: Just to remind the committee, this was a time-to-event, not a change-from-baseline analysis, so regression to the mean I don't think would apply here.

Also, looking at the difference in the mean number of lifetime suicides, lifetime hospitalizations to prevent suicide was at baseline. There wasn't statistical difference.

While I'm up here, I'd also like to address Dr. Wang's question regarding the psychopathology of the schizoaffective and schizophrenic subgroups. We've done the analysis in the mean time. Do we have a slide right now? That was quick.

(Slide)

We've shown in the overview slide

regarding the total score on the PANSS, it was about 85 overall. Actually, in the schizoaffective group it was about 81, in the schizophrenic closer to 85. The mean change from baseline was 20 and 21 points for schizoaffective disorder and Clozaril and Zyprexa, respectively, and 20 to 21 points in the schizophrenic group. So about the same baseline PANSS score in schizoaffective and schizophrenic patients, and pretty much the same change from baseline at endpoint. And that difference isn't statistically significant, less than .001.

Showing a comparable efficacy with respect to changes in psychopathology, as introduced by the PANSS.

(Slide)

Okay. Repeating what I said. Again, these are schizophrenic and schizoaffective patients in each subgroup -- schizophrenic patients, mean baseline PANSS total score, a little bit higher in the schizophrenic group, but the change from baseline around 20 in all four subgroups -- again, highly significantly different from baseline.

DR. OREN: Dr. Katz.

DR. KATZ: I would just say that it's an active control trial that doesn't show a difference

between treatments, it's hard to interpret that. I don't know if it's a critical point here, but I don't know what to make of it.

DR. OREN: So, again, is one study, or is this one study good enough to show what we need to show. Dr. Hamer?

DR. HAMER: I'm curious, does the sponsor have any other clinical trials of suicidality underway?

DR. ZANINELLI: No.

DR. OREN: Dr. Hamer, could I ask you to comment on whether the single trial you think would be adequate to support some kind of a claim?

DR. HAMER: I'm going to equivocate. If this were a blinded trial, I'd be really happy with it.

DR. OREN: Dr. Wang, do you want to comment on this?

DR. WANG: It puts a lot of pressure to make sure that the -- particularly the EPI -- the ERI study is methodologically rigorous, which it has its limits. And the overall much larger effect in the observational study suggests that there is some bias to it, but how much of it is potentially bias and how much of it is real effect is hard to say.

DR. OREN: Dr. Katz.

DR. KATZ: Do you want to take a view on whether or not the dataset, as it is, supports approval with the one study and confirmatory evidence standard?

DR. WANG: Okay, I'll take a stand. Given it's an epidemiologic study -- I'm talking about the ERI study now, and just focusing on, okay, you have one trial, you also have some observational EPI data, how good is that EPI data, and its okay, it has its limits. So I'll say as far as using non-RCD data, it's got its problems, but it's about probably the best you're going to do.

DR. KATZ: But that's only half the standard, that's the confirmatory evidence standard. The other part of the standard is whether or not the one trial that we have is robust enough to, in conjunction with the EPI study, make an approvable package.

DR. WANG: To some extent, the implications -- I'll give you an answer. To some extent, the question is -- we're being asked should the indication be enlarged because that will hinge on what our answer is to this. And in a sense, we're being asked to do a quick decision analysis in our

head and say, okay, what happens if this -- I mean, it's a much larger question.

I ultimately, doing my quick one in my head -- you know, quick decision analysis -- think that even if InterSePT is wrong, and let's say it's completely biased and this benefit we're seeing is just way off the mark and there's no benefit at all. I've been swayed by the kind of comments that Dr. Goldman was saying earlier, that in the face of a whole bunch of decreasing risks, potentially greater benefits such as the MED analysis, even if we're completely wrong, the expansion may not be that awful a thing. So, ultimately, I'm a little bit less perturbed by whether there's a chance that this is biased, a little bit less than I would be in another situation. So, it meets my standard, if that's --

DR. KATZ: I guess the question is whether it meets our standard.

(Laughter.)

Let me try and parse it out because it really is important for us to understand the thinking of all the committee members. Forget the standard, the one study plus confirmatory -- just put that -- let's not talk about that, but let's just talk about the study, the InterSePT study, and whether or not you

think it's a robustly positive study, with all its warts. Let me just ask you that simple -- well, it's not a simple question -- but that single question.

DR. WANG: It's not robustly positive, for all the reasons we've been talking about, but it is -- it's robust in the sense that there's so little -- if it's real, if it's not completely explainable by bias, then this is robust because there's so little to actually treat suicidality, and the effect size was actually impressive, you know, when you do the calculation. I saw your calculation. It's actually very impressive from a public health point of view. So, it has warts. It isn't maybe robust, in my typical use of the word robust, but maybe it's robust enough.

DR. OREN: Dr. Hamer.

DR. HAMER: I want to rephrase my vote. Assuming that the blinding issue does not bother the FDA, then I think this study had an impressive effect size, and I think the cumulative weight of the epidemiological studies that are out there paired with this are persuasive.

DR. KATZ: We're not going to get you to say whether or not the blinding upsets you very much, are we?

DR. HAMER: No, not at all.

(Laughter.)

DR. OREN: Jean Bronstein, you haven't commented recently.

MS. BRONSTEIN: I don't feel statistically up to the group here, but I really do think that the study has offered us something for this population that we really need to consider, and it may not be perfect, but I think my vote goes to offering this for the psychotic population.

DR. OREN: Has everyone addressed this specific question? Dr. Cook, did you?

DR. ORTIZ: Yes, I did.

DR. OREN: Okay. I think since the drug is already out on the market, the questions that arise are different perhaps than introducing something entirely new to the market. In that context, I think a single trial like this is good enough to support a claim focusing on suicidality, at least the schizophrenia. Do you want us to talk about --

DR. KATZ: I'm just wondering why the fact that it's already available affects your decision about what the standard ought to be.

DR. OREN: Well, I think relying on a single study puts a lot of eggs in one basket. I

think the fundamental question is when a drug is available, clinicians can use it in an off-label basis and will feel free to do so if the data is out there. And I think the -- from that perspective, the amount of data that the study provides to perhaps guide clinicians in using this for this indication would be useful to them, and I think it would be reasonable to have official imprimatur behind.

DR. LAUGHREN: Let me just comment that I see this situation as quite different than the usual situation where we borrow evidence from other data for a drug. For example, if we have acute efficacy data for an antipsychotic drug, we might be willing to rely on one trial for long-term efficacy. But I see this as a distinct claim. In fact, the evidence shows that there's a separation between the antipsychotic effect and the effect on suicidality.

DR. OREN: I think at least in terms of -- and this gets into specific wording -- but if for the claim of emergent suicidal ideation or emergent suicidality, that is something different than -- and this goes back to your question -- than lifelong treatment with that. I think this is an important clinical area where there isn't a good armamentarian to use, and therefore that increases the potential

urgency for considering this indication.

DR. LAUGHREN: I just want to make sure that what I'm hearing from -- when you say yes, you're basing your decision on the evidence in hand, what we have in front of us, the single study and whatever confirmatory evidence we have in hand to support this new claim.

DR. OREN: Do you want us to address specific language kind of questions now, or do you want us to turn to olanzapine?

DR. LAUGHREN: Why don't we talk about the olanzapine issue and how it should be thought of relative to olanzapine.

DR. OREN: Dr. Cook.

DR. COOK: Well, it seems to me there was a concerted deliberation about choosing a reasonable active comparator, and so I don't think you can make a statement about olanzapine. It could just as easily have been Resperidon (phonetic). The logic for choosing this one doesn't seem to be a reason to make -- I mean, obviously there's always a concern when you're comparing two things, one might have gotten worse, but all the evidence here suggests that clozapine was better, not that olanzapine is worse.

DR. OREN: Dr. Winoker.

DR. WINOKER: I'm not sure of your exact question, but something that was sent to us sort of posed three answers making specific reference to olanzapine, sort of extrapolating to all other atypicals, or just making a comment against standard treatment, and I would very much favor the third of those options. I think it's clearly problematic to try to extend from olanzapine to the whole broad category since, as Dr. Meltzer's comment, we're not sure of the subtle pharmacological differences that might play into this. So, to me, that would be the most appropriate.

DR. LAUGHREN: This relates very directly to the precise language we would use in describing both the trial and the claim in labeling, and the choices open to us are to -- in some cases, we've done this -- is to simply state that clozapine was superior to a standard drug. We wouldn't even have to mention the drug, even though many people would know what the drug was, and the claim itself would not need to say anything at all about a comparison, it would simply state that it has this benefit. So, that clearly is an option.

DR. WINOKER: And that's one that I would favor for the reasons I mentioned.

DR. OREN: Dr. Mehta.

DR. MEHTA: When you describe the study, I don't know how you're going to do it without putting the side-effect data, without putting the control agent name.

DR. LAUGHREN: Well, it will be a challenge for us, but it's something we've done in other settings. We have managed to describe comparisons without naming the comparator.

DR. OREN: Dr. Katz.

DR. KATZ: The question, I think, is whether or not the study, as conducted, truly demonstrates superiority to the comparator, in this case olanzapine. That's a difficult -- in general, in comparative studies, it's a difficult conclusion to draw largely because you have to worry about whether or not you really had a fair comparison to the comparator. In this study, you can think of it in worse case -- unless it made the patients worse -- but, barring that, you can think of it sort of as a placebo, and so you can conclude that the drug had an effect, but it's difficult typically in these sorts of studies to say that it was truly -- you know for a fact that it was better than the comparator, again, because the question of what's a fair comparison in

terms of dose of the comparator, and that sort of thing, is a complex issue. So, as Tom says, we have in the past not identified active controls in other settings.

DR. OREN: Ms. Bronstein.

MS. BRONSTEIN: I don't know whether this is valid, but it was interesting to me to note that the number of other drugs used with Zyprexa were much higher, and in managing patients that's more difficult. So, that impressed me that the Zyprexa was a more difficult drug to manage for this patient population.

DR. OREN: Dr. Wang.

DR. WANG: Another reason to think about not naming the comparator is -- I mean, in addition to just -- maybe there's a little bit making less of a definitive statement based on data that we might still harbor a little bit of doubt about. Another reason is just thinking about down the line for the practitioner who has a patient who is on olanzapine, who suicides or something. Does this box them in? Are they in legal difficulty because the clinician didn't have the patient on a regimen for high risk? If you name that comparator, you might get the physician in trouble.

DR. KATZ: I don't know if that's really

a consideration that we ordinarily think about here. Again, we generally decide whether or not the data support a particular claim, and if they do, they get that claim. If we think it's misleading to conclude that the investigational drug was better than the control, we won't put that, again, for reasons of interpretation of the trial, not so much because somebody might get into trouble if they do this or that.

DR. OREN: The most conservative thing to say is just that it's better than nothing. It treats --

DR. KATZ: As Tom points out, that's an option, not so much to say it's better than nothing, but just to say it's effective. I mean, that's typically how we decide whether something is effective.

DR. OREN: Dr. Ryan.

DR. RYAN: In all the evidence so far, we have no available data that suggests there's differential antisuicide over suicide-promoting, I guess, effects of the different atypicals and, indeed, no evidence that there's differential effects of the atypicals and the classic antipsychotics, right? So, given that, we simply think this was an exemplar of

the whole class, and that's the reason for not mentioning it? Because everything that was presented here -- and I'm not an expert in this area -- there's no evidence that one is better than another excepting clozapine.

DR. KATZ: Again, one option is that you would just -- since only olanzapine was studied, one option is to say Clozaril is better than olanzapine in preventing suicide. I mean, that's one reasonable option. That's ostensibly what was shown in the study. But what I'm saying is that we may be reluctant to do that because we're not sure that olanzapine was used -- besides the fact that it's unblinded and who knows how patients were actually dosed and what the motivation for dosing with a given drug was, given that the investigators had new-treatment assignment -- we don't know that it was a strictly fair comparison to olanzapine. So, that would be the reason for not mentioning it.

DR. RYAN: I was trying to agree with you, it's just that I gave such a long answer it was hard to know that I was agreeing.

(Laughter.)

But, in addition, it might be misleading to the practitioner to emphasize that one single

compound rather than the fact that this is probably better than a lot of them, or something.

DR. OREN: Dr. Katz, in your comment, you said that one is better than the other in preventing suicide. In fact, the data from the study did not show that, and I think that's why the language that is used here is critical to whatever we'd vote on in the end.

Anything else on the olanzapine question?

(No response.)

Do you want us to address the adequacy of suicidality outcome? Probably that's a key thing because that would be part of the language.

DR. KATZ: I think we've discussed that. I think most people have voted that this was -- the package is sufficient for approval, so I think that's covered.

DR. OREN: Do you want anything further?

DR. KATZ: I don't think so, other than to say thanks very much, it's obviously a very challenging issue, a lot of subtleties, and I appreciate very much your work on this.

Let me also just mention that this is Sandy Titus' last meeting as the Executive Secretary for this and for the PCNS Advisory Committee. She's

moving on to other things. She's done a tremendous amount of work for a number of years working with us, and we'll miss her, and thank you very much. Thanks for everything you've done.

(Applause.)

DR. OREN: This meeting is adjourned.

(Whereupon, at 3:15 p.m., the meeting of the Psychopharmacological Drugs Advisory Committee was concluded.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Psychopharmacological Drugs Advisory Committee Meeting

Before: FDA-CDER

Date: November 4, 2002

Place: Gaithersburg, Maryland

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.