other would change a great deal.

So you know, at best, we can look at those and have some kind of a gestalt interpretation, but I'm not sure what also to make of 42 confidence intervals.

DR. TAMMINGA: From a statistician's point of view, do you want to comment on Dr. Califf's observation that perhaps the new antipsychotics look more like each other than not?

DR. HAMER: No.

(Laughter.)

DR. CALIFF: Could we ask Dr. Moss' opinion? He's probably looked at as much of this data as anyone.

DR. MOSS: Well, I think that you're dealing with such a small sample size on this study, there's 30 patients with some drop-outs or 33 patients with some drop-outs, and the problem of multiplicity further compounds it.

So I think you could come to any conclusion you want, that they look similar, they look different, because of the very small sample size.

What strikes me is that the magnitude of the QT interval change of 20 milliseconds in 30 patients or 33 patients is quite considerable as just a baseline value, and that was the peak effect from this study, and that's just more than one ordinarily sees with drugs that are given in this manner.

So in the order of the hierarchy, we saw that this came in second in terms of QT prolongation. To draw any significant conclusion from the difference is impossible because of the sample size and the range of the confidence intervals, and with a larger sample size, the confidence intervals would shrink, and you might be able to make some statement, but I don't think you can claim that there's an overlap of these drugs because of the limited number of patients that have been studied.

When I have a chance, I'd like to address the issue of the multiple drugs because I think that's a very central and critical issue.

DR. TAMMINGA: I have one more question that I'd like to ask about this slide, then we can let Dr. Harrigan sit down.

This study was done at peak plasma levels, and so these are the only data we have for ziprasidone and these drugs at their maximal plasma levels.

From your Phase II/III studies, what was the QT prolongation in the more ordinary way where we would have more of our numbers? Was it around 20?

DR. HARRIGAN: No. In the ziprasidone program?

DR. TAMMINGA: Yes.

DR. HARRIGAN: No. In a short-term fixed-dose dataset, where you had patients who stayed at those fixed

doses they're in, the range was 6 to 10 milliseconds, being 10 milliseconds at the highest recommended dose of a 160.

If you look at the entire Phase II/III database, with patients being treated with flexible doses, and ECGs obtained at random times of day, reflecting, you know, the wide patient population taking the doses as prescribed by the investigator, the change is about 4 milliseconds.

DR. TAMMINGA: So it seems to me, Dr. Moss, I don't know -- and I'd like you to comment on this, that the number that we should use, that we might compare to other numbers, would be randomly selected QTc intervals, which would be more in the range of 10, and this QTc interval in the range of 20 would be more of a maximal drug concentration interval.

DR. MOSS: That is correct, but it also has the implication that there's a dose-response effect, and that is, if you're talking about random doses and random concentrations with a QT interval that's 4 to 6 milliseconds, and now you're talking about a peak concentration, even though they didn't show a concentration effect, that would suggest that there is a dose-response effect, and I'd be interested in Dr. Harrigan's response to that.

DR. HARRIGAN: Well, there certainly seem to be

in the short-term fixed-dose dataset an increase in QTc with increasing dose.

If one looks at the highest dose in that short-term fixe-dose dataset, the mean QTc effect did not increase further.

If one looks at the highest concentration, the individuals at the highest concentrations in the Phase II/III database, there does not seem to be a signal that the QTc effect has increased in proportion to their serum concentrations.

Nonetheless, the data out there is sparse enough that a mathematical demonstration of that as a fact is certainly not possible.

DR. LINDENFELD: Dr. Harrigan, while you're there, I have one slightly off-the-subject topic.

You told us that the M9 metabolite is an L-type calcium channel blocker. So that would be expected to slow the heart rate if you shifted more of the metabolism to that side by blocking cytochrome 3A4.

With ketoconazole, was there a change in heart rate between the groups that got the metabolic inhibitor and those that didn't? Because if there is a difference in heart rate of bradycardia, we might view that as a problem or possible --

DR. HARRIGAN: Let me take a few steps. It's

in the briefing document in one of the tables. If it is, it's not more than a one or two beat per minute. The ziprasidone increased the heart rate in both the presence and absence of a metabolic inhibitor. It was four and a half beats in the presence, and I think Dr. Brater's looking it up, it wasn't more than one or two beats different from that.

DR. TAMMINGA: If you need a few minutes, we can go on to some other questions. Dr. Hamer has a pressing question.

DR. HAMER: Actually, I want to follow up on something that you said, Dr. Tamminga, and it's something I've wondered about at many of these meetings.

From what little I know about pharmacokinetics, population pharmacokinetics has only relatively recently become more extensively developed and extensively used, and traditional pharmacokinetics seems to pretend that basically all of us individuals have the same pharmacokinetics.

So when you've talked about, well, we've taken these EKGs at "peak levels," i.e. however long after the dose for a given particular drug, that's really pretending that all the people that took the dose are absorbing and metabolizing this drug at the same rate, and it could well be very, very different.

So we really have no idea how close -- I mean, it's probably closer than just taking them randomly, but we really do have no idea how close to peak in any given individual these measurements actually occurred, is that correct?

Could someone who knows a lot more about pharmacokinetics than I do talk about that?

DR. TAMMINGA: Certainly one would expect these EKGs to be closer to the peak than random EKGs throughout the data, and I think that was the point of the study.

Dr. Laughren.

DR. LAUGHREN: Actually, I wanted to comment on the overall design of the study and a problem in knowing, you know, what the change from baseline means for the other drugs.

There was no placebo group here. So I don't know what the smaller change means for the other drugs, but I do know that in studies that have included a placebo, and I believe that you showed a slide, Ed, earlier, having both haloperidol and placebo along with ziprasidone, that basically showed no difference between haloperidol and placebo in QTc effect.

We have data from multiple other trials, including the seven-arm trial that Dr. Dubitsky presented, that looks at three different doses of haloperidol, 4A and

16, against placebo, again showing completely flat curves, an absence of any apparent QTc effect.

So I think you have to factor all of those other data, you know, into this interpretation of this study that doesn't have a placebo control.

DR. HARRIGAN: Can we follow up on that? I mean, I agree that the therapeutic trials with haloperidol have not shown a QTc effect with haloperidol in our program or in the programs you've seen obviously.

We do have some concentration QTc data from Study 054 with haloperidol, and I wondered if Dr. Thomas Ludden would be available and allowed to present that just very briefly.

DR. LUDDEN: Can we have Slide M134?

This is a graph of the QTc change from baseline, using a baseline correction, versus the haloperidol serum concentration. The two-day values, which was during a titration phase, the lowest levels shown to the left there in yellow.

The next set of levels are in white which represent at steady state, and then the orange levels are with the metabolic inhibitor, and the large squares represent the means of those data, both in regard to concentration and to response.

Could I have Figure 236, please? This is

PK236.

Okay. Now, that's the same data essentially with a regression line shown through it, and that is a significant regression line for that dataset. It's performed using a mixed effect modeling approach, the population approach that was referred to a few minutes ago, in trying to keep the correlation or the identity of an individual intact in the data analysis. It's not like treating those data points as being completely independent because some of them arise in the same individuals. But one can get a significant regression from that.

Now, I would point out that the interaction study worked quite well for Haldol, that it actually moves the concentration nicely to the right in this study, and so it did stress Haldol fairly well in changing the exposure.

DR. TAMMINGA: Dr. Winokur.

DR. WINOKUR: I wanted to try to come back and pick up on the discussion that Dr. Hamer started with the design of that study because I think it's -- I'm sorry.

DR. TAMMINGA: Let's finish first with Haldol discussions, if you don't mind.

DR. WINOKUR: Sure.

DR. TAMMINGA: Dr. Laughren, do you have another comment in response to this?

DR. LAUGHREN: I don't know how to interpret

that graph. I mean, again, all I'm doing is falling back on our very extensive database in which, you know, haloperidol is used as a control, and studies that include placebo, where you never see any difference.

It's puzzling, you know, why that should show up here. I don't know what it means.

DR. TAMMINGA: Dr. Katz.

DR. KATZ: The variability around those means are rather large, at least for the greater concentration, it's not up any more, and, of course, patients weren't randomized to particular concentrations, those that fell out of the dose they were on.

So I'm inclined to agree with Tom. It's hard to know exactly what that means against the backdrop of empirical evidence, which suggests it really isn't very different from placebo.

The point being that if it's really not different from placebo, I don't know if that slide, Ed, that you had about Study 54, if you put those back up, if that's possible.

If you accept as an assumption that Haldol's equivalent to placebo in that study, and you subtract the other measurements for the other drugs, the other QTc measurements, you see that ziprasidone does sort of stand out.

I think if you look at the steady state in the baseline correction, in the Framingham correction, without metabolic inhibitor, you see there really isn't any overlap with the confidence intervals between ziprasidone and the other drugs. Thioridazine, of course, is a separate issue, but Haldol's higher than the others.

So if you consider that as sort of a placebo or, you know, a surrogate for placebo response, you really see that ziprasidone does sort of distinguish itself, and we've tried to make the case that we don't think that the Bazett is the appropriate correction. Obviously things look a little different on the Bazett side of things, but if you believe that that doesn't correct appropriately for heart rate, if you look at the other two, which sort of probably we believe are a little bit more accurate as far as correcting for heart rate, you see that ziprasidone really does sort of stand out, again if you consider as Haldol as sort of a placebo, even if you don't.

DR. HARRIGAN: We have a little bit of frustration probably with the analyses.

The Bazett formula was the prospectively-declared formula in the protocol for analysis of QTc, and with the Bazett formula, as we pointed out earlier, there are a large number of drugs that appear to have an effect.

Now, if you move to another correction formula,

and there are good reasons to consider doing that, then it seems to us that haloperidol pretty clearly has an effect. If you dissect that data further, then there's a concentration effect relationship with haloperidol and QTc.

So it seems from our point of view that if you pick one correction formula or the other, one correction approach or the other, and either way, there are certainly other antipsychotics which cause a QTc prolongation and actually fairly close to the neighborhood of ziprasidone.

DR. TAMMINGA: From a cardiologist's point of view, what do these differences make? Well, what do these differences look like?

DR. LINDENFELD: I think we've been having trouble answering that all day.

In any individual patient, I think -- and please, everybody, add to this -- a 20 millisecond increase would not be a huge increase, and I don't think if it was in the normal range of EKG of QT interval, I don't know that it would make any of us stop a drug. If it went from 400 to 420, I doubt that any of us would stop the drug at that point.

But I think that's a difference in what it means in large populations where there will be some people who will prolong substantially more.

DR. TAMMINGA: Could you comment also on the

differences between the medications that were just up?

DR. LINDENFELD: Do I think there are real differences? I guess I think ziprasidone stands out a little bit as to have more QT prolongation than the others, yes.

DR. CALIFF: I think JoAnn said it quite well. I would just add just the point of frustration that the numbers studied are small. We're talking about three million patients. It would seem worthwhile to get little bit bigger sample sizes so we could potentially distinguish one drug from another.

The other point I'd just make here is one reason we're all so much in the dark, there's no empirical base of research. I think as Dr. Throckmorton pointed out, despite all 50 drugs having this QT prolongation problem, there's very little data that relates the QT prolongation to the risk of arrhythmias across the different classes of drugs. It's really quite remarkable.

DR. LINDENFELD: Maybe if I could, I'd like to ask Dr. Moss a question.

In terms of risk, Dr. Moss, do you think we're picking out a highly-susceptible population? So is the risk the greatest in the first several months or is it an on-going cumulative risk per year, do you think?

DR. MOSS: Well, let me answer a couple of

questions.

The first one of does 20 milliseconds make a difference, well, in a given individual patient, no. The question is, does this represent a signal? That's the real question that's out there. That is, does a 20 millisecond change, which is a substantial change, a highly-significant change, does that represent a signal that there's going to be some group of patients out there that are going to have a much larger change?

So that, I think, is an issue, and so you can't really interpret the 20 millisecond per se interval.

Now, your other question related to?

DR. LINDENFELD: Are we picking out susceptible patients whose risks would be primarily in the first few months of this therapy or is this likely to be a cumulative risk year after year?

DR. MOSS: I don't think we know, but I believe that the risk is just short-term, unless they have evidence that the QT interval resolves or accommodates over time. I haven't seen any evidence to that effect.

DR. TAMMINGA: Dr. Moss, what do you make of the rest of the data that Pfizer reported to us, that, say, with the metabolic inhibitor, the QT interval did not go up, and that with the overdose cases, there weren't substantial or gigantic QT interval changes, and then the

lack of syncopal episodes, that at least Pfizer put those together for us in a bundle to kind of look at, it seemed to me, to answer the question or to provide some data to the question that you posed?

DR. MOSS: They're very reassuring. I mean, the fact that although the number of overdose cases is relatively small, they didn't see any clear pattern of QT prolongation. That's very, very useful information, and every case becomes extremely important.

So that this information that they've shown has been reassuring in that regard.

DR. TAMMINGA: We'll get back to Dr. Winokur's questions.

DR. WINOKUR: Well, it was initially stimulated by Dr. Hamer's comment, but it may also fit in with the discussion that Dr. Katz and Dr. Laughren brought up as well.

I wanted to remind myself and mention to the committee and others that, as I understand it, this study was done in a way that is actually quite different than most previous study for which we have such data, and this was something that came out of the discussions with the division after the initial review, and I guess I would see it differently than the point that Dr. Hamer was making.

You know, certainly there's inter-individual

variability, but a way to reduce variance and to get a more accurate signal is to have a study done in as consistent a manner as possible, and the time selected for doing the EKG was geared to the time of Cmax, and actually they did three EKGs an hour apart.

So they really bracketed the time that would be expected. I think that's a significant change from what I understand to be the usual approach. So to me, that would be an important step in making a statistician happy.

The other thing is it concerns me as to whether the concerns about the data with haloperidol being different might also relate to this being a very different paradigm that was used, and therefore, you know, instead of falling back into going with numbers that we're familiar with, but those numbers were really derived from a quite different experimental protocol, then, you know, that might be a reason for things looking different.

We actually heard about rather different numbers as a function of the usual way of collecting such data in the larger studies, you know, where they got a quite different estimate as opposed to doing it in this specified way to specifically tie into the Cmax.

DR. TAMMINGA: What I would add, Dr. Winokur, about that, about placebo periods and previous studies, is that oftentimes in antipsychotic drug trials, placebo is

not as drug-free as you would wish because placebo periods are oftentimes aborted, and EPS as a side effect usually continues on through the placebo period.

I think it's as drug-free as we can probably provide, but it isn't fully drug-free. I don't know how that pertains to the present discussion.

Dr. Moss had said that he wanted to come back to the study of drug-drug interactions, which I think is an important topic.

DR. MOSS: Well, it has to do with the question that was raised about multiple drugs, and these patients are likely to be on multiple drugs.

Now, within the psychiatric drugs, I would suspect the possible overlap with other antipsychotic drugs as well as antidepressants, and although there is a table here that relates to their experience in really, I suspect, what is the earlier Phase II/Phase III trials, it was really observational data, never clear trial data. It's just what they happened to be on.

It would seem to me that there's also, as one is getting into the age 40+ age group, that generally the four most frequently-used non-psychiatric drugs are ACE inhibitors, diuretics, beta blockers, and calcium channel blockers, and it would seem to me that it would be worthwhile to have some information on this in some

appropriate way.

So that's the one issue that was raised about drugs, and I think that we just don't really have substantial data to properly interpret that. It's conceivable that could also be accrued post-approval, but I'm just saying that that information really is not interpretable at the present time.

Then, the other issue that was raised, which is, I think, an important one, is the bradycardia issue, because bradycardia is really known to be a significant trigger in patients with QT prolongation, that this is what seems to enhance the abnormality of the repolarization, and so we don't really have any information during sleep or during other times where, say, Holter information would be helpful to see if there is some type of change later, during a bradycardic rate or what have you.

So these are two issues. I think they're relevant issues. I don't think we can answer them on the basis of the data that's available, but it would seem to me this is something that is relevant from the clinical use of this medication, particularly in drug combinations, and some of the drugs themselves slow the heart rate, like beta blockers, et cetera.

So these issues are open. I wish we could answer them. I cannot give you specific information, but

they're out there.

DR. HARRIGAN: Dr. Tamminga? Sorry. Snuck in behind you.

Just two things to address Dr. Lindenfeld's question. The heart rate, mean heart rate, went from -- with ziprasidone in the absence of metabolic inhibitor 4.6b per minute increase, with ketoconazole 3.6b per minute increase in the mean.

Another point is in response to Dr. Moss raising the issue of drug interactions, we probably haven't, I think, surveyed sufficiently the drug interaction data available on ziprasidone.

I wonder if Dr. Craig Brater from Indiana University would be able to just provide a brief summary of that?

DR. TAMMINGA: Do you think that would be helpful, Dr. Moss?

DR. MOSS: Couldn't hurt.

DR. HARRIGAN: Thank you.

DR. BRATER: As you heard, I'm Craig Brater. I'm from Indiana University.

I can't speak, I don't think, to pharmacodynamic interactions, but if you're thinking about them, you've also got to have some corner of your brain that must also be thinking about pharmacokinetic

interactions, and so let me say a few words about that.

As you saw and as has been inferred, there have been a number of interaction studies that have been performed to look at that, and if you stand way back and look at this, and I can show you the specific data if you want to delve into that, one of the things that strikes you is that the kinetic interactions, disease effects, et cetera, are not very great in terms of their magnitude.

I think it's important to keep a frame of reference that the bioavailability of this drug is 60 percent, and so when you see drug-drug interactions that cause big increases in serum concentrations, it's usually because they have low bioavailability. They're being metabolized by the intestinal epithelium.

You block that with an interacting drug, and all of a sudden, you get a greatly-enhanced bioavailability, in addition to a decreased ability to eliminate the drug once it's in the system. Typical example of that is terfenadine, typical example of that.

But if you have a 60 percent bioavailability to start with, the most you can go is to a 100, and so you're not going to see a big delta in that fashion.

But if you look at these data, and you ask yourselves what are the ways that you can permute the system, ketoconazole has already been mentioned, and

remember what ketoconazole does. It's the most potent inhibitor of 3A4. So it's going to shunt everything down that other pathway. It's going to shunt things to M9, and it's going to shunt things to ziprasidone.

Another aspect of ketoconazole is if there is any secretory elimination of the drug or M9 through biliary secretion, if part of that is by peak glucoprotein, it will also block that.

So again, ketoconazole serves as a very good tool to really stress the metabolic system to its capacity, and you see about at most a 40 percent increase in exposure. So it's not very much.

If you look at liver disease, the patients with the most severe liver disease, it's about a 35 percent increase in exposure.

If you look at elderly, it's about a 20 percent, and actually if you take the extremes and look at exposure in an elderly female compared to a young male, it's about a 40 percent increase. I think if you turn it around and you say what happens if I use an inducer like carbamazepine, it's about a 40 percent decrease in exposure.

So the numbers that you keep coming up with is that if you stress the system to its max, either by age, demographics, disease or drug interaction, you get about a

40 percent change in exposure, and I think that's an important frame of reference for you to keep in your deliberations in terms of polypharmacy.

What might happen with multiple drugs? What if you have a patient with liver disease, and then, all of a sudden, you put them on ketoconazole? Does that mean that you get 40 percent plus 40 percent? So now there's an 80 percent exposure? No.

There's a lot of internal consistency in these data in that if you -- as you heard, about a quarter to a third of the metabolic elimination of this drug is through CYP pathways. That would allow you to predict that if you completely shut off those pathways, you would get about -- guess the number -- a 40 percent increase in exposure, and indeed that's what you see with ketoconazole.

So you would not have additivity in a situation like that, if you got essentially the maximal effect by either an interacting drug or by disease or what have you. If you layered something else on top of that, you would not expect to see additional exposure.

So again I think that paints sort of a frame of reference in terms of what you're going to see in terms of kinetics, is this magic 40 percent number. How that affects, again I have to say I can't get into the business about dynamics.

I'm not sure if the data can be looked at in that fashion. I don't know if there's any population information, but in terms of pure kinetics, the boundaries are reasonably narrow.

DR. CALIFF: Craig, I'm just trying to understand the overdose information.

If you have a dose-response effect, and you have an overdose, I mean, from other data about QT prolonging drugs and IKr channels, is there some theoretical threshold or leveling off? How would you explain someone with an overdose not having a substantial prolongation of the QT?

DR. BRATER: I'm not an expert on IKr channels and that kind of thing, but I guess you have to basically presume that the slope of the concentration response relationship is very shallow or you've got a -- you do have an upper asymptote that has been essentially defined within this database, though statistically you can't fit the curve and meet the technical criteria to say that it does have an upper asymptote.

But, I mean, you've got more than the overdose data. You've also got those outliers that were out there. The only way I can explain that is that there's some plateauing that goes on.

DR. CALIFF: And then, just to reiterate one

more time, I heard you say it, and I just wanted to check, if we have no knowledge of what would happen if someone took quinidine or sotalol or dofetilide on top of this drug?

DR. BRATER: I don't personally. I don't know if others here do. People are shaking their heads no.

DR. MOSS: Could I ask a question? If one goes higher in the dose to patients in studying dose-response effect, do adverse side effects prohibit one from going to higher doses?

That is, as I understand it, the highest dose is the 200 milligrams a day. If one went to 400 milligrams a day, in terms of testing, is that precluded by side effects? Maybe that's already been done in earlier phases of the trial.

DR. BRATER: I'll have to turn that back over to Dr. Harrigan.

DR. HARRIGAN: No. The 200 milligram per day dose was associated with increased side effects, and in clinical trials, we did not exceed that dose. We really haven't exceeded that dose in the clinical development program or experimentally.

There are increased adverse effects of various sorts, including some extra-prandial symptoms, at doses in that range.

DR. MOSS: Could I get a comment from Regulatory on that point?

DR. LAUGHREN: You mean about whether or not we'd like to see a full exploration of the dose-response curve even in normals?

I mean, clearly, we would, and I think that's sort of, you know, what we're reaching here. Because of the remarkable stability of the pharmacokinetics of this compound, you're not learning about that by trying to block the clearance, and so the fact is that we don't have any good data, any systematic data, on what the QT effect is at, say, a doubling of the therapeutic dose, and that's sort of an unknown.

DR. HARRIGAN: Normal volunteers would not tolerate really even therapeutic doses of this atypical antipsychotic or any of the atypical antipsychotics that people are using that are prescribed, and we have not deliberately run a patient study at overdose at those high dose range.

DR. CALIFF: Why wouldn't they tolerate it? If someone with psychosis could tolerate it, why couldn't a normal volunteer?

DR. TAMMINGA: It's quite common that normal volunteers don't tolerate any of the dose levels for any of the antipsychotics that people with schizophrenia do.

DR. HARRIGAN: I agree. I mean, some of it is the Alpha 1 effect, which normal volunteers don't tolerate that patients who become acclimated to and tolerate fairly well.

There's one other point, if I can digress just a little bit, that's another perspective on the haloperidol effect. If one were to treat the haloperidol as a placebo, with the non-Bazett correction formula, then that would reduce the mean effect of the ziprasidone and QTc to something south of 10 milliseconds, be somewhere between 5 and 10 milliseconds, in order to subtract that out as a placebo effect which I think Dr. Katz was suggesting you consider doing for some of the other agents in Study 054.

DR. TAMMINGA: Dr. Katz.

DR. KATZ: Well, yes, it does decrease. I mean, people have been talking about 20 millisecond prolongation, and we agree that if you use the maneuver that you just mentioned, it brings it down.

I think we brought it to around 10 or something in that ball park in general.

DR. TAMMINGA: Dr. Throckmorton.

DR. THROCKMORTON: Yes, just a comment about the Number 10 milliseconds.

Given the absence of information about as much of an effect of a doubling of the drug dose, I'd be a

little cautious about extrapolating to exactly what would happen at 300 or a doubling of the dose, something like that.

I mean, we imagine that it would be linear or something like that. That is, that you'd have some smaller higher number. I don't know, 14 or whatever. We don't have a lot of drugs to really base that sort of inference on.

DR. TAMMINGA: Dr. Marder.

DR. MARDER: I'm wondering if it would be all right to change the topic just a little bit. I wanted to address something that was brought up in the consultation that we got from the Division of Cardiorenal Drug Products.

There was suggested that evaluating the risk of QT prolongation against the risk of, you know, factors, such as lipids and weight, was not valid because increases in weight and lipids could be detected by a clinician, and then a change in the pharmacotherapy could be made to reduce that risk.

I question whether that's relevant in the real world for a couple of reasons. First, even in the setting of optimal care, where clinicians are, you know, weighing their patients and monitoring lipids closely, still patients are gaining weight, and it still remains -- I mean, in most clinics where patients are on the newer

drugs, they're not being changed, which is the reality of practice.

Secondly, the reason that they're not is because what does the clinician change to in order to reduce the risk?

The drugs that appear to have the least risk of QTc prolongation seem to be a group of, from what I gather, high potency, older antipsychotics, but if one looks at treatment guidelines that have been developed by some individuals in the Texas guidelines and other consensus statements, those drugs are also considered second-line agents.

I know FDA doesn't consider them, but many clinicians have come to think of them as second-line agents because they may be associated with a higher risk of tardive dyskinesia or other risks.

So the clinician is left with the group of agents which we've been talking about, the three drugs which are first-line agents, and all of those cause substantial weight gain.

Even if one accepts that quetiapine may cause or risperidone may cause slightly less weight gain, the amount in some individuals is substantial, and given that this is such a common problem, I think that there are very few alternatives for clinicians.

So I'm just addressing that argument, which I don't really consider invalid. I still think that the risk of these other factors needs to be weighed against the risk of the QTc prolongation.

DR. THROCKMORTON: I guess I win. I don't think the consultation was making any regards judgment as regards to which of those was a thing to be concerned about or even the relative concern that should, you know, sort of burden of concern for the two things.

I think the consult was raising an issue of which of the two groups of adverse events are manageable through relatively easy mechanisms, and which of the adverse events is one for which we have a difficult time predicting individuals that are at risk and identifying that risk before an adverse event.

So you have a significant concern, weight gain, lipid change and those sorts of things. Yes, you're right. We may have a hard time intervening in those if they occur, but we don't have any difficulties identifying them through things that we do all of the time.

On the other hand, QT prolongation, as we've all heard today, trying to identify an individual at risk is extraordinarily difficult, and the consequences of failing to identify that risk in an individual is irreversible, and so the concern was that you're trading a

potentially irreversible adverse event that you have a difficult time predicting will occur for an equally serious or an alternate significant adverse event but one that is amenable perhaps to other therapies and is readily identifiable.

I hope I'm not putting into words --

DR. TAMMINGA: I would add actually another feature to this that may be important in that I suppose what we're talking about is theoretical risk or hypothetical risk in that this is a risk that we all assume is there, but we don't see any signal for it, except the 20 millisecond signal.

Dr. Califf is going to correct me.

DR. CALIFF: No, I'm not, actually. I'm just going to pile on and say that although not gaining weight is a very important thing, and I think an important issue to consider, we also cannot jump to the conclusion that drug-induced changes in weight or lipids or diabetes control necessarily impact on the down-the-road events we're trying to prevent.

I mean, we don't care what our lipids are, unless we have a vascular event, which is what lipids predict, but, you know, I would just point out the lesson we learned from hormone replacement therapy in the last five years.

Beautiful effects on lipids, not so much on triglycerides as here, and yet, you know, no prevention of cardiac events in one secondary prevention trial and an increase in thrombosis.

So the risks on both sides of that equation are hypothetical, except for weight in and of itself as something that's personally important and may affect adherence.

DR. TAMMINGA: And there's a far different incidence of risk, I guess you'd call it, between cardiac event and between weight gain in that weight gain is very common.

DR. THROCKMORTON: Are you arguing for outcome trials now in this population?

DR. CALIFF: I don't know how you can listen to this and not -- I mean, you know, this is all resolvable by randomizing a few thousand patients in each group, and if I, you know, was a person that had this problem, I would want to know. I wouldn't want hypothetical risks and benefits. I would want truly measured risks and benefits, and I know the NIMH is beginning to fund some studies that are looking at this, but, you know, we're all talking about hypothetical things here based on surrogates that we can't presume accurately predict what's going to happen to patients.

DR. TAMMINGA: Dr. Oren.

DR. OREN: Just in the last couple of minutes, the discussion has introduced again what the ziprasidone may do as far as lowering lipids.

I think that we don't have an adequate database to address that potential benefit. Again, the sponsor this morning was not able to provide us with data showing what happens to people with different baseline lipid levels.

So that unless we knew, for example, that people with the high baseline lipid levels have lowering of their lipid levels, it would be hard to make direct comments on that specific point.

DR. TAMMINGA: Dr. Cook.

DR. COOK: Actually, I wanted to follow up on where this was headed, and I don't want to debate the completeness of it, and that's what concerns us all, but we focused appropriately on the QTc, and in some ways, there's some concern, but then I want to actually ask, particularly the cardiologist review of the -- I think there are about 4,500 exposures to this over about 1,700 patient years, with mortality that's lower than placebo, which is relevant, and equal to comparators.

Now, the problem, of course, is the sample size, and in direct comparison to ziprasidone, it's not so high, but I'd just like your comments, and perhaps Dr.

Hamer's comments on how much we can take from that.

The one thing we obviously don't have is particularly the fact that even if we have people only on one drug, they're probably not going to be washed out from another antipsychotic.

So aside from the fact that we have almost no data on concomitant psychotropic use, there do seem to be a lot of patient exposures here in patient years. So I'd be curious about those as outcomes. I mean, that's the outcome we care about, not the QTc.

DR. TAMMINGA: Dr. Laughren.

DR. LAUGHREN: Before Dr. Califf comments, let me just add one additional piece of information about what reassurance, if any, one can draw from the fact that the overall mortality in the NDA database for ziprasidone is no different than other recent antipsychotic NDAs.

For this drug sertindole that we talked about a little earlier, the overall mortality in the NDA database was also right in that ball park, and that drug turned out to be a problem in terms of sudden death.

So I'm not sure how much reassurance one can draw from this overall mortality figure from a relatively small NDA database.

DR. COOK: Okay. I know that's a problem, particularly with the sample size, but was it the same size

database?

And Number 2, when sertindole was pulled, was it clear that it had a higher mortality or was it pulled because of some cases -- I mean, this is the issue. The issue is overall mortality.

Are patients that you put on this medication more likely to die? I recognize a single event or a set of events can sort of captivate people emotionally, but the issue is are patients dying or not in many ways?

DR. LAUGHREN: The overall person-time experience was in the same ball park as what we're seeing for the others, and in terms of the decision-making about sertindole, I really can't comment on that, but Dr. Dubitsky showed you earlier the reasoning, the public reasoning on the part of other regulatory agencies, and it was based on cases of torsade and sudden death in the public experience.

DR. COOK: I don't want to minimize those, but if we're -- I mean, many of these questions are public health-related questions, and overall mortality seems to be the big concern to me at least.

DR. TAMMINGA: Dr. Fyer.

DR. FYER: I'd like to disagree a little bit with Ed about this, in that, I mean, this is probably a big leap, but it does seem to me that what we're talking about

with the QTc is a relatively rare event, and, so that the kinds of sample sizes that you're going to need whereby it's going to affect mean values in terms of risk factors, et cetera, are going to be huge, and I think way beyond anything that anybody's going to do.

I do a lot of, as Ed does, complex disorder genetics in that similar problems arise, and you sort of get used to dealing with it, but for me, on the advisory board, the issue really is that I sort of feel like it's our job to protect that particular subgroup of people who may have a very low chance of having gotten into these, you know, samples, but for whom there is possibly in the data we've seen today about QTc prolongation evidence that they do exist.

What concerns me is that the drug will be approved and go on the market, and another incident like Seldane and antibiotics will occur, and it's easy to say, well, that's a very low percentage of people, but for the people involved, you know, that's the end, and I'm not sort of taking the position that we shouldn't approve the drug under this kind of situation, but again what I said earlier is that I take very seriously the responsibility for, you know, protecting in a very rigorous way, you know, any possibility that that will occur, and that we have to accept that mean data is not going to really address that

issue at this point.

DR. COOK: I just have to respond that I share your concern and think about my own patients as potential fatalities and thinking about this, and then, I guess, the only other question to follow up is, could the cardiologists tell us what the effect of screening would be, and if this is approved, what level of screening they would recommend, and would that at all reassure us or not about this hypothetical risk?

DR. TAMMINGA: We're going to take Dr. Califf's response to Dr. Fyer's question first before that question.

DR. CALIFF: I think, Dr. Cook, I tend to side with him a little bit on the original point he made on this issue, and it's one reason in cardiorenal we try to look at all cause mortality, because I think the case has been made here that it's possible that you might even have an increase in risk of death due to long QT, and you might have a decrease in risk of death due to lowering of lipids and better weight and better diabetes control, and, you know, in the end, people don't care what the cause of death is, they care what their overall risk of death is, and so it's very conceivable you could have offsetting issues here, one favorable, one detrimental, and the question is which outweighs the other?

On the other point of the degree of exposure, I

think there are two issues here. One is sample size and years of exposure. The other is the representativeness of the population, and there's been a tendency in FDA-related clinical trials to enroll patient populations which are not as sick or complicated as the patients who are eventually going to be treated when the drug gets on the market. That's where a lot of problems have occurred.

I think the sponsor made a pretty good case that these were reasonably representative patients, although we don't have all the data in front of us to come to our own conclusion on that, but I would argue strongly that looking at total mortality is really the best way to look at it.

DR. TAMMINGA: Dr. Harrigan?

DR. HARRIGAN: Can I just take one moment to try to address a point that Dr. Califf made earlier, and that I think may be a point of confusion?

We wouldn't be trying to suggest that ziprasidone saves lives by lowering cholesterol and lowering body weight. It's not a cholesterol-lowering agent or a weight-loss drug. It's a drug that doesn't share the risks of treatment alternatives which aggravate those cardiovascular risk factors, which exacerbate those cardiovascular risk factors.

So to the extent that we have some

understanding of what aggravation of those risk factors, increasing body weight, increasing cholesterol, increasing triglycerides, to the extent that we have some idea of what risks those changes carry, then it's avoidance of those risks that we think is the key property for ziprasidone.

DR. CALIFF: I mean, again, they're somewhat hypothetical. For example, most drugs that improve diabetes control also result in an increase in weight.

So the problem is when you deal with surrogates for cardiovascular disease, there's so many unknowns and confounding influences of different surrogates, that it's very hard to be sure what you're going to get without measuring it.

I mean, we've been through this so many times. Still, I think hypothetically, the case that's being made is pretty strong as hypothetical things go.

DR. TAMMINGA: And what do you think is very strong, if you could be clear about that?

DR. CALIFF: Well, if you believe that drugs that cause an increase in LDL cholesterol and an increase in weight lead to an increase in the risk of future cardiovascular events, and that this drug doesn't do that, the connection is very plausible.

I'm just making a case that we've seen a lot of plausible things that turned out not to be right when we

actually measured them.

DR. THROCKMORTON: Yes. I'd echo that, just to remind the audience that there's another compound that Pfizer has, of course, that has had similarly-lowered lipids, that is Doxazocin, but had a reported adverse outcome as regards to some cardiovascular events.

I'm certainly not saying that we know that those things are in fact true or connected or anything else. I think your point about being very careful of accepting non-prespecified surrogates as evidence of benefit is warranted.

DR. TAMMINGA: Dr. Rudorfer.

DR. RUDORFER: Yes. I just wanted to make a slight paradigm shift just to put in a couple words that some of the risk factors that we've been talking about related to weight and lipids also apply to the other side of the equation, namely the benefit side, because, I mean, I found the public testimony very moving this afternoon, that in fact factors that might increase treatment adherence should not be discounted, and I think the question of whether effect of weight and lipids reduce cardiac risk, I agree with Dr. Oren's comment that these studies were not designed to ask that question, and we really can't answer it, but I think independent of that, the fact that those data add to the benefit side of the

equation, we should keep in mind.

DR. TAMMINGA: Dr. Laughren.

DR. LAUGHREN: In line with Dr. Califf's earlier comments, do you think that there ought to be an actual demonstration of improved treatment adherence?

DR. TAMMINGA: Do you mean by Pfizer or in the real world, in some other place?

DR. LAUGHREN: Well, again, you know, we've been talking a lot about theoretical risks and theoretical benefits. It seems to me that that's perhaps another one that hasn't actually been empirically demonstrated, and, you know, if that were proposed as a theoretical benefit to offset the theoretical risk of increased sudden death, should that be subjected to empirical testing rather than making the assumption that the patients will adhere better because of less weight gain and so forth?

I mean, it seems to me that it's another theoretical advantage that perhaps has not been empirically demonstrated.

DR. CALIFF: Yes. I'm not sure I understood when you say about Pfizer or are in the real world. I think Pfizer sells its drugs in the real world. So I would assume that one could pretty easily do a study that would show improved adherence, if in fact the way the lack of weight gain results in better adherence.

DR. TAMMINGA: I didn't mean to exclude Pfizer from the real world. The NIMH is currently doing a study, and I suspect that ziprasidone would be included in that study, were it approved, where this kind of data might be collected, although I don't know for sure.

DR. MARDER: My recollection of the protocol is that it will be included, if it's approved.

DR. TAMMINGA: And compliance data will be collected?

DR. MARDER: Yes. That study will measure treatment adherence. It will also measure a lot of the cardiovascular factors as well.

DR. TAMMINGA: Dr. Winokur.

DR. WINOKUR: Dr. Cook raised a question before which to me was a pretty important pragmatic one, which I'd like to come back to, again putting it into context.

I think we currently use a fair number of medications that have a lot of complexities and initially had some major safety and health concerns, and we're kind of accustomed to having to do a lot of monitoring. Depakote might be one good example of that, which -- I'm sorry? Many. Right. I mean, we can go on and on about that.

But Dr. Cook raised a question about screening and monitoring with respect to, you know, EKG, and I don't

know if there would be any other measures, but to what extent would that, just from a strictly pragmatic point of view, be something that we could use constructively on clinical grounds or is this something that would not be aided that much in terms of safety issues by good clinical management of cases?

DR. MOSS: Well, certainly screening would be of interest. The question is, are you talking about screening in terms of entry of patients in starting the drug or monitor screening as occurring during periodic follow-up?

I suspect probably more the latter from --

DR. WINOKUR: Well, really, when we use Depakote now, we do baseline liver function tests because we don't want to start somebody on that drug without knowing that their liver function is okay, and then, once they're on it, we repeat it periodically.

So I mean, that's a paradigm we're pretty familiar with, and I would think of both determining that it would be a reasonable agent to select initially, not take somebody, you know, that had a QTc of 500 at baseline, but also for those people that might be especially responsive to that drug.

In other words, I'm not talking about a research study. I'm just talking about in terms of good

clinical practice, what we would do or teach our residents. Would these kind of measures in your opinion be helpful in really actually addressing the kind of concern that Dr. Fyer raised about, you know, our responsibility to protect our patients?

DR. MOSS: I think it would be very reasonable, particularly in the start-up, as one gets a large amount of experience to see what the pattern of the follow-up electrocardiograms are.

I think that over a period of six months or so of a goodly number of patients, one would have an idea that this drug is safe. I think that would be very useful as certainly a screening for the start-up, but the follow-up, what we're looking for is is this signal really representative of something that one's going to see when one's treating thousands of patients, and that would be useful, extremely useful information.

DR. CALIFF: Just out of interest, I wonder what the actual adherence to your LFTs is in practice. If their adherence is good, it would be quite unusual compared to other things we're looking at, but measuring QT interval is not necessarily easy for the average person to do but could be done, and I think Pfizer is getting a lot of experience with dofetilide. It's just coming on the market now with measuring a lot of QT intervals. So it can be

done.

DR. TAMMINGA: But it would be useful to add after this comment that most people with schizophrenia are actually treated in the public sector, so that the common place for them to get their medications would be in community mental health centers, places that may not even have an EKG machine, let alone a physician that might be able to be qualified to read an EKG.

Dr. Laughren.

DR. LAUGHREN: Can I just add a comment? Based on the data that Pfizer showed earlier, looking at baseline EKG versus change in QTc, it looked like patients with relatively high baseline QTcs had the least change, and perhaps it's regression to the mean, but I guess that raises a question of what the value is of getting a baseline EKG here?

DR. CALIFF: Yes. I would think that if there was going to be screening, it would be on a steady state dose, would probably be a more valuable time to look for those who developed a lot of QT prolongation on treatment.

DR. MOSS: I'd be a little bit hesitant on the basis of 33 patients to make some of that interpretation. That is, it may well be valid that the higher baseline QTc in fact have the least increment. It's just atypical of what we've generally seen, and so it's a question mark in

my mind.

DR. TAMMINGA: I think progression to the mean data was not on the 33. I could be wrong. What I think was on the total Phase II/III dataset. I don't know if we want to see that again.

Dr. Katz, you may want to make a remark while we're waiting for Pfizer to get that slide up.

DR. KATZ: I think it was in the total dataset. We monitor a lot of things. Clinically, lots of things are monitored. For example, LFTs are monitored in Depakote and many other drugs.

DR. HARRIGAN: That's true.

DR. KATZ: The problem is we don't really know necessarily what to do with the results or whether or not they actually predict what you're worried about or whether or not when you see something, by that time it's irreversible. So people do these things, and you've asked this sort of analogous question with monitoring EKGs here, that I think we still don't know if you see a 30 millisecond increase in somebody that started out at 420, what does it mean?

I still don't think we've heard an answer. Maybe we can't get an answer to that question, but I don't think we've heard an answer about whether or not we think that sort of change matters to anybody, and what would you

do if you saw it?

Dr. Moss, you said that if smaller changes in the QTc might be a risk, but the risk is probably extraordinarily small. I wonder what that statement is based on.

DR. MOSS: It's not based on good science. That, I can tell you.

(Laughter.)

DR. MOSS: It's based more on just a large amount of non-specific observational information of clinicians who've treated patients, that the patients who have minimal change in QTc, by minimal change.

If you start at 420 and go to 450 or so, there's just been remarkably few events in cardiologists' experience or anybody else's experience that's been reported. So that, as Dr. Ruskin said earlier, virtually the vast majority of events have been in those patients over 500. We don't think that that's an absolute threshold, but the risk seems to progressively increase, and that's where it becomes clinically evident.

I don't know that one has better information than that.

DR. TAMMINGA: Dr. Katz.

DR. KATZ: Yes. I'd just like to ask Doug, I think on the sotalol data you presented, you showed that

there was a relationship between torsade, the incidence of torsade, and change in QTc, but I don't recall whether or not that was linked to any threshold or, you know, approximate threshold or whether or not it was really -- I mean, I think there are other problems with that sort of data. It wasn't randomized, you know, or that sort of thing. But it seemed to be linked to change.

DR. THROCKMORTON: They did look at that, and in fact, in the sotalol label, there are two tables that report the sponsor's analysis of extent of QT prolongation from baseline by, I don't know, tens of milliseconds, and then another by the incidence of torsade for patients whose QT goes over 500, the incidence of of torsade for people who go over 550, and the incidence of torsade for people who go over, I think, 600, something like that, and in both of those analysis, there is a relationship. That is, the people who go over 500 had a certain incidence, 550 a higher incidence still, and 600 was even higher than 550.

The problem is that, as you say, those data were collected for patients who had torsade events. We don't know how many people did not have torsade events but still had QTs of 550 or 600.

But I think that -- I mean, correct me, I believe that is the only place where that's actually sort of been looked at, and in that one case, there was a

relationship between how many people went way far over 500 and the incidence of torsade.

DR. KATZ: Of course, that's confounded, too, because probably the people who went over 500 or 600 are the people that had the biggest change, too.

DR. THROCKMORTON: Right.

DR. KATZ: So one wonders what happens if you see that sort of change, if you start out at, I don't know, 380, and you go to 460. I don't know.

DR. THROCKMORTON: Yes. There's one other point, if I could, just from a regulatory standpoint. I think there are three labels that say if you go too long, you should stop the drug or sort of recommend that. Sotalol, bepridil and dofetilide all have sort of recommendations, saying, you know, if you measure the QTc on ECG, and it's greater than 500, or in the case of bepridil, it's 520, for reasons that I haven't been with the agency long enough to know why it's 520 instead of 500, you should stop the drug.

But other than those -- and I'm not sure what data that was based on. Those are the only three that -- I believe maybe moxi. That could be the other one. Has explicit instructions for recommending discontinuation for an extreme prolongation of QT.

DR. TAMMINGA: And it's not the case in other

drugs, other non-psychiatric drugs, that are known to prolong QT?

DR. THROCKMORTON: Not that I'm aware of.

DR. KORVICK: For the moxifloxacin, we advise to not start patients that have prolonged QT.

DR. TAMMINGA: Of course, in the database that we heard today, no one, I believe, had a QT over 500 at baseline in the whole II/III dataset. So that the incidence of people with schizophrenia, who require treatment, who have prolonged QT, is quite low.

Yes, Dr. Oren.

DR. OREN: A question for Dr. Moss. I realize we're still at best at the beginning of the dawn of the era of pharmacogenomics, but in reference to your presentation, if we knew more about HERG polymorphisms, would we be better able to quantify or qualify the cardiac risks of this drug?

DR. MOSS: Yes, to a degree, but it's going to be at an immense -- one's going to need an immense number of patients to understand the association with polymorphisms, and one's going to also have to relate each of the polymorphisms to expression studies to see what effects they actually have, even to a minor degree, on the potassium current.

There's already known about a 130 different

mutations in the HERG gene to date, and that's not counting the polymorphisms. So it becomes a question of enormous numbers. The Genome Project's not going to make life simpler.

DR. TAMMINGA: Well, we've done an awful lot of discussing this afternoon. We may have even exhausted our questions for our consultant cardiologists but I'm not sure.

Dr. Katz.

DR. KATZ: I have another question. Something has been made of the terfenadine data which suggests that in the absence of metabolic inhibition, the prolongation of the QTc is somewhere on the order of 18 milliseconds or something like that, and the fact that there have been no reports of arrhythmias in the absence of metabolic inhibition with terfenadine is put forth as evidence that you can tolerate that sort of a change in QTc, and it really doesn't pose a risk.

For the moment, forgetting about the vagaries of postmarketing reporting and whether or not you really are hearing about cases that they occur, the question I had had to do with the duration of the QTc prolongation.

My understanding with terfenadine is that it reaches Cmax, and it comes down rapidly, and so I'm wondering, do we have any evidence about the duration of

the effect on the QTc with ziprasidone, maybe with any drugs, but specifically with ziprasidone?

Study 054 measured at Cmax, and the attempt was made to measure Cmax. Do we know anything about that? By the way, do we think that that might even be important? I'll direct the latter to the cardiologists since we're in the realm of the hypothetical for most of the afternoon.

DR. HARRIGAN: We concentrated the ECG measurements around that predicted time of Cmax. We did not collect serum measurements or ECGs around the clock in those patients during that period, nor did we plot out a time concentration curve, such as I think you're describing.

DR. KATZ: And let me just ask the second part again directly to the cardiologists. Is that something that you think would matter?

DR. MOSS: Well, if I understand your question, does the increase of 20 milliseconds matter?

DR. KATZ: What I'm asking is, if you're increased to 20 milliseconds for an hour or if you're increased to 20 milliseconds for seven hours or for 10 minutes, does the --

DR. MOSS: I think one's dealing with a probability of an event, and the minute you increase the exposure, you would think that there would be some increase

in the likelihood and the probability of an event. So the duration of exposure would certainly be important.

DR. KATZ: Well, just to follow up, do people think that would be an important bit of information to obtain, let's say, with this drug? Add that to the list of questions yet to be answered.

DR. TAMMINGA: As I recall from some of the other drugs that we saw in our preparation material, would it be reasonable to assume that the QT prolongation change might follow the kinetics of the drug? Might follow the blood levels? That was my question.

DR. MOSS: The answer is yes, they would certainly be related to the blood level. That was one of the peculiarities, that as one got higher, it didn't seem to keep going up. There seemed to be a plateau, but at least in the lower range, there did seem to be a dose-response effect.

Bob?

DR. CALIFF: That would make a lot of sense, but it would seem to be a fairly straightforward thing to measure, also, to be sure about, and it is an important part of the consideration of some of the drugs used to treat atrial fibrillation, to know the time course of the prolongation. For example, if you need to treat with other drugs due to an emergency situation.

DR. TAMMINGA: Dr. Cook.

DR. COOK: I'm sorry. I'm jumping back to the discussion of pharmacogenomics and concern and really, I guess, this is a question for clarification.

One of the ways that we have of knowing about variation is that based on population history, various groups differ in drug response, sort of the basis of pharmacogenetics, and my question, I suppose, is one I should have asked earlier this morning, but I did want to ask it before we go further.

It's what evidence do we have that more than Caucasians, we have safety data for this drug, considering variability across populations, efficacy as well?

DR. TAMMINGA: So you'd like the company to show us some race data?

DR. COOK: Yes. Ethnicity. I don't think race exists.

DR. HARRIGAN: The efficacy data has been analyzed with a number of cofactors, covariates, and race, gender or age were not factors.

In terms of the QTc, Slide M83 --

DR. COOK: Let me just take them as they come.

DR. HARRIGAN: Sure.

DR. COOK: But I need to know what representation you had of different ethnic groups.

DR. HARRIGAN: Yes.

DR. COOK: Did you have sufficient numbers to demonstrate efficacy by those different groups?

DR. HARRIGAN: Sure. G2. So here's the Phase II/III program. We set this alongside the comparator groups. So for ziprasidone, 4,571 patients in the Phase II/III program. This is cumulative up to 5 February this year.

You can see 3,200 of those patients were Caucasian, approximately 700 or about 16 percent of the total black, and 16 percent other.

DR. TAMMINGA: What would the other be mainly?

DR. HARRIGAN: Well, the other would include Asian, Hispanic. That would probably be most. I don't have it precisely.

DR. MOSS: Is the pharmacokinetics similar in various racial groups?

DR. HARRIGAN: Yes. We looked at that with population pharmacokinetics. I think, Dr. Brater, you wish to address that?

DR. BRATER: Yes. That was looked at with the population pharmacokinetics, which had what, 2,000 -- Tom, what was the number? Pardon me? 453 subjects, and there's no gender, no race, no ethnicity effect.

DR. COOK: Did I interrupt you from showing

something else?

DR. HARRIGAN: Whatever else you would like to see. We --

DR. COOK: You were hopefully going to show QTc by ethnicity.

DR. HARRIGAN: Sure. That would be M83 to start, yes, by dose. Thank you.

Similar to the graph we looked at earlier by gender, we're looking at the short-term fixed-dose placebo-control trials, with each dose group represented, with white being in green, the blue black, and the red other.

As you can see the numbers, at less than 40 milligrams, then 40, 80, 120, 160, and 200 milligrams or more. There seemed to be no systematic differences there. Some variability in the data, of course, but no suggestion that there's a greater mean effect in either of the other racial groups compared to Caucasian.

Dr. Brater.

DR. BRATER: I'll just insert myself one more time. Another issue here potentially is whether or not there are any ethnic differences in any of the drug-metabolizing enzymes. 3A4, the aldehyde oxidase, and one that we really haven't talked about that adds the methyl group on there, TMT it's called, and all three of those enzymes do not, do not have polymorphisms. So they all

have sort of a Gaussian distribution. So there are no ethnic-related differences in those, in contrast to, say, 2D6 and some of the others.

DR. TAMMINGA: Well, the committee has two specific questions to vote on, and then three additional questions to discuss. The discussions that we've had this afternoon so far have been very productive about the voting. I'm not sure they've prepared us to vote in one way or the other.

Have we discussed pretty much the items that you had indicated, Dr. Laughren, or do you see big holes in what we've discussed?

DR. LAUGHREN: I think most of the issues have been discussed. There hasn't been quite as much discussion of potential studies perhaps. Some discussion of that but not a lot.

DR. TAMMINGA: Would you suggest to us what the committee can suggest about potential studies? For instance, that potential studies be done before or after or what would we be suggesting to you?

DR. LAUGHREN: Well, you know, you could suggest both the timing, and it could be before, it could be before, and the general nature of the kinds of studies that you would propose.

Dr. Califf, for example, was proposing, as I

understood it, fairly large comparative outcome studies, looking at things like, you know, perhaps overall mortality. Another outcome one might look at is sudden unexplained death, but you also might look at things like treatment adherence as a potential benefit in a large outcome study.

So those kinds of issues, and then, the other type of study that I had suggested earlier on to think about would be a study to show benefits on the efficacy side. In other words, the kind of trial that was done with Clozapine.

DR. MARDER: I mean, to me, there are some obvious studies that need to be done, and whether they're pre or post I think depends upon other discussions.

But I do think by having such a limitation of dose and not knowing the -- if this drug is approved, it would likely be administered by some individuals at a higher dose than recommended.

So I think we should have some idea about what happens at higher doses or higher plasma concentrations. The drug will be taken by -- the number of elderly patients, particularly those over 70, was relatively small. So I think knowing about cardiovascular factors in the elderly seems obvious.

You know, there may be others I don't know

about, cardiac monitoring and things like that. Those would be things for the cardiologists to recommend.

DR. TAMMINGA: Dr. Winokur.

DR. WINOKUR: While we're on the topic of studies, I do believe that there are going to be almost immediately studies in the larger effectiveness program, as I understand it, that will involve ziprasidone, if it's available.

The issue from our discussions that seems crucial to me, that we would have more information -- I mean, I could certainly accept it being -- you know, Phase IV post-marketing relates to the issue of in the context of using other drugs, because that clearly is going to happen.

We just know that's going to happen. We've heard from the cardiologist experts that that's an issue of potential importance and health importance, which they can't really advise us on further without any information, and I think that's not going to be the kind of data that will come in a systematic scientifically-rigorous way that will also be clinically applicable from the other kinds of more naturalistic studies that are in the process of being formed up.

So that would be one area that I would -- and again, I'm not talking about the drug-drug interaction issue. I'm talking specifically about two different drugs

that will be used, that both in theory could affect QTc, and we need to know how in combination they affect things, and what kind of additional health concerns they raise.

DR. LINDENFELD: Yes. I think we'd certainly, as Rob mentioned earlier, would like to see some data on beta blockers and at least the rate-lowering calcium blockers and diuretics that was on a slide but wasn't really mentioned, that hypokalemia is an important predisposing risk for torsade, and I think that makes diuretics very important here, too.

So you'd like to see a group of patients with those commonly-used drugs evaluated.

DR. TAMMINGA: I'm not exactly sure if Dr. Califf is coming back, but his study, of course, was the large study that would be large enough to evaluate the sudden death risk.

Would either one of you like to speak to that?

DR. MOSS: I don't think he was proposing that as a precondition for approval. I don't think that was his intent at all. He, I think, was just saying it would be wonderful to have that type of data, but I don't think he was proposing that as a preapproval.

I think just the comment about the medicines, what one's really talking about is are the additive effects of the medications on the QT, not the interaction effects,

and these are really important considerations.

The studies that have been done have been the interaction effects, seeing if there's alteration in the metabolism of the drug, et cetera, but what one is talking about is the potential additive effects.

What percentage of these patients are also on tricyclic antidepressants, for example? Small number?

DR. TAMMINGA: Not small. It would be 20 to 30 to 40, 20 to 40 percent, 20 to 35 percent, plus many of them are on mood stabilizers.

I bet that Dr. Marder would have a more accurate estimate than me. What percentage of schizophrenic patients are on, for instance, mood stabilizers and antidepressants?

DR. MARDER: I'd say probably at least half.

DR. TAMMINGA: Dr. Casey.

DR. CASEY: The antidepressant medicines are now much more likely to be SSRIs rather than tricyclics, as we are not using those as first- or even second-line treatments for depression.

So we've taken some of that risk out of the equation by using SSRIs. I'd agree with Dr. Marder. In general, probably half of the patients with schizophrenia may be taking another psychotropic drug.

DR. TAMMINGA: Dr. Malone.

DR. MALONE: You had mentioned various age groups. The other age group would be to study children, especially the effect on QTc, because they probably will be administered these medications if they're approved.

DR. TAMMINGA: Have there been any studies at all in the under-18 age group?

DR. HARRIGAN: I'd like to ask Dr. Craig Brater to discuss that.

DR. BRATER: There have been two, and those have been kinetic dynamic studies, and most particularly to get to the QT question, the heart of the batting order, that's Slide Number 66, where you will see -- and these go down to average age in the youngest group was 7, and you see the colored symbols in here, and then on the background is all of the other data that you've already seen.

We were given information that one of your panel members who couldn't be here today wanted specifically to know about QTs that went above 480. Here's your 480 line. You notice there are no colors that go up there. The biggest QT is about 440 in these children.

DR. TAMMINGA: And what is the age of the pink, and what's the age of the blue?

DR. BRATER: Well, the age range here, there were three groups, and they were dosed according to body weight, and the lowest body weight for the youngest age,

that group, the average age was 7.6. The middle group was average age of 11, and the oldest group was average age of 14.

DR. MALONE: What was the sample size?

DR. BRATER: I'm sorry?

DR. MALONE: What was the N for those groups?

DR. BRATER: In the group with the age of 14, 8, the middle group, 7, and the youngest and lightest weight 8 years, N of 8. So there should be 23 dots on there.

DR. COOK: And to clarify, this is not done at peak levels. This was determined more at trough, like the other Phase II/III?

DR. BRATER: I don't know if I can answer that. It was all collected within one hour of an ECG, but I don't know if it was collected -- an attempt to make it at peak. That would imply to me that they were random.

DR. TAMMINGA: Thank you.

While there aren't many data in children, it may be more than anybody else has.

I wonder if there's any additional discussion or additional points for discussion that people would like to bring up before we start to consider the questions we have to vote on, which would first be the efficacy question and would secondly be the safety question.

(No response.)

DR. TAMMINGA: If there aren't any additional areas of comment, then I could just review that we would really be voting on the adequacy of the database that we've heard presented to us.

That would speak to both the efficacy and the safety of this drug to be used for the treatment of schizophrenia, and the first question that we would want to vote on would be, has the sponsor provided evidence from more than one adequate and well-controlled clinical investigation that supports the conclusion that ziprasidone is effective for the treatment of schizophrenia?

Now, I think we'll probably be prepared to go around the table and vote on that, and we could start with Dr. Moss. Dr. Moss is not voting. I think we'll start with Dr. Grady-Weliky. If you could turn on your microphone.

DR. GRADY-WELIKY: I would say yes.

DR. TAMMINGA: Dr. Oren?

DR. OREN: Yes.

DR. TAMMINGA: Dr. Ortiz?

DR. ORTIZ: I agree that efficacy's been demonstrated.

DR. TAMMINGA: Dr. Hamer?

DR. HAMER: Yes.

DR. TAMMINGA: Dr. Marder?

DR. MARDER: Yes.

DR. TAMMINGA: Dr. Lindenfeld?

DR. LINDENFELD: Yes.

DR. TAMMINGA: Dr. Rudorfer?

DR. RUDORFER: Yes.

DR. TAMMINGA: Dr. Cook?

DR. COOK: Sorry, more than a yes. Yes, but only 18 and above, and only for this specific indication of several that the medication would be considered for.

DR. TAMMINGA: I think that's what we're voting for, isn't it, Dr. Laughren? We're voting for the adult population, and we're voting for schizophrenia?

DR. LAUGHREN: Right.

DR. COOK: I'm sorry. I just had to comment because this is probably the only time this committee is likely to vote on indications for this medication, and absent a similar effort for other indications, including those that are psychotic but not schizophrenia, the question is limited, and off-label use is likely to exceed that of the on-label use. So that's a concern.

DR. TAMMINGA: Dr. Winokur?

DR. WINOKUR: Yes.

DR. TAMMINGA: Dr. Malone?

DR. MALONE: Yes.

DR. TAMMINGA: Well, that was a pretty clear sweep, but it also was not the more thorny of the questions. Oh, yes. I'm yes, also.

DR. TITUS: There are 11 yeses.

DR. TAMMINGA: Now, the next question that we have to vote on, has the sponsor provided evidence that ziprasidone is safe when used in the treatment of schizophrenia?

Included in the answer to this question, of course, is really the topic that we've been discussing all afternoon, and after we get done voting for this question, we'll still have a chance to address, although not vote on, the other issues that Dr. Laughren laid out for us.

If you'd like to start again around the table?

DR. GRADY-WELIKY: I was actually hoping we could start on the other side.

(Laughter.)

DR. GRADY-WELIKY: It's a harder question. I guess my thought is that I'm going to say yes, with a caveat that I think there needs to be more work after this. I think that there's a lot of question that was raised around, you know, what the QTc interval really means, if there's a way to screen for it.

I think Dr. Fyer's question about how much, you know, what's the difference, if it's 60 milliseconds or 20

milliseconds, starting at a baseline of 320 milliseconds, or if it's 20 starting at 440.

So I think we certainly need to have more data, but I think outside of that, my vote would be yes.

DR. TAMMINGA: Dr. Oren?

DR. OREN: My vote would be yes, with the encouragement that the FDA use all of its powers to ensure that safety is fully assured in the practice and the use of the drug, and that the public hears the message that the FDA provides with the labeling.

DR. ORTIZ: I think I'm going with a qualified yes. I think following Dr. Cook, my concern would be the elderly and what is lacking in information about the elderly, and what Dr. Lindenfeld has suggested about interactions with beta blockers and calcium channel blockers, which are so commonly used in the elderly, and as a geriatric psychiatrist, I'm particularly concerned about that, but my vote is yes.

DR. TAMMINGA: Dr. Hamer?

DR. HAMER: I'm going to do something I don't think I've ever done before at one of these meetings, which is I'm going to abstain because I just don't feel that I'm comfortable enough with or know enough about the relationship of the lengthened QTc intervals to the risk of arrhythmias and related illnesses, and I haven't gathered

enough information at this meeting to really enable me to interpret that correctly.

DR. MARDER: Yes.

DR. LINDENFELD: This is a difficult question for me because I think it involves what is safe, and that's a relative, what is safe. So do I think this drug is perfectly safe? No. My suspicion is that there will be an excess of torsade with this drug, particularly when more drugs are added as you see the drug used in the real world.

So is it perfectly safe? Again, you know, I guess this gets down to will there be an excess risk of torsade? I think from the data we have, we would guess that there will be. I think that the risk will be relatively low.

So I don't know quite how to answer that safe, unless you want to define it for me more precisely.

DR. TAMMINGA: The safe is qualified by has the sponsor provided evidence that ziprasidone is safe when used in the treatment of schizophrenia?

DR. LINDENFELD: I would say no.

DR. TAMMINGA: Dr. Katz?

DR. KATZ: Well, I think it's a fair question for sure. I think when we say safe, I think we mean in this question placed here whether or not you think there is sufficient information available at the moment about the

toxicity, so that we could write adequate labeling, so that the drug could be used, so that it's appropriate that the drug could be used with appropriately-written labeling at this moment, given the information we have.

DR. LINDENFELD: Again, I don't want to be difficult, but I think it's a difficult question. I think that labeling could be written to minimize the risk, but I think there will be a small but excess risk probably with this drug, based on what we know about other drugs that prolong the QT interval.

DR. KATZ: Fair enough, but I think we're asking you, given your belief about what you think the risk is or will be, whether or not you think it's appropriate to market it at this time.

DR. LINDENFELD: Not without other data about use of additional drugs with this drug.

DR. TAMMINGA: Dr. Rudorfer?

DR. RUDORFER: I would say yes. My concerns, I think, can be addressed with labeling and post-marketing issues that we'll talk about.

DR. TAMMINGA: Dr. Cook?

DR. COOK: Yes. I would say yes, and again we're going to have to have a discussion about how strong the labeling would be, and in my sense, it's going to be quite strong and is going to exclude use of concomitant

medications that may cause a problem.

DR. WINOKUR: Yes.

DR. MALONE: I'm not sure -- we had evidence that labeling doesn't -- well, at least the "Dear Doctor" letter doesn't seem to be paid much attention to.

Does the FDA have post-marketing things they can do different from one drug than another or is everything the same? I guess that's a question I'm asking.

What could be done post-marketing to assure that there is clear follow-up about these cardiac risks?

DR. KATZ: Well, there are things that can be done. There are things called Phase IV commitments. In other words, where we require a sponsor to perform additional studies once the drug is approved. There are mechanisms by which we could restrict the distribution of the drug once it's approved, so that only certain physicians or only certain centers, you know, could have the drug available.

There are registries that we could talk about possibly setting up so that the first X numbers of patients or some reasonable sample are followed prospectively. So there are things that can be done once the drug is approved.

DR. MALONE: I would say yes, if there are some specific things that are set up to do follow-up that are

somewhat different than most medications.

DR. TAMMINGA: My vote is yes.

DR. TITUS: So we have one abstention, one no, and nine yeses.

DR. TAMMINGA: This particular vote on safety came along with a lot of caveats, and I wonder if it might be useful to the FDA to have from us the most specific ideas about those caveats.

DR. LAUGHREN: Yes. Anything you can say along those lines would be helpful.

DR. TAMMINGA: Dr. Grady?

DR. GRADY-WELIKY: I think there are two things that I think are critical, and I think the first relates to the drug-drug interaction with the concomitant medications, and whether or not there's going to be a labeling issue there we can talk about.

But I think given the patient population that we're dealing with, it will be on multiple medications. So I think that risk needs to be looked at in the form of a study.

The other is the labeling question that was raised by a number of people. I think like Dr. Malone, I have concerns about whether or not physicians will follow that, based on the data that Dr. Rodriguez, I believe, presented.

So those are the two things that I think really need to get looked at and talked about. Perhaps the labeling -- since this is my first meeting, I don't know all the details about the labeling, but that's something that maybe we can get addressed here.

DR. TAMMINGA: Dr. Marder.

DR. MARDER: Well, in the labeling, I would make it very clear that there is very little experience with doses over a 160 milligrams a day, and that just strong language to discourage that because that's unknown territory, and there could be serious problems.

Also, it could very well be that the maintenance data showed that a dose of 40 milligrams -- I mean, 40 was as good as 80 as good as 160, and for physicians to reduce the dose as quickly as possible over the long run might increase the safety of the drug. Those kinds of statements might be helpful.

DR. TAMMINGA: I would add a recommendation for a dose escalation study above a 160 milligrams.

Dr. Hamer.

DR. HAMER: As long as we're talking about labeling and notwithstanding the fact that I abstained on the safety vote, Dr. Rodriguez used the phrase "label fatigue." That was you, right?

DR. RODRIGUEZ: Yes.

DR. HAMER: Which I actually thought was a wonderful phrase. I wonder if there's any evidence, though, that the initial language in a label, when a drug is first approved, is somehow intended to better than these repeated changes, "Dear Doctor" letters, and so on, so that notwithstanding label fatigue, if the label is sort of written strongly in the first place, that will shape the behavior on the part of the physician to prescribe it.

DR. RODRIGUEZ: We don't have information on that, but it's certainly something that the sponsor can be encouraged to look at.

DR. TAMMINGA: Dr. Cook.

DR. KORVICK: Well, I think, just to follow, just to make another statement, I agree with Dr. Rodriguez, but I think it also impacts the kind of marketing that the company can do, because that's based on the language that's in the label, which may turn --

DR. COOK: I'm sorry. I want to make a very strong plea for patient package inserts and any other approaches. Obviously, I know that NAMI and other groups will be effective in this way and would encourage the FDA to work with groups like NAMI.

The more we educate the patients and their families, the more that we'll have another safeguard in place there.

DR. WINOKUR: Just to repeat the same theme that we've been talking about, but now we're talking about labeling, I think the fact that it's been clearly acknowledged that we don't have information about additive effects with other drugs that could affect QTc, we just don't have information about that, and that totally changes how we would feel about, you know, the safety potential needs to be clearly communicated.

DR. TAMMINGA: Dr. Malone, have all of your caveats been attended to in what people have been saying or would you like to add something?

DR. MALONE: Well, I'm a child psychiatrist, so clinically, I see drugs given to children a lot. What I see happening is as soon as a drug hits the market, a lot of children end up on the drug, and I think that's a particular concern with ziprasidone.

So if somehow the insert or the advertising would strongly indicate that it hadn't been tested in children very well, and that we don't know what the QTc effects will be in children.

DR. TAMMINGA: We might want to recommend studies in children.

DR. MALONE: Yes. I would also want to recommend studies in children, but that could take awhile to get done, and by the time that gets done, if the drug's

on the market, it could have been prescribed many times.

DR. HAMER: I do think the labeling ought to strongly indicate the potential risks associated with prolonged QTc intervals, regardless of how well that's quantified and how well you all understand them.

We haven't yet talked about one of the other questions, which is, what prominence should the risk be given in the labeling, and I'm not at all sure that this really requires a black box warning, but the warnings certainly needs to be there.

DR. TAMMINGA: What other recommendations would people give about a black box or a warning statement?

Dr. Moss.

DR. MOSS: Well, it's not addressing exactly that question, but I do feel it's important to get higher doses. I think it's really critical. It's surely going to be used in higher doses, above a 160 milligrams, and so they have some data on 200 milligrams, and it would seem to me that they ought to look at some higher doses just to make sure that there in fact is a plateau. That would be extremely reassuring with regard to the QT interval question.

DR. TAMMINGA: Dr. Malone.

DR. MALONE: How does a black box affect how the drug is advertised? I mean, what patients or

physicians are often influenced by is by drug reps coming around and leaving advertisements.

I don't think very many people read the drug inserts or the PDR. So that the most influential thing is the advertising, and I'm not sure how any of these things influence what is written in the advertisement.

DR. TAMMINGA: Dr. Laughren or Dr. Katz.

DR. KATZ: Unfortunately, I don't know exactly either, but I know that if there's a black box, it certainly has an effect. It's got to be in the ads. It's, I think, got to be on anything that is handed out that's imprinted with the name, this sort of thing.

There are definitely more requirements for a drug vis a vis advertising and promotion if it has a box warning.

DR. LINDENFELD: I would think at least you'd want to have a strong warning that the drug right now should not be used with other drugs that are known to prolong the QT interval with what we know now. I would think that would be a very important and strong warning to make.

DR. HAMER: And as Dr. Laughren originally mentioned perhaps and others, also used with other drugs that inhibit the cytochrome P450, was it, 1A4, was it? I don't know. But, you know, other drugs that potentially

could interact with it in terms of inhibition.

DR. OREN: Dr. Laughren specifically asked if a compliance study should be required. I think it would be to the company's marketing advantage if they sponsored such a study. I'm not sure if that needs to be a preapproval requirement, especially because in many ways, the proof of the pudding with the drug will be if people in fact are compliant with it.

Obviously there are problems with labeling issues, and people have been buying boxes of cigarettes for 30 years that say right out on the box, this will kill you if you use it, and people still use it. So labeling is difficult, but maybe one innovation could be -- and I don't know if this is currently within the FDA's purview, if marketing representatives, when talking about the drug, whether at conventions or in meetings with physicians, could emphasize the known or the potential risks with QTcs because certainly hearing a negative from a marketing representative is a novel feature that might attract people's attention.

DR. LAUGHREN: Well, promotion directly follows from labeling. So we have a lot of control in what we put in labeling, and that does influence the promotion.

DR. TAMMINGA: Dr. Laughren.

DR. LAUGHREN: Could we have some more

discussion about some of the other items under Question 4, first-line versus second-line, and then, there's already been some comment on a patient medication guide, but I don't think everyone here's had a chance to comment on that? Maybe there's universal agreement on that. I can't tell.

DR. TAMMINGA: The medication guide for patients was something that Dr. Cowdry in his public remarks actually recommended, and I don't think that -- there may not be a single physician who wouldn't really concur with that.

I don't know how much of an innovation that would be. Is that common to have patient guides written by the FDA?

DR. LAUGHREN: It's more common. I mean, we're using them more and more, and again the idea is to provide key information to patients and their families, to guide them in their use of the drug, and what they should be telling their physicians about, you know, their other medications and perhaps other conditions they may have that may be influenced, you know, by interacting with the drug in some way.

So more and more, we're using those when there's something useful that can be conveyed that would impact on their care.

DR. TAMMINGA: I think what's particularly fortunate about that now is that the National NAMI has actually initiated a program to have consumers and families become more informed and become more active in these kinds of issues.

Dr. Cook.

DR. COOK: There's a particular point to educate about in this case, and this comes back to what Dr. Cowdry said. There are some things patients need to know to call the physician immediately or head to the ER right away, and others that they need to know, well, that's tough, kind of stick it out.

One of my concerns is by the history of these medications, patients may have actually gotten used to the idea that lightheadedness is okay and actually counseled, oh, you're going to feel lightheaded from this medication, but in this setting, obviously not all lightheadedness is a severe event, but it may be a prelude to a fatal arrhythmia. Education of what it is and how to describe it to your physician would be helpful.

DR. TAMMINGA: Dr. Marder.

DR. MARDER: What would be most useful would be a patient information which wasn't specific to ziprasidone, but that related to antipsychotic drugs, and that had the advantage, you know, the advantages and disadvantages of

the different drugs rather than a specific one for ziprasidone.

Now, that may be difficult to do, and it's a big leap forward to start with ziprasidone, but I think in the long run, it would be most useful to have it for this group of compounds.

DR. LAUGHREN: If we had head-to-head comparisons of all the drugs that generated good data, then we could write those kinds of inserts. I'm not sure that we're at that point.

DR. TAMMINGA: Dr. Katz.

DR. KATZ: Yes. Not to beat it into the ground, but before the committee discusses these other subsections of Question 4, first-line versus second-line, we've had some discussion about box warning, but I don't really have a good feel from the committee as to whether or not people think a box warning specifically is necessary or not necessary, and Dr. Hamer was pretty clear. You said you didn't think it needed to be a box warning.

But I just don't have a sense of the committee on that specific question.

DR. TAMMINGA: Dr. Malone.

DR. MALONE: I was thinking it was necessary. I was thinking that a box warning with some of this was necessary at this point in time at least.

DR. TAMMINGA: Would any of the other committee like to weigh in? It's really a box warning of a hypothetical risk?

DR. MALONE: Well, in my box warning, I would also put that the effect of QTc in children and adolescents is fairly unknown, and it is known that it does have a definite effect in adults, so that there should be extra caution.

DR. LAUGHREN: Maybe it would be helpful to give a little bit of discussion and background on what the general policy is about when we use the box as opposed to not using the box.

It's generally for a very serious event, an event that, you know, we feel very strongly is related to taking the drug. Generally, in my experience, it's when the events, you know, have actually been realized, and you're more likely to include a box if there's some important information you can convey in the box that might prevent the event from happening, if there's some kind of monitoring or screening or something or some kind of advice you can give that might help to detect or predict, you know, prevent the event from happening.

So it's sort of some general background about when we use boxes. I mean, just as an example, in this recent labeling change for thioridazine, we did use the

black box, but, of course, there, you know, that decision was in part based on the fact that there have been a number of post-marketing reports and other literature reports of actual cases of torsade occurring with thioridazine.

DR. TAMMINGA: Dr. Katz.

DR. KATZ: I would just add one other aspect, which is that not only do we necessarily only restrict it to cases where we think there's something you can do to prevent it, but also if we think it's a serious and a significant enough risk that it might affect your decision as to whether or not to use the drug in the first place.

DR. TAMMINGA: One might wonder whether you could have something like an invisible box that you could activate whenever there was an event that became apparent.

DR. GRADY-WELIKY: With the better understanding of what a black box means, I guess my sense would be I don't think we know enough right now to make it a black box warning, that the company hasn't shown us data that shows any torsade or any significant clinical event based on the QTc interval change. So I would say no to the black box.

DR. LINDENFELD: They also haven't shown you any data on any other drugs, and I would just be cautious about -- at least somewhere in there, it would be my strong feeling that they ought to say something in a very strong

way about using other drugs that are known to prolong the QT interval when combined with this, and I think we're also talking about using this drug by physicians who don't usually think about prolonging the QT interval, and who might not be aware of the very large number of drugs or the fairly large number of drugs that do prolong the QT interval.

I think while we don't know the precise risk, and it may be very low with this drug alone, most of us would guess that the risk would go up substantially when combined with other drugs that are known to prolong the QT interval.

DR. OREN: This comment is directed specifically and only to the black box question. I think that the only places we see black boxes are in the obituary sections of the newspaper as well as in the PDR, and I think that without that level or near that level of danger, we would be risking the situation of crying wolf and causing label fatigue if we used a black box prematurely.

I think all of the warnings and all of the concerns that have been expressed here should be in the labeling and in the education, but I would personally encourage holding off on the black box at this point.

DR. COOK: Okay. I'm not that strongly in support of the black box, but I moved in that direction

with the idea that basically relates to what's happened with thioridazine. It's going to be a lot harder, I think, to make an impression with the black box after years of not having it and then moving toward having it.

It also shows that perhaps the only difference between -- and I know there's some other quantitative differences, but they're not sufficiently reassuring to me. The biggest difference between sertindole, thioridazine and this medication is that we have post-marketing data that showed the deaths.

So I'm coming back to your comment that although we could be reassured by the mortality data, that without the post-marketing data, we have a drug that prolongs QT, which may be a severe risk, and we should tell people that up front.

Now, if it turns out to be unwarranted, I'd be much more feeling like people's behavior could change in the easing-up side than the tightening-up. I'm not a 100 percent on this, but that's sort of how I lean on it.

DR. TAMMINGA: Dr. Katz.

DR. KATZ: Well, there are, I think, other differences between this drug and sertindole, other than the post-marketing reports, which is that about 7 or 8 percent of patients in that development program had QTcs greater than 500 milliseconds, and the mean increase in QTc

was greater on certain as it is here. But, right, there were no other cases.

DR. WINOKUR: Just to weigh in, since we're kind of informally polling, I'm not in favor of the black box. I agree with the gist of the comment that you made before, that we've seen actually quite a bit of data on the population that's been studied, and then we've also discussed the importance of the QTc findings and the vagaries of interpreting that and extrapolating that.

So we certainly need to be attentive to that and need more data, and again many of us have addressed the concerns about when other drugs are on the scene, but I think that's a different type of labeling and advising at this point than what would be implicated with the black box.

DR. TAMMINGA: Dr. Marder.

DR. MARDER: Well, I'm going to be very ambiguous in this answer, but I think guiding clinicians to make sure that patients aren't taking other drugs that prolong the QT interval and making sure that they're not using excessive doses, if it takes a black box to save lives in that particular -- if it does work that way insofar as the labeling and the advertising, and it would really save lives by preventing clinicians from doing that, I could be convinced to support it, and if there was

something in between, like bold print or something like that, that would guide clinicians to do that, and that that had to be part of the marketing of the compound, that would make me feel better.

DR. KATZ: There are bolded warnings as opposed to boxed warnings, which are usually bolded, also. How they actually influence anybody's behavior is another question.

DR. TAMMINGA: Does the FDA have any ability to influence something like a company's activity in educating the physicians during the post-marketing period?

DR. KATZ: Yes, I think we do. I think that's something that could probably be worked out between the agency and the sponsor.

DR. TAMMINGA: In this particular situation, especially as Dr. Lindenfeld pointed out, that this drug will be used by people not characteristically used to looking for cardiac abnormalities or changes in cardiac parameters, it may be that Pfizer could take a lead in doing some educational work amongst psychiatrists.

DR. ORTIZ: I think I'm the last one to vote on the black box, and my feeling is that the incidence of torsade de pointes and the overdose data don't suggest to me that a black box is necessary. But I think a strong warning is.

DR. TAMMINGA: We haven't yet addressed Dr. Laughren's question about first-line versus second-line status, and I don't want to really end before we address that to some degree.

Dr. Marder may be the one amongst us who has a lot of experience in this area, and you might want to lead off the discussion.

DR. MARDER: Well, I was going to ask a question. Does first-line versus second-line mean that the drug should -- one way to interpret it, that the drug should only be considered after other drugs have been considered, the other is that this drug should only be used after other drugs have been shown to have problems.

What's your interpretation of first-line versus second-line?

DR. KATZ: Well, I think you can write labeling any way you want. So I don't think there is a specific definition. I would say in most cases, in my experience, when we talk about second-line, the labeling says something along the lines of where other appropriate drugs have failed, but you could easily say or when the patient's not a candidate for other available treatments. So it could be both.

Usually I think in practice, it's when other drugs have failed, but you could do it any way you want.

DR. LAUGHREN: Very often, the language includes both failures and patients who can't tolerate other appropriate drugs. So if that's what you meant by it.

DR. KATZ: Well, that's one way to fail on a drug, is to not be able to tolerate it, but if you're asking whether or not you can call second-line, you can call usage second-line when other drugs haven't been tried, but you think they're not going to work. Usually we ask that the other drugs be tried, if there's no compelling reason not to.

DR. LAUGHREN: Actually, if I could just add another comment, another issue along these lines, when we make a drug a second-line drug, is the question of whether or not you actually have evidence that the drug works in patients who are in some sense refractoried to other drugs.

You know, we have not been, you know, uniform about requiring that. For example, the change that we've just made with the drug thioridazine, we've made it a second-line drug, but that's clearly in the absence of any systematically-collected data that it's superior in patients who've failed in other drugs.

So we could go either way with that, and again one of the questions that I posed is whether or not you think, you know, there should be data here on the efficacy

side to suggest some benefits, you know, over other drugs in the class.

DR. MARDER: Let me just put out, it would seem to me that in healthy individuals, treated at a dose of about 80 milligrams a day, it hasn't reached the threshold for me that would make it a second-line drug.

On the other hand, in some settings where clinicians are treating vulnerable populations and are escalating the dose, it might not be, but based on that, my tendency would not be to add the term "second line" but just make it sure that clinicians as they prescribe it consider these other problems with the drug.

DR. TAMMINGA: Dr. Winokur.

DR. WINOKUR: I feel strongly, based on what we've had presented and heard, that it should be in the first line, and I think there are at least a couple of reasons for that opinion.

First of all, I think that the notion of showing that a new drug in our field is better than what's currently out there is a really tough standard, and I would take almost any therapeutic category and wonder, except for very selected cases, when and how it's been possible to show that.

What we've had is a lot of drugs that have been shown to be comparably effective, but once they're out

there, as we know clinically, we often find they have great utility in selected niches, but it's kind of at a different phase.

The drug and our understanding of how to use it appropriately will be greatly disadvantaged if it's immediately relegated to second-line status, especially when we've seen data to at least equate it to standard accepted first-line drugs. We have no reason to feel that from an efficacy perspective, it's inferior, and I think we may learn over time about ways that it's particularly clinically valuable, and so the only additional reason to put it in the second-line status is, in my understanding of that, if there were health concerns that ought to cause it to be really held back, and we've already kind of had that discussion.

DR. TAMMINGA: Dr. Rudorfer.

DR. RUDORFER: Yes, I agree. I think it would be a mistake to force people to start off on the wrong foot, to have an unfortunate experience with a different drug first, but I think our efforts should be directed at alerting clinicians that thoughtfulness is required to use this drug, that it just shouldn't be casually introduced because it's the newest thing around.

DR. TAMMINGA: Anybody else want to weigh in on the first- or second-line question? Dr. Ortiz.

DR. ORTIZ: Yes. I think I'd agree that the data that we've been presented and the information certainly makes it a very reasonable first-line choice.

DR. TAMMINGA: I wonder if there might be additional comments on the other topic that Dr. Laughren brought up about whether or not we would recommend that the company look for a special niche or a special treatment group where efficacy was superior.

When I was looking through some of the initial material, it really wasn't in the neuroleptic refractory group that it seemed to me there was some indication that ziprasidone might be superior but rather in cognitive dysfunction, and one might wonder whether a recommendation to look for superiority in the area of the treatment of cognitive dysfunction.

I don't know why one -- the company's probably in the process of doing it, but whether something like that might be useful.

DR. GRADY-WELIKY: It's not exactly a comment on what you just asked, but in terms of recommendations for additional studies, post-approval, if that's the decision, one would be to look more closely at women receiving ziprasidone.

I think Dr. Lindenfeld brought up the idea, and it's in the back of the material, that women are more

likely to have prolonged QTcs, and the numbers were fairly small, at least in the 054 study. So that would be one suggestion.

I think the other thought would be to look at a broader group, as Dr. Cook raised, in terms of the ethnic groups. I think the company did a great job at having a large number of non-Caucasian subjects, but it's not clear who's in that other category, and we do know that there's a lot of differences across ethnic groups, particularly in Asian and Hispanic populations.

DR. TAMMINGA: Dr. Winokur.

DR. WINOKUR: I think early in his presentation, Dr. Harrigan did a very nice job of pointing out that as is true with other of the atypicals, this drug has a very unique pharmacology that may lend itself to notions about specific utility and efficacy, and I'm sure between the company's efforts and very capable clinicians out there in the field working with the populations, there will be a lot of ideas about how to apply that.

But, you know, again the point is that I think we can really think about looking at the match of clinical needs and opportunities and pharmacological distinctiveness that may help to get past the sort of broader studies that have to be done to bring things to this point, so we can vote on the first question that we had to vote on but can't

really get to the point of kind of dissecting out the kinds of questions that that agenda would raise.

DR. TAMMINGA: Do you think that those studies might be driven by the field, indeed not be required by the FDA? I would ask Dr. Laughren and Dr. Katz if they have any more questions that they'd like the committee to address or if you think that we've covered our pink sheets.

DR. LAUGHREN: I guess my final question would be again on the first study that was proposed here, whether or not the committee thinks that there should be strong encouragement or requirement that some kind of study be done to try and come up with an estimate of what the risk might be, some kind of quantitative estimate, recognizing that that's perhaps a very difficult study to do, but it's an unknown here, and it's possible that we may never or not for a long time know the answer to that question, if we were to rely solely on post-marketing reporting, because unless a drug that has some marginally greater effect on the QT results in a lot of cases of torsade, we're not likely to pick up a small differential increase in post-marketing reporting of sudden deaths.

So that's just sort of, you know, one remaining question. How strongly should we push for that kind of study, again recognizing it's a difficult study to do?

DR. TAMMINGA: Dr. Califf, who was one of the

people who seemed a strong supporter of that, is not here. Maybe Dr. Moss or Dr. Lindenfeld would like to lead off on this question.

DR. LINDENFELD: I'd be interested in Dr. Moss' comments, too, but I think it would be important to have additional data on people who are on a substantial number of other medications, particularly some of those ones that increase the QT interval a small amount but do affect the QT interval.

DR. MOSS: I would agree with that. I personally think the most important thing is to do just simply a very simple higher dose there. I would be very reassured if higher dose did not increase the QT interval. I think that this would bode very, very well.

I think to require outcome events, that's going to get reported anyway. They should be encouraged to, but I don't know how you can actually make that a requirement.

DR. LAUGHREN: So you would be reassured by just a better exploration of the dose-response for QT, basically?

DR. MOSS: I would, indeed. That would be very reassuring. I think the data they've presented has been very, very solid, but the one area that we don't know, we just have really a small dose above what is the 160 milligram dose, and to have a 240 or 300 milligram dose in

a relatively small number of patients, just to see if there is a dose effect, if in fact there's not, that would be reassuring.

DR. TAMMINGA: If there aren't any more comments from the committee or questions from the FDA, I'll take the prerogative to thank the committee for working hard all day, to thank Pfizer for presenting, and for the FDA for inviting us all.

Thank you.

(Whereupon, at 4:56 p.m., the meeting was adjourned.)