that may have effect upon the HERG channel and what their implications are. The number of patients with genetic mutations is very small. What we don't know is how many patients are out there with minor modifications, what we call polymorphisms of the channel, that may be a factor contributing to some differential sensitivity between patients.

Now, this is an oversimplification and I only want to use it as emphasis. We actually use the RR interval before the measurement of the QT. But the measurement of the QT, as was nicely pointed out by Dr. Harrigan, has its errors in measurement, and this is the reason why it's important to have unbiased central measurement of the QT interval, and with enough patients, those measurement errors can even out. But it ends up as a quantitative measurement and is, of course, what is most sensitive to any statistical test. So this is just a schema of what is generally done.

Now, the relationship between the QT interval and the cycle length is curvilinear, and the longer the cycle length, the greater the QT interval, and the reverse is the case, as was pointed out earlier. What I happen to have drawn in in terms of the upper boundary here is based upon the Bazett formula of the square root. At a heart rate of 60 beats per minute or a cycle length of 1 second,

one is talking about an upper limit of normal by the Bazett formula of about 440 milliseconds. This is just a general approach.

But as was also mentioned, it's more complicated because you could do any of a number of different formula, from the Fridericia formula that uses the cube root to various types of linear formulas. Generally, in the range that one is dealing with for these types of studies, where the heart rate is between roughly 60 and 80, you're in a range here where no real formula makes very much difference. The problem comes when a drug has a very significant effect upon the cycle length, an increase in heart rate or a significant decrease in heart rate in terms of magnitude as well as significance, that other formulas and more appropriate formulas seem to be better indicated.

But in what we're dealing with today, I personally don't think it makes very much difference whether one uses a cube root formula or a square root formula or a linear formula. If you're looking for change, it's going to be very, very similar.

So these are the three standard formulas that tend to be used most, the QT with the Bazett, the QT with the Fridericia using the cube root, and the so-called Framingham or linear expression formula. The FDA has

become more intrigued by using correction formulas based upon the population of patients that one is generally dealing with, and this does give a little bit more precision because the fact of the matter is the Bazett formula is based originally on only 20 patients. I mean, it's not a very big sample on which to base a lot of interpretation.

So the Framingham formula is based on a much larger population of patients. It's a little bit more cumbersome to use, and for the area of heart rate that we're dealing with, these give really roughly equivalent effects, particularly if one is looking for the change of effect, the delta effect.

Now, what I'm showing here is based upon a large experience from the genetic long QT syndrome, and it's trying to get at some idea of the QT interval and risk. We've been aware for some time that the patients with the longer QT intervals have the greater risk. This information was developed before there was the genetic identification of patients who were affected and unaffected. So this includes a large population of patients, upwards of 1,000 or more, in which we had long-term follow-up and looking at the risk as a function of the QT interval.

Let me say at first that this is a continuous

expression, the QT interval, and it does appear that the interval does influence the risk, even when we don't do it quantitatively and, as I say, just looking at the patients who have had episodes for the most part are the ones who have had the longer QT interval. But when we try to actually model this, we come out with an exponential risk assessment in which the risk related to the exponent of this base, if you will, and the risk being an increment of the millisecond increase above the baseline. It turns out to be each unit being 10 milliseconds. So we take the milliseconds and just simply divide by 10.

So just in a rough comparison, once again based upon the genetic QT interval population, if we start with a QTc of a maximum of 440 milliseconds, we'll take this as our arbitrary reference, and 1.05 raised to the zero power would be a relative risk of 1. If we go up to 500 milliseconds -- that is, a 60-millisecond increase or a 6 unit increase in this exponent -- we see a relative risk of 1.4 relative to the baseline QT interval. If we go to an extreme value of 640 milliseconds, we're talking about a relative risk of a person experiencing an arrhythmic event in the range of 2.8-fold greater than the patients who have a 440-millisecond baseline or a comparative individual with a 440-millisecond QT interval.

So the point I want to emphasize is that there

is not an absolute cutoff. There is some continuum of risk. I think that the extrapolation to drug-induced prolongation has to be taken with a grain of salt, because this information is based upon a genetic population of which some patients had QT prolongations and were affected and some weren't. But for the most part, the longer the QT, the greater the likelihood they were affected genetically, and also the greater the QT interval, the greater the likelihood of an episode, either a syncopal episode or a fatal arrhythmic event.

I wouldn't want you to get hung up on these specific numbers, but it's fair to say that there is an increase in risk with greater QT prolongation, and probably the cutoff that's been used of 500 milliseconds is just based more on common sense than specific numbers. But if we try to quantify it, we're talking about a risk over any period of time -- a month, a year, 10 years -- of being 1.4-fold greater than patients who have a normal or a reference QT interval.

This is just to point out the type of concern if one happens to record it in terms of an episode. Obviously, you could consider this either a syncopal episode if it terminates or a fatal episode if it continues in this way. But this is fundamentally what the FDA is concerned about, trying to protect patients who might have

this type of episode related to a drug as opposed to spontaneously. This is just the continuation of this. This patient just happened to stop, so this patient had a syncopal episode. You can see the QT prolongation here very clearly. In fact, this is a genetic disorder in this particular slide that I'm showing.

Now, let me just get into the issues that are really what we're dealing with. In one way or another, the greater the QT prolongation, the greater the risk. We've put it in an exponential form, and I'm sure there can be more precision about this in the future.

The second issue is the magnitude of the QT signal. Most of the time, what's reported is the mean or median delta QTc interval, and this is what we've heard a lot about. Because one is trying to determine if this is a meaningful signal or not, and one is generally dealing with a relatively small study population relative to the population that's going to have the drug administered if it's approved, a mean QTc of 10 milliseconds or 20 milliseconds doesn't sound very long. But the question is, what are the outliers? That was the reason for looking at the range of values and the outliers, particularly the highest ones.

These were reported earlier this morning by Dr. Harrigan. So this magnitude of effect, what one is

particularly looking for is any signal. Now, how much does one interpret a signal on 33 patients as opposed to 33,000 patients is an area of extrapolation. That's really where the judgment comes in, and there are no simple answers. But this is really one of the issues that is faced by any advisory group.

Then the other thing is to look at the effect of the drug on the QTc, and now we're talking about direct effects. That is, does the drug have an effect upon the IKr channel? This was studied in this particular situation, and this is now being done in a very regular way with expression studies in which one can put in the potassium channel into an embryonic kidney cell or an atrial tumor cell and actually express the gene, the normal gene, the normal channel, and then study the dose concentration in the preclinical studies.

So, does the drug have an effect on the ion channel? Sotalol and cisapride are yes, and so is the drug under consideration. So there were studies that were reported in the handout in the booklet that was provided. These are the direct effects, and one can get some idea of what is the likelihood of getting into problems clinically depending upon the magnitude of the effect that one sees in preclinical in vitro expression studies.

Then one is looking for interactions, and one

is looking for two types of interactions, what can be referred to as drug-drug interactions, the classical one being the terfenadine-ketoconazole one that we're all familiar with. But there are also drug-gene interactions which we don't completely understand. Those rare individuals with mutations, long QT syndrome, would be more likely to get into problems, and the one patient who did get into problems apparently had at least a baseline QT interval that put him in that category.

But what we don't understand and there is no information available at the present time is that there are polymorphisms in the gene. The gene does not necessarily express itself in terms of QT prolongation, but such individuals may be more sensitive to the drug, and one would never see this in a small sample population. That's why it becomes an issue after the drug is released. So these are important considerations, the direct effects and indirect interactions. Indirect interactions are tough to pick out statistically on small sample size populations.

Then the final slide is what are really the questions. It seems to me the questions go in some order like this.

Do the preclinical studies indicate an effect on ventricular repolarization? It seems to me that's done in expression studies or in some animal models, and that's

an important starting point. If the drug has major effects in preclinical studies, it probably doesn't get to the clinical realm.

Do clinical studies indicate a QT signal? Now, we're not looking for, in small samples, does the QT produce mortality, because we wouldn't have enough patients, but is there a signal that's present.

And what is the magnitude of the signal? Because we do feel there is some relationship between the length of the QT interval and the occurrence of arrhythmic events.

Then the fourth question, are there potential drug interactions? I think this was what was addressed in the request that was made for the 054 study.

Then finally, does the drug have unique characteristics?

As a clinical cardiologist and with interest in QTc, this is the way I tend to look at these issues. Thank you very much.

DR. TAMMINGA: Thank you, Dr. Moss.

We'll turn now to the presentation of Dr. Dubitsky. Dr. Greg Dubitsky is a medical officer at the Psychiatric Drug Products Group in the FDA.

DR. DUBITSKY: Good morning, Dr. Tamminga and members of the committee. This morning I'd just like to

take a few minutes to present some important clinical data regarding three antipsychotic agents that I think are pretty well accepted by most people to have some cardiac effects of substantial importance; namely, thioridazine, pimozide, and sertindole. I'd also like to present the regulatory actions that we've taken with respect to these drugs in response to these data.

I'd like to start with thioridazine or Mellaril. If you go back and look at some of the data in our files on Mellaril from the late 1950s and early 1960s, there's really very little mention of any EKG effect or sudden death, anything like that. In fact, this is one of the first reports suggesting that thioridazine might have adverse cardiac effects. It's reported by some of our Canadian colleagues and describes 28 electrocardiograms that showed an effect of thioridazine on ventricular repolarization.

Next slide.

For several years, Mellaril has been on the market and has had some mention of ECG effects in the labeling, but it's been rather inconspicuously labeled, until we got into the 1990s with a heightened awareness and sensitivity to the QT effects of drugs. The first data I'd like to present come from a study that was done in Sweden by Hartigan-Go. This was published a few years ago. It

was a randomized, double-blind, three-period crossover study, a single dose that looked at two doses of thioridazine, 10 and 50 milligrams, and placebo, with a one-week washout in-between the periods. This study was done in nine healthy males who were relatively young. All the subjects completed the study, and all were rapid hydroxylators of debrisoquin.

Next slide.

Just focusing here, this study does have a lot of data, but I'm just going to focus for our purposes on the QTc data from this study. This is a graph that showed, following single doses of placebo, 10 and 50 milligrams of thioridazine, what the changes were in the Bazett-corrected QTc. I think it's pretty clear that the maximal effect was seen at about four hours post-dose. Looking at that, you can see that for 50 milligrams of thioridazine, there was about a 23-millisecond change from baseline, or probably about a 28- to 30-millisecond increase over placebo at the four-hour time point. For both doses of thioridazine at that time point, the changes were statistically significantly higher than for placebo.

Next slide.

There were no adverse cardiac effects or events reported in that study, and the QTc's were generally under 440 milliseconds. However, we did take these results with

a grain of salt because we felt that the effects seen here may in fact underestimate the experience that would actually occur in clinical practice, because these were single doses, they were low doses compared to what's usually used in clinical practice, which is probably more like 300 or 400 milligrams a day. The study was done in healthy volunteers who were taking no concomitant medication.

Next slide.

The next piece of data comes from Study 054, which has already been discussed at some length, so I'll just hit the high points with respect to QTc and cardiac effects. As was described, this was an open-label parallel group study in which patients were titrated to ziprasidone, thioridazine, haloperidol, at these dose levels. There were also the other atypical antipsychotics that were used. But for my purposes here, I'm just going to focus on these three treatment arms. ECGs were done at the estimated Tmax at steady state.

Next slide.

The results without inhibitor, using the Bazett correction, were as shown here. The change for ziprasidone was about 20.3 milliseconds, with a 95 percent confidence interval of 14 to 26 in 31 patients. Thioridazine was considerably higher, and if you look at the 95 percent

confidence intervals, they really don't quite overlap. Haloperidol was at about 4.7 milliseconds, considerably less than ziprasidone and thioridazine.

Next slide.

Looking at the categorical change in QTc from baseline, I'd just point out here that most of the ziprasidone patients -- or, actually, very few of the ziprasidone patients had changes from baseline greater than or equal to 60 milliseconds, and very few greater than or equal to 75 milliseconds. The percentages were somewhat less than thioridazine but considerably higher than in the haloperidol arm. No subject in this study had a QTc greater than or equal to 500 milliseconds.

Next slide.

In terms of clinical events, there were no deaths or other serious adverse events in this study. There were no episodes documented of torsade de pointes, and no syncopal episodes reported.

Next slide.

Again, focusing on thioridazine, which is the main thing I'm talking about right now, there are several reports in the MedWatch database, in our postmarketing surveillance database, and from the medical literature with thioridazine of cases of torsade de pointes, other types of ventricular tachycardia, and sudden unexplained deaths.

Next slide.

These data really constituted the bulk of the evidence that we used to request some significant labeling changes this year, and as Dr. Laughren pointed out, there has been a "Dear Doctor" letter sent out to highlight these changes. One, of course, is a black box warning that does summarize the cardiac risks that we feel are associated with thioridazine. We have made it a second-line agent, and we have restricted the indication to schizophrenia. Previously there were some other non-psychotic conditions for which it was indicated in the PDR.

We've added a number of contraindications specifically with respect to drug-drug interactions. It does seem that patients who are poor hydroxylators of debrisoquin do develop significantly elevated levels of thioridazine, so we have contraindicated its use with inhibitors of CYP2D6. It's also contraindicated with fluvoxamine, propranolol and pindolol, since those drugs have been shown to elevate thioridazine levels. And, of course, it's contraindicated with other drugs that prolong the QT interval. As well, we've contraindicated it in patients with congenital long QT syndrome and in patients known to be CYP2D6 poor metabolizers.

Finally, we have recommended that all patients on thioridazine have baseline and periodic

electrocardiograms and serum potassium levels.

Next slide.

I'd like to move on to the second drug, which is pimozide. I don't have a lot of data to present, but the data I will present are from an electrocardiography report from three studies that were done in acute schizophrenia back in the early 1980s. This report essentially pools the data from these studies, and they were double-blind treatment studies that used pimozide and thioridazine treatment arms, with a pimozide dose in the range of 20 to 80 milligrams a day, a thioridazine dose of 200 to 800 milligrams a day. EKGs were recorded pretreatment and after 5 to 12 days of treatment with pimozide and thioridazine.

Next slide.

Unfortunately, these studies were interrupted due to three serious adverse events that occurred in pimozide patients. In these studies there were two sudden deaths that occurred at doses of 70 and 80 milligrams a day. Those patients had rather substantial increases in the QTc levels, at or above 500 milliseconds, and there was a third patient who had grand mal seizures and documented episodes of ventricular tachycardia. That patient was being treated with 80 milligrams a day and actually had an increased QTc at baseline of 560 milliseconds, which

persisted on follow-up.

It is interesting to note that among the pimozide patients, there were six patients who did have an increase in QTc greater than or equal to 100 milliseconds who apparently didn't have any significant cardiac events.

Next slide.

To summarize the QTc findings, after 5 to 12 days on pimozide -- and, by the way, the lower range there of 5 days or so probably isn't even enough to attain steady state with pimozide, which has a half-life of about 50 hours. But the changes that were seen, there was a mean change from baseline of about 50 milliseconds in the QTc. Fifteen percent of the patients on pimozide had a QTc greater than or equal to 500 milliseconds. Looking at the categorical change from baseline, you can see that a little over half, 55 percent had an increase greater than or equal to 50 milliseconds, and about 1 in 10 had an increase greater than or equal to 100 milliseconds.

Again, this is data from the early 1980s, prior to the FDA approval of pimozide for Tourette's.

Next slide.

In response to these data primarily, pimozide was approved but was not indicated for the treatment of schizophrenia. It's indicated as a second-line agent for the use in Tourette's disorder. It has been

contraindicated in patients with prolonged QTc's, with cardiovascular disease, and with drugs that prolong the QT interval. Baseline and periodic ECGs are recommended, and we have placed limitations on the maximum dose, which I believe now is about 10 milligrams a day, considerably less than what you saw on the serious adverse events.

Recently we've also contraindicated the use of pimozide with CYP3A inhibitors, such as ketoconazole, based on some data that does suggest that 3A is the primary metabolic pathway of pimozide and patients taking such drugs can develop quite marked increases in QTc and serious cardiac events.

Next slide.

The last drug some of you may remember was presented to the committee almost four years ago to this date, in July of 1996. It was the subject of NDA 20-644, sertindole, which was considered for approval as an antipsychotic agent. There were three adequate and well-controlled Phase II/III studies that contributed ECG data, and the findings were pretty much consistent across the three studies, so I'm just going to focus on one of the fixed-dose studies, Study 113.

Next slide.

Study 113 was an eight-week randomized double-blind study that had six fixed-dose parallel treatment

arms, three sertindole arms that used doses of 12, 20, and 24 milligrams a day, three haloperidol arms using 4, 8, and 16 milligrams a day, and placebo. It was conducted in 497 inpatients with schizophrenia, and a little bit atypical for many of our trials, this study did not exclude patients with significant cardiac defects. They essentially took all comers. The ECGs were done about every two weeks in this study.

Next slide.

To summarize the results, across the top are the seven treatment arms, placebo, three sertindole fixed doses, three haloperidol fixed doses. You can see that for sertindole, the drug of interest here, the mean change from baseline to the final reading was statistically significantly greater than in the placebo group, where there was actually a slight decrease. Just for your information, the target dose range that was being considered I believe at that time was about 12 to 20 milligrams a day. But at the two higher sertindole doses, at 20 and 24 milligrams a day, there were increases in the QTc of 20 and 22 milliseconds respectively. This was not seen in the haloperidol arms.

Likewise, if you look at the percentage of patients who had QTc readings greater than or equal to 500 milliseconds, I think, as was presented earlier, in the two

higher sertindole arms, 7 and 8 percent met those criteria. None of the haloperidol patients met the criteria.

Next slide.

Looking at the broader sertindole NDA database that included over 1,400 patients with about 476 person years of exposure, there were some relevant clinical findings that I believe we spent considerable time grappling with at that time. There were 12 sudden unexplained deaths, or SUDs. There was no symptomatic torsade documented, but of all the person time, there were only 30 to 40 hours of monitored time on telemetry on sertindole. So we really couldn't be certain that perhaps we had missed some torsade. There were also 23 cases of syncope. Unfortunately, 22 of those patients did not have any relevant ECG data at the time of the event.

Next slide.

There was considerable time spent about four years ago trying to discuss the meaning of these data with respect to the cardiac risk of sertindole, and the question was posed to the committee: Has the sponsor provided evidence that sertindole is safe when used for the treatment of psychotic disorders? There was somewhat of a split vote; four voted yes, two voted no. We took it, I think, with a huge grain of salt, and the outcome was that, to date, sertindole is not yet on the market in the U.S.

Next slide.

Subsequently, just to report some of the foreign experience with sertindole, in December of 1998 sertindole was voluntarily withdrawn from the U.K. due to several reports of cardiac arrhythmias and sudden deaths. This was in a December 1998 message from the Medicines Control Agency. More recently, in January of this year, European marketing authorization for sertindole has been suspended based on spontaneous adverse event data from the U.K. postmarketing database. This information is on the Internet. There have been reports of sudden unexplained deaths and fatal arrhythmias.

If you look at them as a percentage of all the adverse event reports for particular drugs, the percentage is several-fold higher for sertindole compared to olanzapine and risperidone. That is cited as the main evidence that they've suspended marketing authorization in Europe for sertindole.

I think that's it. Hopefully that will provide a little bit of framework for you to consider the cardiac safety of ziprasidone.

DR. TAMMINGA: Thank you very much, Dr. Dubitsky.

We'll go on now with the FDA presentations and hear from Dr. Douglas Throckmorton, who is from the

Division of Cardiorenal Drug Products, Anti-Arrhythmics, and Other Cardiovascular Drugs.

Dr. Throckmorton.

DR. THROCKMORTON: As a member of the Division of Cardiorenal Drug Products at the FDA, I was asked to summarize the Division's experience regarding compounds that prolong the QT. I believe that I have the good fortune of not having to mention further either corrections of QT or potassium channels. However, I would like to remark that there are two aspects of the Division's experience with regard to QT prolongation.

First, our experience has been consultative, and we've been involved in the review of the majority of the compounds that have been under discussion today. In particular, the Division's consultation for ziprasidone was performed by Dr. Maryann Gordon and has been provided to the advisory committee previously.

I will not focus my attention on this consultative role, although I'd be happy to answer questions about any of those aspects I'm familiar with. Instead, I would prefer to review those cardiovascular compounds that have also been shown to affect the QT interval.

If I could have the next slide.

I'd like to discuss two general issues. First

I'd like to give the advisory committee some general sense about how the Division has approached approval of compounds that prolong the QT interval. In this regard, I'll look at two broad classes of compounds. The first class that I've chosen are the anti-arrhythmics developed for super-ventricular arrhythmias, atrial fibrillation, atrial flutter, and the examples I'll discuss are dofetilide and sotalol. The second class of compounds I'll look at is a compound called bepridil, developed as an anti-anginal, although it was also found to have a marked effect on the incidence of both QT prolongation and torsade.

The second issue that will be woven into these reviews will be an overview of the body of data available within the cardiovascular arena that allows us to make general comments about the association between QT prolongation and adverse clinical cardiovascular events.

If I could have the next slide, please.

Dofetilide and sotalol were both approved for the treatment of atrial arrhythmias, even though they are both known to prolong QT and to cause torsade. Their approvability was also a possibility despite their pronounced effect on QT, first because it is known that their ability to affect cardiac repolarization was intrinsic to their mechanism as anti-arrhythmics, so that despite the fact that they prolonged QT was not something

that made it impossible for them to obtain approval. Instead, the developers of these compounds demonstrated three additional things.

First, they were able to demonstrate a symptomatic benefit in the populations at risk. They were also able to obtain point estimates of mortality in populations at high risk for arrhythmic events, as well as in the target population that the drugs were developed for. And finally, in both cases, the sponsors undertook an adequate characterization of the factors that could lead to increased risk for torsade in a patient also taking these products, and I'll comment on what that adequate characterization might mean a bit further later on.

If I could have the next slide.

D,L,-sotalol, which I'll call sotalol from now on, is a Class 3 anti-arrhythmic that carries an approval for the treatment of life-threatening ventricular arrhythmias, as well as for the maintenance of normal sinus rhythm in patients with atrial arrhythmias. I'll focus on the second indication. It's been found to have a mean effect on the QTc prolongation between 10 and 40 milliseconds at the therapeutic doses, around 160 milligrams to 640 milligrams per day, in a dose-dependent fashion, and to also influence the incidence of torsade in a similar way.

The next slide, please. This slide summarizes the totality of the sotalol data that we have linking change in dose of sotalol along the X axis with a change in the mean QTc interval, shown in green, and a change in the incidence of torsade, shown in yellow. Dr. Moss has suggested that there is an exponential association in the long QTc interval database. I don't honestly know what these curves would fit, although it would be interesting to do as an exercise. There are several points to be made.

The first point is to note that these graphs have been constructed from an extraordinarily large database, almost 7,000 patients that have received the drug in doses that vary by almost an order of magnitude, ranging between 80 milligrams per day and up to almost 800 milligrams per day. This particularly large, particularly broad database allows us to make important inferences about the relationship between prolongation of QTc and the incidence of severe cardiac events, in this case torsade. You can imagine that if a narrower range of doses had been explored, say between 70 and 150 milligrams, the observed change in the mean QTc would have been much smaller, and the relationship between that change and any change in the incidence of torsade would have been next to impossible to elucidate. This is an argument for broad dose exploration, I believe.

For sotalol, then, there is a continuous relationship between drug dose, concentration of mean QTc, and the incidence of torsade. We believe that there is no step function change here. That is, it is continuous and gradual. Again, given the large numbers, we can make that inference with more comfort.

Next slide, please.

Remember, I said that sotalol had a known effect prolonged QT, but that was because that was intrinsic to its mechanism of action. It was also possible for us to consider it as approvable for a symptomatic claim. The things in addition to demonstrating symptomatic benefit that the sponsor did was provide point estimates for mortality in patients at high risk for arrhythmic events, as well as patients in the target population for the compound.

This slide summarizes the Julian trial, which is a trial in a post-myocardial infarction trial, patients perceived to be at high risk for arrhythmias. The notion here was not that the product demonstrate that it is statistically significantly superior or anything like that. What we needed to have was information that the product was not significantly adversely affecting mortality with relationship to placebo. Actually, strike the word "significantly." We wanted point estimates without really

getting too hung up about confidence intervals. We wanted to know that this product did not look too much like other agents that we know have significant cardiac mortality of a kind that would have shown up in this kind of trial as mortality exceeding placebo.

In fact, they succeeded. Sotalol had a point estimate had a point estimate that was advantageous relative to placebo at one year.

Next slide, please.

The next thing that the sponsor also did was look at, again, point estimate for mortality in the population that the drug was being developed for. In this case, patients with atrial fibrillation and flutter. You can see that in a small database, a robust database but with relatively few deaths, there was no signal that sotalol had an adverse effect on mortality either with regard to quinidine, another anti-arrhythmic that's known to cause torsade, or relative to placebo.

So the sponsor was able to convince us that there was no net adverse effect, and that we would be able to define the potential benefit, this potential symptomatic benefit to the patient and the informed physician, and they could determine whether the pro-arrhythmic risk that we had well characterized was worth taking the drug.

Next slide, please.

To move to dofetilide, it is similarly a Class 3 anti-arrhythmic. It lacks the beta-blocking activity that D,L,-sotalol has but is otherwise similar. It has been approved for maintenance of normal sinus rhythm and conversion of atrial fibrillation flutter to normal sinus rhythm. It also has a pronounced effect on QTc, a mean 34-millisecond placebo-subtracted prolongation in the Phase II/III trials, and a dose-dependent concentration-dependent effect on mean QTc ranging between about 5 milliseconds and 20 milliseconds at doses in the therapeutic range, between 125 and 500 micrograms twice a day.

Next slide, please.

Dofetilide, like sotalol, has a relatively robust patient population, about 1,300 patients in this particular analysis. Looking at the relationship between, in this case, torsade and the incidence of ventricular fibrillation in the database, I've said before that there was a relationship between QTc prolongation and torsade, although I haven't shown those data.

As you can see, at the higher doses, the incidence of both torsade and ventricular fibrillation increased. Although the greater than 500 microgram twice a day group is very small in this particular graph, the incidence in that population was quite high. This again defined the association between torsade, QTc prolongation,

and in this case severe arrhythmic clinical adverse events.

Next slide, please.

Similar to what was performed for sotalol, the company undertook the task of obtaining mortality information in a high-risk population, as well as in the population to be served. The DIAMOND CHF and MI trials enrolled patients with structural heart disease and congestive heart failure. You can see that the mortality rates were substantially elevated. But again, dofetilide was on the advantageous side of the point estimate as regards mortality. There was no evidence that it had a substantial adverse effect relative to placebo.

In the target population on the next slide, in the supraventricular arrhythmia trials, dofetilide mortality when compared with placebo in the atrial fibrillation-flutter-SVT population has a ratio of 1.1 when adjusted for baseline characteristics, suggesting again that there was no signal for marked adverse mortality. So a symptomatic claim, a claim for conversion of atrial fibrillation was approvable because there was no substantial, demonstrable adverse mortality effect.

Next slide, please.

Dofetilide also did a very interesting thing, not prospectively, not because the Division required it, but as a way of exploring whether dose adjustment could in

some fashion be shown to adjust the risk that the patient population would have for suffering clinically adverse events, in this case torsade. What they did was, about halfway through their development program, they began to require that renal function be measured or calculated using Cockroft-Gault and dose adjusted based on that renal function.

In addition, they required baseline ECGs to determine whether the patient was eligible, and started dofetilide under continuous ECG monitoring with dose adjustment for marked prolongation of the QT. At the end of the NDA, in a retrospective fashion, they looked at the incidence of torsade in the two groups; that is, the group before dose adjustment, if you will, based on renal function, and the group after. Those results are on the next slide.

The bar on the left, the green bar, shows the incidence of torsade in the population prior to the initiation of renal clearance adjustment, and the bars on the right show the incidence in the three large trials after. I don't want to make large amounts out of this in the regulatory sense because it was something the sponsor chose to do. This analysis was something the sponsor had chosen to do on their own, not something that we required. But I think it serves as a model for investigation of those

factors, during the NDA development investigation of those factors that may mitigate the risk of significant cardiovascular events following the approval of the product.

In this case, as a result of this and discussions with the agency, the dofetilide and the sotalol labels in fact recommend hospitalization and adjustment based on calculated renal clearance.

Next slide, please.

To summarize the experience in the atrial fibrillation flutter trials, then, these two products had dose-dependent effects on QT, QTc, torsade, and ventricular fibrillation for dofetilide. Again, because the effects on QTc and torsade were anticipated, the sponsors were able to perform other things to obtain approval. In particular, they obtained mortality information, and they characterized those factors placing the patients taking the product at increased risk for torsade. They explored a broad dose range of their product, and they explored other risk factors, and in particular I'm using the example of dofetilide and renal function.

There's been a lot of discussion today about the effect of marked prolongation of QTc as far as risk for torsade. The sotalol database also has an analysis of that sort, and I believe it's the only database -- the

cardiologist can correct me if I'm wrong -- the only database that's been robust enough to look at that. There are problems with those sorts of analyses, but we can talk about that in the afternoon if the advisory committee is interested.

Next slide, please.

To turn to the other class of drugs that we have approved in the agency despite knowledge of their effect on QT and torsade, I'd like to talk about bepridil, which is a drug that we know both causes marked prolongation of QT and torsade, which is a characteristic not seen with other anti-anginals that are currently approved. So on the surface, that's bad and you would say that would make it quite difficult for bepridil to obtain approval, and you're right. It would have normally.

What bepridil undertook to show, however, was that they had a unique advantage. That is, they had efficacy in a population currently not served by the available therapies. In this case, they took a population that was resistant to current anti-anginals and demonstrated that they were able to affect anti-anginal efficacy there.

Next slide, please.

Just to summarize briefly, bepridil is a calcium channel blocker. It is approved as a second-line

agent for the treatment of chronic stable angina in patients who are intolerant or resistant to other anti-anginals. It has a mean effect on the QTc of between 30 and 70 milliseconds. Importantly, about 5 percent of the patients who took bepridil during the NDA had greater than a 25 percent increase in their QTc, which roughly takes you out into the 500 to 540 millisecond range, something like that. In the NDA database there were cases of torsade, and in the postmarketing in France, 147, something like that, cases of torsade were reported. So the association between the compound and torsade is unquestioned.

Next slide, please.

The trial that bepridil performed was to take 86 patients who had stable angina refractory to diltiazem, a calcium channel blocker used commonly in this disorder, and randomized them equally to diltiazem or bepridil. What they were able to demonstrate was that bepridil was a more effective anti-anginal in this population measured by the means that we use to commonly assess anti-anginal efficacy: exercise stress testing markers; time to onset of angina with exercise; time to 1 millimeter ST-segment depression on an ECG during exercise; and total exercise time.

Next slide, please.

So bepridil, despite its dose-dependent effects on QT and the clear association with torsade, was an

approvable agent as a second-line agent because it demonstrated clear efficacy in a group of patients not currently served by other available therapies.

Next slide, please.

To summarize the experience of the Division of Cardiorenal Drug Products, then, regarding compounds that prolong QT, the use of cardiovascular drugs that prolong the mean QT in a dose-dependent fashion has been associated with an increased risk for torsade and sudden death. In the databases that we have, they're substantially large, that risk appears to be continuous, and over a broad dose range. There doesn't seem to be an upper limit where the risk does not continue to increase.

Next.

Cardiac drugs that seek approval for treating symptoms -- that is, atrial arrhythmia, for instance -- have been approved with the following: demonstration of symptomatic benefit, and sufficient information to adequately describe the nature of the arrhythmic risk during use of the compound. That includes such information as description of the drug effect over a broad dose range, exploration of potential factors that modify the arrhythmic risk, and point estimates of total mortality in high-risk populations and target populations, again to make sure that there is no large adverse mortal effect.

Next, please.

Cardiac drugs that cause QT prolongation can also be approved as second-line therapies by demonstrating a symptomatic benefit in a resistant population. I think in this regard, our division is in agreement with the approach taken by the Neuropharm Division as well and comments they made earlier.

Thank you.

DR. TAMMINGA: Thank you, Dr. Throckmorton, for your presentation.

Now we'll hear from Dr. Chowdhury. Dr. Chowdhury is from the FDA, from the Pulmonary and Allergy Drug Products, and he'll talk about antihistamines and QT.

DR. CHOWDHURY: I'm going to make a very brief presentation talking about antihistamines and not use any specific data for any of these molecules. I'm going to talk about antihistamines and the view that we at the Division of Pulmonary and Allergy Drugs have taken in evaluation of antihistamines that are known to prolong QT or potentially can prolong QT.

In my brief presentation for the next 5 to 10 minutes, I will not specifically go into any database. The one which is relevant has been covered adequately, which is the terfenadine database. What I will go into is basically the philosophy that we have taken in looking into these

drugs and the thought process that has gone into our evaluation of these drugs.

Now, before I go into the antihistamines itself, I should point out that the drug class we're talking about is indicated for allergic rhinitis. The disease is not life-threatening, and the whole risk-benefit ratio here is pretty different than perhaps the drug classes that we're discussing here. So the advisory committee might like to take that into consideration.

Antihistamines classically are off two generations. For the contemporary relationship, they are classified as first-generations and second-generations, and I have named them here just for the sake of reference. Typically, the first-generation antihistamines are the older ones, and as you're aware of, are associated with a lot of adverse events, specifically sedation, decreased psychomotor function, and anticholinergic effects.

The second-generations are more newer antihistamines, and they are free of these adverse events. However, the price that perhaps one pays for these benefits is the risk of QT prolongation. Some of them cause QT prolongation and have been associated with torsade. Because of that, for any antihistamine, particularly the newer second-generation antihistamines, we are always sensitized to QT prolongation and possible effects that it

can have on ultimate approvability decisions.

In my talk here, I will focus on four antihistamines that have some history in U.S. marketing: terfenadine, which we have heard about; astemizole, which we have not, however this actually goes in parallel with terfenadine in terms of QT prolongation, torsade, and the marketing history. Both of these drugs were marketed in the U.S., and the FDA has determined that they cause serious cardiac problems, and both have been withdrawn from marketing. So all of the second-generations, what we have left in the market, are cetirizine, loratadine, and fexofenadine. For the next few minutes, I'll basically compare and contrast all of these drugs and try to get a feeling of how we're looking at these drugs and potential new drugs of the class which we have looked at.

Next transparency.

This is an overview summary looking at the points that you have talked about here, which are QT prolongation, PK interaction, and ultimate association with cases of torsade. The drugs here are listed alphabetically, and the asterisks are the two drugs which have been withdrawn because of convincing cases of torsade postmarketing. Just to point out, these are very rare events. For terfenadine, it took a long marketing, long postmarketing experience to actually pick up these events.

Now it has become essentially the poster child for torsade. However, they are very rare events to pick up.

Having said that, most of these drugs have significant PK interactions to the extent of log or much more with classic CYP3A4 inhibitors, and the QT prolongation with these drugs at the recommended doses do occur. For astemizole, 10 QD is the proposed recommended dose. At that dose, in the label before it got withdrawn, the QT prolongation was about 7 milliseconds or so, and we have heard that number before today.

For terfenadine, perhaps the same number. Going to the label, at about five times the recommended dose, the QT prolongation was 46. So these are two drugs with these two boxes checked as yes, which really has led into torsade and ultimately withdrawal.

Looking at three other drugs which are on the market right now, cetirizine, fexofenadine, and loratadine. Fexofenadine and loratadine have some interaction, although very small. In terms of percentage, perhaps 1/64 percent or so increase in the AU when given concomitantly with ketoconazole. However, these drugs do not prolong QT in clinical trials.

Going to cetirizine, it does not have an interaction. If one looks at the QT effect, perhaps it is not there. In the product label, if you look at it, out of

four studies, only one study showed some QT prolongation. This is again not consistently seen. However, this drug does not have an interaction.

So essentially, if these two, which is interaction and QT prolongation, are present, we looked at them really very conservatively, and the ones which do not have both of them so far have been okay.

Now, when we look at antihistamines from a marketing approvability standpoint, we have to look at the cardiac arrhythmias and the risk for that. I won't go into the list here, just to point out that the list is very exhaustive, very extensive. Possibly one can add more factors here, but the bottom line here is that it is very difficult to really control for all the risk factors, predict for all of them. As a result, we have taken the position that almost any convincing QT prolongation for a drug which has got an indication which is very minor is potentially a risk factor for torsade, and it's very difficult to really control for all the risk factors and label accordingly.

When we look at the QT effect, of course we have heard about the clinical studies, and that's where we really look at. The clinical studies that we usually look at are the drug interaction studies which we have heard this morning about, and also the high-dose safety studies

at a steady-state level. Sometimes, depending on what we see in the clinical studies, we obviously go into preclinical. Dr. Moss has summarized those for us.

So when we look at an antihistamine, we look at the whole picture. Does it prolong QT in the whole animal model? Does it prolong the action potential duration in in vitro models; for example, Purkinje fibers? Does it have clinical effect? And look at the ion channels in micro studies. Looking at the whole picture, we try to come to a consensus whether it prolongs QT or not, and in the clinical study, if it has prolonged QT in a dose-dependent fashion, we really become very conservative on antihistamines.

The last summary slide here. So basically, for looking at antihistamines that potentially can prolong QT, we have taken the philosophical approach that any convincing dose-dependent prolongation of cardiac repolarization is a concern, and that is extremely heightened if a concomitant interaction with other drugs that can increase the plasma concentration significantly is present.

Secondly, we have taken the position because, as I said before, patients who are at risk for serious cardiac arrhythmias or the magnitude of QT prolongation that can produce arrhythmias, is very difficult to predict,

and perhaps there's not much consensus on that magnitude that is at risk. We have heard before, and we will probably hear later on, that from the antihistamine experience, particularly with terfenadine and also with other drugs, that a label warning, contraindication warning, box warning and others has really not been effective. For terfenadine, after the box warning went out, there were still cases of inappropriate use, torsade and death.

So having said all of this, for an antihistamine which is really for allergic rhinitis, which is a trivial perhaps disease, not life-threatening, any risk is really an unacceptable risk. So the bottom line here is, if you see any dose-dependent QT prolongation which is convincing in clinical studies, if there's interaction that can potentially lead into high exposure, then that risk really is unacceptable for an antihistamine. So I just point this out for the advisory committee here to take into consideration, that our approach really depends on what the drug is, what the indication is. Again, for allergic rhinitis, as you're aware of, there are other antihistamines available, other modalities of treatment available, and really there's no benefit of having a QT-prolonging antihistamine over existing therapies for allergic rhinitis.

Thank you very much.

DR. TAMMINGA: Thank you, Dr. Chowdhury.

We'll now hear from Dr. Joyce Korvick from the FDA, from the Division of Special Pathogens and Immunological Drug Products.

Dr. Korvick.

DR. KORVICK: Thank you. I hope you can hear me.

In the interest of time, I'll try to keep my comments brief and give the committee and advisors a simple snapshot of some of the data that was recently reviewed by the agency regarding the quinolones. These are a class of anti-infective drug products.

Next slide, please.

I'm going to give you a little bit of background, the setting we find ourselves in with these drugs, different than antipsychotic drugs, some data on the drugs recently approved, comparison of selected characteristics of interest, and then go into some considerations and approach to regulatory actions.

Next slide.

I think that, in contrast to some of the drugs you've been talking about earlier, we have to remember that antibiotics for the most part are prescribed for 14 days or less. Previously we have noted that there may be some

effects with the macrolides. These are drugs like erythromycin, chlorithromycin and so forth. However, you know in the postmarket experience, the effect on QT prolongation and ultimate sudden death, unexplained death does not seem to be particularly large.

Finally, I think in the setting of reviewing these quinolones, sparfloxacin approved in the early 1990s was a drug, one of the first quinolones that extended the spectrum of quinolones beyond that of the Gram-negative organisms that you're familiar with that cyprofloxacin treats for urinary tract infection. We also approved grepafloxacin in 1997. Trying to assess the postmarketing record regarding QT abnormalities or sudden unexplained death is relatively difficult, because both of these drugs suffer from low-volume use. So calculating the actual estimated rate is difficult. But when that was done, it was seen that sparfloxacin, there was some suggestion that sparfloxacin may be the most potently active prolonger of QT and have some effect in the postmarketing arena.

Next slide.

During the time that we were reviewing moxifloxacin and gatifloxacin late last year, the Glaxo company spontaneously withdrew grepafloxacin from the market. In the original labeling, there was some understanding based on one PK study that there may be some

QT prolonging effect, but that was not well understood. Then in the postmarketing, there was additional information accrued that suggested that might be a real effect, and there were several cases that were reported that are currently under review within the agency of clinical effects.

Now I'd like to turn comments to moxifloxacin. These are only a few data that I'm going to present. The extensive database was reviewed before our Anti-Infectives Advisory Committee, and those slides can be found at the FDA Website, if anybody is interested.

Next slide.

In front of the Anti-Infectives Advisory Committee, we did grapple, much as you all are doing here, with the QT issue. We touched upon the preclinical data and the Phase I/II PK studies, of which there was a lot. The preclinical data did suggest some prolongation in the animal models. Because of the studies that were done in preclinical and Phase I/II, the company elected to do -- which is relatively unusual for antibiotics -- paired EKGs in the Phase III studies. So we had a lot of that data to review, and I'll show a little bit of that subsequently.

We also had our postmarketing colleagues from OPDRA do a review of the postmarketing experience for approved antibiotics, and we looked at some of those

profiles.

Next.

In the preclinical animal data, it was noted that there were significant changes in the animal models, but this was related to a rapid infusion, and that was seen at extreme doses.

Next slide.

As I mentioned, this was their Phase III experience. This includes moxi and the comparator drugs, and these were studies of pneumonia mostly. But these were the patients available for safety, and they did pair the EKGs, and when they looked at the valid paired EKGs, they came down to 559 on the 400 milligram daily dose of moxifloxacin and 515 for the comparator.

Next slide.

Out of this experience, we saw a mean QTc of 5, and that includes a few other patients. The numbers are a little different. But this was compared to some of the patients who were on chlorithromycin, and we mentioned earlier that we were interested in macrolides, and it seemed that the mean change was 2 for that. Overall, for all of the comparators, which included betalactams and some other quinolones -- levofloxacin being one -- they calculated a mean change of zero. So this was what we saw. This drug was being administered orally on a daily basis.

From a PK study, we had this dose relationship, and between the solid purple bars, that would be the concentration that you would expect. The actual concentration was measured with the recommended dose of either 200 or 400 milligrams. That was done in 181 patients. But you see for the most part the measurement of the delta QTc sort of is lumped into the area where we would expect the Cmax on the approved dose. So we would like to see, as an agency, a little bit more on the extremes, as has been mentioned earlier. We'd like to see what kind of slope we would really get if we pushed the dose, to try to understand better the dose relationship of this drug to the QT prolongation.

Also to mention, this is a relatively shallow slope.

Next slide.

Again, when moxifloxacin was studied in IV formulation, they got a delta QTc in the PK studies of around 12. This number probably is a little bit lower because, again, it depends on the rapidity of the infusion rate, and in some of these studies the higher numbers were seen in the 15-minute infusion. Currently, moxifloxacin is approved in the oral dose, and there are ongoing studies and data that are looking into the IV dose. You can see here that there were placebos in these PK studies where you

could see a mean prolongation of 3.5. So I think that is of interest when we include those to see what the variability is in QTc.

In summary, then, for the moxifloxacin, the IKr was blocked at three times the concentration that it took with ciprofloxacin. There were ADP studies where, again, it was 50 micromolar compared to the prolongation caused by a lot smaller dose concentration of sparfloxacin. As you get the feel, I think in our group we're looking at sparfloxacin as maybe the most active prolonger of QT in the quinolone class. There were dose prolongations in animals and humans. I mentioned the delta QTc.

As far as outliers, in the large Phase III studies that we reported, they saw three patients that had QTc's measured on drug that were greater than 500. One of those patients had hypokalemia. Another patient had preexisting right bundle branch block. The third patient had no associated underlying diseases. In the control group, there was one patient that was an outlier. Again, with additional analysis, it was noted that there were increased changes with hypokalemia.

Just to mention that because of the animal experience, when they were conducting the Phase III studies, they did exclude patients that had prolonged or known cardiac problems and patients that were on

concomitant cardiac drugs that could prolong QT.

Next slide.

Gatifloxacin for comparison was reviewed at the same time. It wasn't taken to the advisory committee. They had preclinical and animal data which seemed to suggest there was much less of an effect on the QT. So when they entered the Phase III studies, they did not do paired EKGs, but they also did not exclude patients with cardiac disease. So in that Phase III experience, we were able to see -- we were looking at adverse events, et cetera, sudden unexplained death, torsade. There was none of that seen in that experience.

Next slide.

Just to show you briefly another one of these dose relationship curves, the little boxes here, and you can see there are only six patients, shows delta QTc at the recommended dose. Again, if you try to calculate what that might be, it might fall out around the minus 1. If you look at the other studies, because there were only small numbers of patients studied, actually monitored for their QTc, it was actually hard to come up with a number to tag on that. But it may be around 3, and we're looking into more information there.

Next.

So this table just summarizes some of the

issues that you've been talking about. It's important to note the elimination pathway. So for moxi, gati, grepa and spar, you see this renal-hepatic here. It's totally renal for gati, hepatic and biliary for these two. The only drug that has an effect on CYP450 is grepafloxacin. As I mentioned, these were the QT changes. All of these drugs probably do have a dose relationship as far as prolonging QT. However, we are trying to work with the companies to establish better what that is, and again, we would like to bracket higher serum concentrations so that we can get a better handle on the slope.

Again, as I mentioned, there were three outliers here. In the 56 patients that were studied for PK for gati, there were no outliers; that is, anyone over 500 milliseconds. There were some considerations in the postmarketing database and cases reported which are currently under review, and I have a comment about that right now. Then in the label for sparfloxacin, it was noted that there were 10 outliers out of the 14,000 patients, which gave you a rate of 0.7.

Going backwards, since spar was the earliest one approved, there was a contraindication written into the label, and the reason that was, even though the number is small for delta QTc, during the Phase III conduct of that study, there were cases of torsade de pointes documented.

Contraindication for grepa at the time of approval was requested by the sponsor being conservative based on some small PK studies that were done showing some small changes in PK QTc relationship.

Finally, we put warnings in the label for moxi and gati because when we looked at this compared to spar and grepa and took other things into consideration, we felt that the warning would be the best. I can show you that in a moment. We also placed an information for patients section in the package insert. So I'll talk about that in a moment.

Again, as you've heard earlier, the unique characteristics of the drug. Does it offer an advantage over the existing drugs in some way? The spectrum of indications. Again, as you've heard, we would not consider using something that prolongs the QT for minor infections. Metabolic pathways and the potential for drug-drug interaction. Both of the drugs we recently approved seem not to have that problem. Again, we're looking at drugs that are being approved for short-term use, not chronic administration, and the route of administration appears to perhaps also be something to consider.

Next slide.

Again, when we did our regulatory action, the advisory committee for moxifloxacin thought that there was

a unique niche for that drug, that it was approvable, that we should include a warning in the label and let people know that this thing could happen. But we didn't know what the clinical consequences were, since in these drugs there were no torsade de pointes. Then we included an information to patients section at the end of the package insert.

This is the label, just an example, and you have a copy of this, so I won't read it to you. But basically, we worded it in the warnings, bolded and in caps, "Gatifloxacin should be avoided in patients with known prolongation of QT interval, with uncorrected hypokalemia, and patients receiving Class IA or Class III anti-arrhythmic agents."

In our Phase IV, we were asking, as I alluded to, for controlled studies, comparing not only within the quinolone class but in the same study looking at some macrolides which are of interest, as they may provide negative and positive controls and getting some ideas on the degree of the delta QTc. Again, at least two times the recommended dose, to try to attempt to bracket that upper concentration serum level.

Finally, in our postmarketing Phase IV commitments, we're not only looking at the passive kind of reporting in the past, but for both drugs we were asking

the companies to put together an active adverse event surveillance protocol, where they would go out and look for problems related to the cardiac unexpected sudden deaths, et cetera.

Finally, our continuing approach to this was that we sent out labels. We promised our advisory committee that we'd go out and look at the class issues, because again we're going back and looking at some older drugs to find out what's going on. So at the office level, we sent letters to all current NDA holders requesting any QT data that they have. We continue to coordinate this effort within the office.

That's all I have. Thank you.

DR. TAMMINGA: Thank you very much, Dr. Korvick.

Our last speaker from the FDA will be Dr. Evelyn Rodriguez, who is the Director from the Division of Drug Risk Evaluation from the Office of Postmarketing Drug Risk Assessment, who will talk about cisapride and compliance with labeling advice.

Dr. Rodriguez.

DR. RODRIGUEZ: Hi. Can you hear me?

Today I'll be talking to you about a risk intervention study that we did for cisapride.

Next slide.

The topics for today's discussion -- I'll try to make it brief because I know I stand between you and lunch -- is to give you a regulatory overview of cisapride, to describe the risk intervention study that was performed through the cooperative agreements that we have in OPDRA, to present some summary conclusions from that, some future directions and possible next steps for this particular drug that we're discussing today.

Next.

This will be the regulatory history and an overview of the study that was performed.

Next.

Cisapride was approved in July of 1993, and we received the first reports of ventricular arrhythmia with an antifungal drug in December of 1994. Multiple "Dear Health Care Practitioner" letters and labeling changes that described new contraindications and warnings for specific drugs and conditions were mailed by the sponsor.

Next.

That culminated in a black box warning, with contraindication for QT interval-prolonging drugs and cardiovascular and medical underlying conditions. It also relegated the drug to a second-line indication and another "Dear Health Professional" letter in June of 1998. I should point out that the only approved indication for this

drug was nocturnal heartburn.

The study objective for the risk intervention study was to describe the impact of the labeling changes through June of 1998, which included contraindications for cytochrome 3A4 enzyme inhibitor drugs, other QT-prolonging drugs, and contraindicated comorbidities. We looked at three separate automated databases, sites A, B, and C, which you'll see later described. We looked at a year before the last "Dear Doctor" letter, and then a year after the "Dear Doctor" letter.

Next.

There were three study sites. One of them was an IPA model with about 3.2 million persons in their overall health care setting. One was a Medicaid managed care model, again with 1.4 million persons. So these are very large databases. Then Site C was an HMO, with about 2 million. These were the cohorts that we assembled before and after the labeling changes, the year before, June 1998, and the year after the labeling change. Site A had about 17,000 persons in the year before labeling, and about 15,000 available for study after, and you can see Site B had about 5,000 in each period, and Site C around 8,000.

Next.

These are the results. Basically, in the year before the labeling change in Site A, there were about 30

percent of persons who received the drug despite contraindications, in Site B about 60 percent, and in Site C about 30 percent again, and virtually no change in the year after labeling. So there was no reduction in contraindicated use following labeling changes as of the "Dear Doctor" letter of June of 1998, and these were the investigators involved in that study. The sites were United Health Care, Tennessee Medicaid, and the Harvard Consortium.

Our summary in the Office of Postmarketing was that risk intervention studies like this are useful to assess the effects of labeling and "Dear Health Care Practitioner" letters. With this particular drug, with the series of labeling changes that had occurred throughout its long history, it does suggest some labeling fatigue. That is, once you make one labeling change and proceed to make yet another and another, it really doesn't seem to have much of an impact on prescribing strategies, and other risk intervention strategies such as targeted education for prescribers and patients may be useful to encourage the implementation of recommended risk management efforts.

Future directions in our opinion in postmarketing would be to determine how prescribers actually interpret the information that we put in "Dear Doctor" letters and how other educational materials will

augment the information in labeling changes and in "Dear Doctor" letters.

Also, we're in the dark, really, to ascertain the best format to really inform prescribers and patients of drug safety concerns. Will PPIs, patient package inserts, have an impact? What kind of information should be provided in medication guides? Will companies' sales force materials, brochures and other kinds of materials delivered directly to physicians and instructed by sales force have an impact on reinforcing drug safety concerns? Will CME courses, for example, as another education method, have an impact?

We need to determine how information and labeling, such as contraindications, warnings, and monitoring recommendations, are actually going to be understood and implemented by prescribers. We need to conduct risk intervention studies on multiple databases, as we did in cisapride, because you saw the variability there, although in all sites there was not much of a difference before and after the last labeling change. But nevertheless, it should reflect the range of health care services delivery systems that we have in the U.S., and we need to validate findings in these automated databases that we use with medical record review.

Possible next steps with regard to this

particular drug that we're discussing today is an incidence study for serious outcomes in automated databases. However, the use of automated databases to look at QT prolongation and torsade de pointes is difficult, if not impossible, to do because the ICD-9 codes that are available to us are very non-specific and are not going to point to these disorders, and because there's likely to be under-ascertainment and underreporting even in those systems.

Perhaps looking at sudden unexplained death is possible, but again, very difficult. We would need to use an unexposed comparator group or a comparator group on a different kind of drug among the patients that we're interested in in order to really glean whether there is an increased risk of sudden death with this particular drug.

Other interventions in terms of risk management would be to institute some sort of EKG monitoring, perhaps recommend that in labeling, perhaps educational interventions with prescribers and for patients, and then to evaluate whether the risk interventions used in labeling or in educational efforts would be achieving the desired goals.

Thank you. That's the end of my presentation.

DR. TAMMINGA: Thank you, Dr. Rodriguez.

The company, Pfizer, has requested to have an

opportunity to respond to the presentations of the FDA, specifically to Dr. Moss' presentation.

Excuse me, Pfizer has withdrawn their request.

Therefore, the committee will have an opportunity now to ask questions to the FDA people who made their very informative presentations. I would suggest that the committee ask pressing questions now to the FDA people and leave less pressing questions until after lunch, and I would suggest that the FDA people answer the questions directly from your seat so you don't have to go up to the podium all the time.

Questions for the FDA presenters?

I'll start out actually with a question for Dr. Dubitsky. In your actions no Mellaril and your recommendations for the target of Mellaril, you said on your slide that it was restricted for an indication for schizophrenia. Is it specifically for schizophrenia or for psychosis in general?

DR. DUBITSKY: Right now, it's for schizophrenia. The reason it was on the slide, I don't know if I mentioned it, but previously it had been indicated for some non-psychotic conditions such as neurotic depression, things like that. But we have eliminated those and right now it's indicated just for schizophrenia.

DR. TAMMINGA: But how about for psychotic non-schizophrenic disorders? That was my question.

DR. DUBITSKY: That is something we're looking at. Right now there's an effort within our group to make labeling more clear as far as the specific indications, and to link those to the indications that were actually studied in the pivotal trials that led to the approval. So if those studies were done in schizophrenic patients primarily, then we are going to label that as indicated just for schizophrenia.

DR. TAMMINGA: Dr. Laughren?

DR. LAUGHREN: This is really part of a larger effort that's underway in the Division to try to make labeling more specific to the indications that were actually studied. It's not limited to psychosis. It's actually been true in the anxiety disorders over the past decade. We've gradually been shifting from the very general psychotropic claims to looking very specifically at the specific entities that were studied. So focusing in this particular label on schizophrenia is part of that effort. You'll be seeing more of that in the future.

DR. TAMMINGA: Other questions for the FDA presentations from the committee?

Dr. Fyer?

DR. FYER: I'm not sure who to direct this to,

maybe to Dr. Moss. I'm a little confused about one aspect of this QTc stuff, and I apologize for that, if I'm sort of asking the obvious.

It seems that there's a definite implication from what we've heard that an interval of over 500 milliseconds is associated with some of these dangerous arrhythmias and torsade de pointes. If I'm incorrect, I hope someone will correct me about that. The thing I'm confused about is whether or not there's any data about the impact of increases over baseline that don't lead to an individual having an interval greater than 500. I don't know if it's just the case that nobody knows or if there have definitely been studies indicating that if somebody has a 360 and they go to 420, that is or isn't associated with some sort of risk. I don't know who to direct this to, maybe Dr. Moss.

DR. TAMMINGA: Dr. Moss, why don't you take a first crack at it.

DR. MOSS: Well, we don't have very clear information on this, to be frank with you. There does seem to be some increase in relative risk as you go from, say, 380 to 440, even though you're still below the level. But you're probably on a lower slope of this exponential curve. So there is an effect there, but it's not probably as great as what you see higher up.

But there's really very little data on that, and in the presentation that was made earlier by Dr. Harrigan, that was an unusual graph showing that the effect, although the mean effect was quite considerable, and the range was quite considerable, it looked like the overall data was a regression to the mean, that those people who had the lowest values had the biggest increase, and those who had high values had the smaller increase. That's most unusual in terms of mechanism, unless one wants to just say from a statistical standpoint that that is likely to happen.

So I don't have a good answer for you, only to say that there's probably some gradient of risk, but it's probably too small to be measured as we understand it and with the numbers that one is dealing with.

DR. TAMMINGA: Yes, Dr. Califf?

DR. CALIFF: Maybe I'll toss something out, and also this is a question for Dr. Throckmorton I think more than anyone else. It seems to me that one cannot generalize, because if I interpreted what you said correctly, and we were certainly there for the really interesting data, interestingly from the same company, on the drug for atrial arrhythmias, it is possible to prolong the QT interval and reduce the overall risk of sudden death, at least in one post-MI study. So I'm not sure that

you can generalize a certain increase in QT interval as necessarily giving you an effect, at least on the risk of death.

DR. TAMMINGA: Except we're talking about a population here that's not primarily a cardiac population.

DR. CALIFF: Well, that's true, although there's a lot of cardiac disease, and I think what we've seen in most cases of toxicity of drugs in populations, it's the high-risk end of the spectrum. It's not the young person who is at highest risk. It's going to be the older person who is on multiple medications with underlying cardiac disease, a lot of which is not diagnosable based on symptoms and history.

DR. TAMMINGA: Dr. Throckmorton?

DR. THROCKMORTON: Yes, I'd agree completely. I know of no clean data set -- Jeremy may correct me on this -- that looks at risk relative to baseline ECG. You have a baseline that's high, you have some higher risk. It would be interesting to have those data. I think it's likely that it is a spectrum, like Dr. Moss said. We have incomplete data about the effect of extreme prolongation from baseline, and again, that suggests that there is some increased risk. But those data are difficult because they come largely from either long QT syndrome or from anti-arrhythmics, from sotalol especially. It's difficult to

look at an anti-arrhythmic population and say absolutely that you can extrapolate that to a quinolone or something like that.

DR. TAMMINGA: Dr. Fyer?

DR. FYER: This is another aspect of this question. The risk of these arrhythmias, as I understand it, this is like a repolarization process that's going on, and you have prolonged repolarization. Is that the physiology that we're talking about? Okay. So how is that related to the advent of these arrhythmias? Maybe that would help in terms of understanding whether people have lower values and just increase.

DR. THROCKMORTON: I'll let all the cardiologists arm wrestle for which one wants to answer the question.

DR. FYER: Nobody knows?

DR. THROCKMORTON: No, they do.

DR. TAMMINGA: Dr. Moss?

DR. MOSS: Well, let me just say that the lengthening of the QT interval is probably a reflection of greater what we call heterogeneity of the electrical repolarization across the myocardium, and as you look across the myocardium, the degree of repolarization varies with different sites. The mid-myocardium seems to have the longest action potentials to begin with, and these are

cells that seem to be most vulnerable to drugs as a general rule. When you see the lengthening of the QT interval, it's actually telling you that there is some greater heterogeneity in repolarization, and it's the heterogeneity that seems to give rise to the arrhythmic potential, allowing for certain types of either reentry or depolarizations; that is, some reflection of further degree of electrical instability.

So it's a measure. It's really a marker, and it's a marker of really some alteration in the underlying electrical activity of the heart that gives rise to these reentrant-triggered arrhythmias or after depolarization-triggered arrhythmias. So it's simply a marker. I wouldn't think the QT itself is the factor, but it's telling you that there's alteration in the electrical activity of the substrate of the myocardium.

DR. TAMMINGA: Could I follow this up with a question to any one of the cardiologists? From what Dr. Califf just said, are we to understand that what you were just talking about, Dr. Moss, is primarily a risk factor in people whose cardiac function is already compromised?

DR. MOSS: Well, not necessarily. Certainly, the people who have underlying cardiac disease seem to be at more or greater vulnerability and greater risk. But the problem with the terfenadines and the other agents, the

antibiotics, have been in people with normal hearts. It's a matter of relative risk. Women seem to be at a little bit greater risk than men in terms of QT prolongation, and this has been well documented in the literature; older people a little bit more than younger people, and people with heart disease. But it's heart to quantitate this information.

DR. TAMMINGA: One question from Pfizer?

DR. RUSKIN: I wondered if I could just add a response? I'm Jeremy Ruskin. I'm a consultant for Pfizer on this drug. Massachusetts General Hospital, Boston.

Dr. Fyer asked a question earlier about the significance of outliers beyond 500 milliseconds, which is I think a critical issue. There are at least some data to speak to that. The number isn't just pulled out of the air.

It comes from the fact that of the reported cases of drug-induced torsade, both with cardiac and non-cardiac drugs, in which a QTc interval was measured at the time of the event, more than 95 percent of the time, those events are associated with QTc's greater than 500 milliseconds, and that's where the interval comes from. So it's not impossible, but it is unusual to see a case of drug-induced torsade with a QTc of less than 500 milliseconds.

DR. LINDENFELD: Dr. Ruskin, if you could clarify, that's at the time of the arrhythmia, the greater than 500? I mean, from someone who recorded an EKG around that time?

DR. RUSKIN: Yes, around the time of the event.

DR. LINDENFELD: It is possible those patients would have a shorter QTc, or have had at other times.

DR. RUSKIN: Certainly. There's a great deal of variability in the QTc, yes.

DR. TAMMINGA: Yes, Dr. Malone?

DR. MALONE: Many of these drugs, once they get approved, get used in children. Are children at a greater risk -- I guess this question is for Dr. Moss -- at a greater risk for these phenomena than adults?

DR. MOSS: If you think the data for adults is incompletely, you should only know that there's virtually no data on children. I think it would be dangerous for us to extrapolate from a long QT syndrome. There's just very, very little data, mainly because these drugs have not been tested in children, and virtually all the pediatricians extrapolate their information from the adults. But there's been very, very little testing, so I don't have an answer. Maybe Dr. Califf does.

DR. CALIFF: You said it. I think it is instructive that under the FDAMA legislation, a study was

finally done with sotalol, which was mentioned as one of the drugs, and there are major dosing issues in children which are not easily explainable, just treating them as small adults. So I think it's largely unknown what the risk is in children.

DR. TAMMINGA: Yes, Dr. Oren?

DR. OREN: Dr. Rodriguez, the cisapride data that you presented are of potential immense public health significance, and I wondered if, from that study, there's been any attempt to validate the automated database on a smaller sample, and specifically to serve physicians directly. If the decision is to prescribe, apparently contrary to labeling, was based on informed decision or based on ignorance?

DR. RODRIGUEZ: The study is as presented. We haven't done any medical record validation or any further steps, and we didn't do a survey. But a comment on doing surveys. Prescribers know, I think, what we should be doing, being a prescriber myself. I think it's worth more to see what actually is being prescribed, and then trying to find out from prescribers what is useful in communicating in labeling, what is not useful in terms of multiple contraindications to put in labeling, and then how feasible it is for them in everyday practice to thoughtfully prescribe and think about the

contraindications and the warnings in labeling.

DR. TAMMINGA: Dr. Fyer?

DR. FYER: Can I just ask you one question about that? I don't know if this is possible, but did you have any ability to look and see whether -- there were no mean differences in the percent of people, but were there any prescriber-specific changes?

DR. RODRIGUEZ: I think you're asking a question about whether we can track individual prescribers. We did not do that. We looked at the overall percent.

DR. FYER: I understand what the data was. I wondered if you had the capacity to do that.

DR. RODRIGUEZ: No, we did not do that. These automated databases I don't think would be able to do that. It would be very difficult to do that.

DR. FYER: Doctors have all kinds of I.D. numbers.

DR. RODRIGUEZ: When I say "able," I think it's because these are FDA funded, and we're limited in terms of cost. So we try to do the simplest study to address the regulatory question at hand, and frequently we have also a very short amount of time in which to do that. So what you describe would be a very labor-intensive study that sponsors can entertain doing.

DR. TAMMINGA: Dr. Katz?

DR. KATZ: Yes, I'd just like to ask Dr. Ruskin for a little more information about the data that you talked about in terms of 95 percent of patients who had a cardiogram done at the time of torsade. Clearly, that doesn't represent the universe of patients with torsade, and obviously patients haven't been randomized to particular QT intervals to see what their incidence of torsade is.

How robust was that data? Are we talking about hundreds and hundreds of cases of torsade, or a few cases of torsade?

DR. RUSKIN: I don't have the precise number. These are not huge numbers. We're talking about a couple of hundred patients with cardiac drugs, and somewhere around 150 or 170 with non-cardiac drugs. So the numbers are relatively small, you're right. Obviously, this is data that is subject to all sorts of reporting biases and so on, because it's not gathered prospectively, and it's not controlled.

I think that most clinicians, though, would agree that, while the magnitude of effect on the QTc is important, that the absolute QTc is probably more important, and going from 380 to 420 is probably significantly less worrisome than going from 460 to, say, 500, or 480 to 530, based on the observations that we make

clinically in those patients who develop torsade. I'd be interested in Dr. Moss' thoughts about that.

These are very hard data to gather, and one is left with anecdotal reports in the literature, and that's where the data is derived from.

DR. TAMMINGA: Dr. Califf?

DR. CALIFF: I would like to pile on here to dispel any myth that these are reliable kinds of data. Through a project with the FDA, Georgetown is putting together a prospective registry of drug-induced torsade. It hasn't been discussed here yet, but the likelihood that the average clinician in the average setting is even going to diagnose torsade is quite small, I think, in patients who get sick and have ventricular arrhythmias. Even at major academic centers, there can be tremendous disputes over what the nature of the rhythm disturbance actually is.

DR. TAMMINGA: Dr. Moss, would you like to weigh in?

DR. MOSS: Well, in response to Dr. Ruskin's question and comment, I would fundamentally concur. We don't have any substantial evidence that the increment of going from 380 to 410 carries any substantial risk. There may be a risk, but it's unmeasurable at the present time, and I don't know that anybody has data on that. The data that's available is in the higher range. So I think it's

unknown, and I would have to say that my suspicion would be that if there is a risk, it's got to be so small that you would need hundreds of thousands to millions of patients to detect anything.

DR. TAMMINGA: Dr. Throckmorton?

DR. THROCKMORTON: The only place that we have any large data does come from the sotalol database. The sponsor for sotalol did do an analysis of torsade related to both extreme prolongation of QT -- that is, incidence over 500 to 550 or 600 milliseconds -- and by change from their baseline. In both those cases, for sotalol, they described a relationship that the longer the extreme prolongation or the larger the change from baseline for an individual patient, the higher the risk for torsade. The problem was that those ECGs were taken at the time of torsade, and we don't know what their normal QT would have been. We also don't know what the incidence of QT over 500 was for patients who did not suffer torsade. So we lack two pieces of information.

But to the extent you could extrapolate, I think that's the only place like that. Now, again, like Dr. Califf said, the dofetilide database might be open to some analysis along those lines and could give some answers maybe.

DR. TAMMINGA: We'll have one last question

from Dr. Hamer before lunch.

DR. HAMER: This question is also to Dr. Moss. I just want to make sure I understand the risk estimates that were presented, where you had a risk at 440, a relative risk of 1, 500 at 1.4, 640 at 2.8. These are absolute or baseline QTc intervals; is that right? So in some sense, they really don't say anything about what happens to a given person or individual if you increase the QTc interval from 440 to 500, or 500 to 640?

DR. MOSS: Well, there seem to be two questions in that. We used the QTc of 440 milliseconds as simply a reference. So we just arbitrarily took that as a reference. The risks that we reported were relative to whatever the risk is at 400. So we use that as a reference of 1.0 so that we can measure the risks above that. So it's not that there's zero risk at 440. We know that there is some risk, but we took that as the arbitrary reference point.

DR. HAMER: No, but I guess the question I'm asking is, these are subjects or patients who, in a sense, walked in the door. You didn't watch them increase their QTc interval from 440 to 500 or 420 to 500 or anything like that. So all this tells you, in a sense, is if a patient walks in the door with this particular QTc interval, then perhaps this is what his risk or risk relative to 440 is,

not what happens if a patient has increased his or her particular QTc interval from one number to another.

DR. MOSS: Yes, our data was cross-sectional. It was not in terms of individual changes.

DR. HAMER: And also, I assume that these risks came from some sort of a logistic regression or some model like that?

DR. MOSS: That is correct. It was actually a Cox model for time-dependent events.

DR. HAMER: Were there confidence intervals associated with them?

DR. MOSS: We did have confidence intervals. What I provided was just the point estimates.

DR. HAMER: If you look at the confidence intervals, do they overlap or do they differ from a relative risk of 1 for the QTc intervals that are higher than 440?

DR. MOSS: The answer is yes, to a degree. That is, the ones that are closest to 440 definitely overlap, and the ones that are higher do not. So it's a continuum, and because of the limited numbers, the confidence intervals do overlap, of course, as you are closer to the 440.

DR. HAMER: Thanks.

DR. TAMMINGA: I think with this question and

this set of answers, we'll adjourn for lunch. It's 1:00, and we'll start promptly at 2:00 with the open public hearing. Thank you very much.

(Whereupon, at 1:00 p.m., the meeting was recessed for lunch, to reconvene at 2:00 p.m.)

AFTERNOON SESSION (2:04 p.m.)

DR. TAMMINGA: If people could take seats, please, we'd like the meeting to come to order.

I'd like to open up the afternoon session of this Psychopharmacological Advisory Committee Meeting, and to open up the afternoon session, we'll have the open public hearing, and we have three speakers for our open public hearing.

The first of our three speakers is Ms. Jacqueline Shannon, who is President of the Board of Directors of the National Alliance for the Mentally Ill.

Ms. Shannon.

MS. SHANNON: Am I in the right place here?

Thank you for this opportunity to present at this public hearing of this committee, and as she said, I'm Jacqueline Shannon. I live in San Angelo, Texas, and I'm President of the Board of Directors of NAMI, the National Alliance for the Mentally Ill.

As the nation's largest organization, representing individuals with serious mental illnesses and their families, in fact, we have over 220,000 members now and 1,200 affiliates nationwide.

We know firsthand and how critical it is to have effective treatment for these brain disorders. In addition to serving as NAMI's president, I'm also the

mother of Greg Shannon. Greg was first diagnosed with schizophrenia 15 years ago, when he was a college senior, and for the past 15 years, Greg and our entire family have struggled through his illness.

But for the last eight years, we've had new hope due to his treatment with the first of the new generation of antipsychotic medications, Clozaril. Since Clozaril or clozapine has arrived on the scene, only a few more of the new atypical new generation medications have been developed and passed the scrutiny of the FDA.

However, with the advent of these ground-breaking advances in psychopharmacology, recovery is now a very real possibility for people with mental illnesses and for increasing numbers of people with schizophrenia. These new medications offer new possibilities for full and productive lives. These treatments can make the difference between hope and despair, recovery and struggle, and even life and death.

For example, Clozaril has made a real difference in my son's life. Where previously he had been hospitalized, in and out of hospitals, for a number of years, in the last eight years, he has not been back in the hospital at all. In fact, he now works two part-time jobs. He lives in his own apartment, drives his own pick-up and is resuming his own life.

Well, not everyone is a candidate for clozapine or Clozaril. In fact, in most states, that particular medication is reserved for kind of a second tier after people don't do very well on a couple of the other new antipsychotic medications that have come on the market, and although these new atypicals often produce superior outcomes by treating a broader range of schizophrenia symptoms, they're different from one another, and people don't react the same to those medications.

Side effect profiles, which differ among the medications, have a significant effect on adherence, and non-adherence, as we all know, has major risks, even sometimes death.

Unfortunately, the new atypical antipsychotic medications that are on the market presently all have one serious side effect in common, and that is of weight gain. Now, weight gain, and I'm not talking just about a little bit, is a real serious problem. It certainly affects adherence, morbidity and quality of life.

Because of its different characteristics, ziprasidone is likely to be an important new addition in the small arsenal of effective new generation medications for schizophrenia and other psychotic disorders.

NAMI members strongly believe that professional judgment and informed consumer choice should be the

determinants in making decisions about what medications to take.

However, it's essential that we have more choices, and NAMI fully supports the research that makes those choices and those decisions possible.

We understand that you have judgments to make today about the risks and benefits of medications in reaching a decision about approval. We would ask that you be sure to consider the full range of risks and benefits in making that judgment.

Absent clear evidence of substantial risk, we would ask that you make information about benefits and risks available and allow professional judgment and consumer choice to weigh these very different drugs in making their decisions and their choices about treatment.

I also would like to make this disclaimer about NAMI. The National Alliance for the Mentally Ill is a non-profit, grassroots, self-help, support and advocacy organization composed of consumers, family members and caring professionals and friends of people with severe mental illnesses, including schizophrenia, bipolar disorder, depression, and the other serious mental illnesses, anxiety disorders and childhood mental illnesses.

We were founded in 1979. We have, as I said,

more than 220,000 members. In addition to support from our membership dues and contributions, NAMI is supported indirectly through the NAMI Anti-Stigma Foundation by unrestricted educational grants from companies in both the pharmaceutical and managed care industries.

But NAMI has a strict policy in not endorsing specific products. Neither Pfizer nor any of its competitors have had input into our testimony, and I'd also like to say that none of the three presenters today, including me, have had any remuneration nor consulting fees from Pfizer.

Thank you.

DR. TAMMINGA: Thank you very much, Mrs. Shannon.

The next speaker will be Ms. Shannon Flynn, who is a consumer member of the National Alliance for the Mentally Ill.

Ms. Flynn.

MS. FLYNN: Good afternoon. My name is Shannon Flynn. I am here today speaking on behalf of the consumer members of NAMI, the National Alliance for the Mentally Ill. I serve as the Chairperson of the Research Committee of NAMI's Consumer Council.

I have been diagnosed with schizoaffective disorder, bipolar type and have been taking atypical

antipsychotics along with medicines to treat mood for the past nine years.

During this time, I have gained an average of about 10 pounds a year, which has accumulated to an unhealthy level. Atypical antipsychotic medications seem to have the mechanism of either increasing appetite or decreasing metabolism, an effect I have observed in myself as well as in the many people with schizophrenia and schizoaffective disorders that I encounter through my support groups and my work.

In fact, it is very unusual for me to meet someone with psychotic illness who is treated with medications that is not overweight, often to a significant degree.

Weight gain caused by atypical antipsychotics increases risks for serious physical illnesses, such as heart disease and diabetes, both of which can have fatal consequences, and it can be just as risky to decide to stop taking these medications and possibly face severe decompensation since weight gain is also a prominent reason for non-compliance.

The atypical antipsychotics, I have found and so have others, are tremendously efficacious drugs in terms of symptom relief, both positive and negative symptoms, and, in general, they have a much better side effect

profile, except for the greater incidence and amount of weight gain as compared to the typical antipsychotics.

I have managed to live successfully with my schizoaffective disorder, thanks to my own efforts, the care of a superb psychiatrist, the support of my family and friends, and, of course, extremely affective medications. I have a full-time job and a Master's degree in Art Therapy.

I facilitate two support groups and serve on the NAMI Consumer Council in an executive position. I have warm relationships with my family, close friends, and a significant other. I would like to continue enjoying these aspects of a full life, but without treatment with atypical antipsychotics, I may not be able to do this.

I am not a doctor. I can't weigh the details of the medical risks, but I encourage you to consider the changes in metabolism and the weight gain as a common and significant problem of many current medications involving both long-term medical risks and shorter-term risks of stopping treatment.

I would like to e able to consider an option to live an enriching life at a normal, healthy weight, as I did before the onset of my illness, although that option might involve other side effects or risks. Together with my doctor, I would want to assess the benefits and the

risks of these different alternatives.

If the risk associated with a novel drug is rare and can be decreased with appropriate screening, I would want to have that choice and so would the many other people with these illnesses.

Thank you for the opportunity to speak with you on behalf of NAMI's consumer members.

DR. TAMMINGA: Thank you, Ms. Flynn. We appreciate hearing your thoughts.

Our next and final public speaker will be Dr. Rex Cowdry, who's the Medical Director of NAMI.

Dr. Cowdry.

DR. COWDRY: Thank you very much, Dr. Tamminga, members of the committee.

I'll be very brief. A lot of what I say just has a slightly different spin from the other presenters. I'd like to speak about three issues very briefly. One is risk assessment, a second is benefits, and a third is the issue of patient information.

On risk assessment, first, I think it is clear that it's understandable, it's human nature to be particularly concerned about severe adverse events, even very rare ones, but I think in weighing this risk, such as it is, and I think from what we heard, it's proven to be a rather illusive and difficult-to-quantify risk,

particularly with this agent, it's also important to take into account the range of other adverse consequences of this illness.

Schizophrenia is not allergic rhinitis. Schizophrenia is one of the major causes of disability in the United States and worldwide. It's a major cause particularly of long-term disability in our younger population.

So one of the questions is what are the full range of risks that may be involved with this disorder, and I would just ask that you not dismiss the impact of problem chronic side effects on issues of adherence, on the one hand, for example, the issues of substantial weight gain, which in our clinical practice, we know is a deterrent to people starting treatment, and it's a deterrent to people continuing treatment, and if I had to identify the one biggest risk to someone with schizophrenia and the biggest public health risk, it's stopping treatment.

The second issue has to do with benefits, and here, we don't have the data we would like. I hope we'll get more data from some of the NIMH research that's starting on a large scale with effectiveness trials with relatively unselected populations to address the question of the relative benefits of different medications and their relative costs, but we know from clinical experience, and

we hear it every day from clinicians who are associated with NAMI, that people who don't respond to one medication, the one atypical medication, may well respond to another. That is very hard to predict.

There's no easy hierarchy of it, and what it means is that the broader our armamentarium, the better position we're in to treat these individuals and make a range of options available to them.

The third comment. The question came up about providing patient guides, and I think NAMI would stand four-square behind the idea of providing patient guides, not just where there's this kind of a discreet risk, but in a much broader way, because I think for many of the medications that we have, there are specific things that an informed consumer ought to know, and that ought to be there in lay language.

It ought to be simple. It ought to be concrete. For example, if tardive dyskinesia is a risk of a medication, there ought to be a little line that says your doctor, you know, at least every six months to a year, ought to look at your mouth and limbs to see if there are any abnormal movements. It ought to outline what people ought to call their doctor about immediately or go to an emergency room about, and this ought to be used much more broadly in marketing and in actually dispensing

pharmaceutical agents.

We've been very actively involved in this. We think one of the ways, given how hard it's proven to change provider behavior through continuing medical education or through labeling or through these other techniques, we think one of the things that is underused and is probably ultimately going to be more effective is providing the information to consumers, who can go in in an individualized way with information that's specific to their drug they're on, and it says, oh, well, for example, with this drug, if an EKG at some point were made part of the labeling, it says I should have gotten an EKG, and I didn't.

I think that kind of input actually, and the Consumer Guide from the FDA may be one approach to that, and we'll be pursuing some of our own approaches, may provide a very hopefully more effective way of changing provider behavior and improving quality of care.

Thank you.

DR. TAMMINGA: Thank you, Dr. Cowdry, and thank you to all of the public speakers for their remarks.

Now I'd like to open the topic directly for the committee's consideration, the consideration of the safety and efficacy of ziprasidone for the treatment of schizophrenia.

Dr. Laughren has made our job a little bit easier in that we have several areas in which some discussion from the committee is requested. I guess that would be a good way to say it.

We've had some discussion this morning, before lunch, about the observed QTc effect, the difference between what's the significance of a change in QTc or leap over a threshold. I wonder if any of the committee has additional comments or questions or whether any of the committee has questions for our cardiology consultants.

(No response.)

DR. TAMMINGA: I could start with actually a question from the committee, from a non-expert, any one of our cardiology consultants on the committee.

Clearly, as the FDA people made, especially Dr. Chowdhury made, emphasized this morning, when he was talking about allergic rhinitis as sniffles, and I'm sure that people have sniffles, don't consider them inconsequential for sure, but schizophrenia for sure is not an illness that that would be in that class. It's an illness with a high mortality, a very, very high morbidity, that lasts a lifetime, for which we don't have any effective treatments.

How do people, how do psychiatrists and physicians and then consumers who consult the physicians,

think about this kind of a risk in that sort of a context?

DR. CALIFF: You know, I thought we had some good discussion about this this morning, that, you know, there's some 50 drugs that have this particular QT prolongation issue, and we certainly on the Cardiorenal Committee had to consider risk-benefit ratio in populations with regard to some other drugs.

The problem that we have here really is that we're considering a real benefit, that is, a demonstration of reduction in symptoms for the mental illness with a somewhat hypothetical risk, because the data just are not there to know what the risk is, and I think this is what makes it so difficult.

I think we felt on the Cardiorenal Panel that where we could quantify the risk and quantify the benefit, that at least you're able to come to a judgment that you may have differences of opinion about, but then you have some substance to discuss.

In this case, we really don't know how to quantify what the risk side of the equation is, but specifically with regard to your question, where there's a demonstrated benefit for a serious illness, I think there's a lot of data to show that patients and doctors are willing to accept an increase in the risk of a rare adverse event, and there are plenty of precedents for that in

cardiovascular drugs.

DR. TAMMINGA: Dr. Fyer.

DR. FYER: Maybe starting a little from where we left off, I guess the difficulty for me in addressing this is -- I mean, I agree with the statement of what the situation is. My concern is that, in reference to what Dr. Cowdry just said, I think there has to be created, if this drug is approved, a situation in which consumers and physicians can really accurately assess what the risk is, and I think the difficulty is, is that as far as I can tell, we can't really tell what the risk for this sudden death is, given the current data, and the structure of drug approval, et cetera, in our particular country right now is such that it's not clear as to how to set up a situation that will simultaneously make the drug available to people who may want to take it, given the unquantifiability of the risks now at the same time as we provide for people who might want more knowledge of the risks, that eventual availability of that data.

I think that for me, that's an issue. I mean, can we set up a mechanism for doing both of those things?

DR. TAMMINGA: I'm not sure that's correct. Maybe Dr. Laughren or Dr. Katz, you could comment on that.

DR. KATZ: Well, there's a couple of things, yes. First of all, there are mechanisms that exist prior

to approval, if you wanted to make the drug available under certain circumstances and yet still continue to accrue data that you think would be necessary to allow you to make a decision about approval.

For example, something like the treatment IND, which would allow you to give the drug out to people who might want it or would be qualified for it, but yet still continue to accrue data.

The other thing is that you can do that post-approval. You can approve it based on the judgment that the risk-benefit ratio, if there really is such a thing, is acceptable with appropriate labeling, but then require studies in Phase IV, whether they're registry-type of studies or whether they're comparative studies. Tom talked a little bit about that.

So I think there are ways. We never have all the information we absolutely want when we decide to approve a drug. So there are ways to do it.

DR. FYER: I understand some of those things, except I guess what concerns me is that in a situation where a drug causes, you know, more weight gain or some discomfort or it might be a little less effective than the next drug, one has a different level of concern in that people might be in the situation that people who died taking Seldane and antibiotics were, where they have no

choice until after the fact, and it seems to me that there needs to be a little more certainty that these studies will actually take place, that information will actually be made available, and that the current state of affairs will be made very, very clear to everybody, which is that, given experience with other drugs, there may or may not be a risk, and we do not know what it is right now.

I mean, you know, Dr. Cowdry talked about having a black box in the thing. I mean, I would anticipate something to that effect, where it's really clear to people that it may be nothing, and it may be something, and we just don't know.

DR. KATZ: Well, again, there are ways to do that. Obviously the reason we're coming to you is to find out whether or not you would recommend that given the amount of data that we have at the moment, the drug is approvable with appropriate labeling.

But there's all sorts of things we can do in labeling. We're very used to expressing and labeling our uncertainty of what information we would like to have is not available, and, you know, then if it's approved, it's up to the prescriber and the patient, but it can be done, I believe.

DR. WINOKUR: I guess I have a little kind of context to place my questions, and then a few questions for

the cardiologists.

I guess for those of us on the committee who are psychiatrists, we're kind of used to not having as much information as we would like to have to address very reasonable questions that other people are posing to us. So maybe it's reassuring that some of our colleagues in other medical disciplines sometimes face that same situation.

But, clearly, what we're thinking through as committee members in part is, on one hand, some laboratory data that shows some different numbers and different circumstances, but then trying to understand how that extrapolates to, you know, meaningful experiences or problems in real patients, and I think Dr. Califf, if I remember, raised an important point/question this morning that I'd like to kind of steer discussion back to, which is what happens when this drug gets out into larger populations, and that would be a -- I mean, I think I can sort of think through for myself kind of how I feel about that 20 millisecond, you know, and what I've heard from the discussion, but there are a few issues that I'd be interested in getting comments, because these are circumstances that, from my psychiatric experience and perspective, I can see coming up that may relate in whether it adds to our expectation about problems or reassures us

that it's not that likely to be an issue.

So let me mention three, and I'm sure there would be others that might be worth discussing. One is the issue of multiple drug use. We've heard, I think, very important data about the metabolic inhibition to drug interaction issue, and I think that was very interesting and important data.

But another type of issue would be drugs that people are likely in this population to be on that would interact, I guess the word would be "pharmacodynamically" or both potentially exerting effects at the site.

You know, from experience, we know that many of these patients will end up on antidepressants, some of which can also have effects, and, you know, many of our colleagues or perhaps ourselves will add in a second antipsychotic drug because people do tend to do, you know, multiple drug-prescribing.

So if any of the cardiologists would have opinions about how a drug with this profile might be viewed in the context of real world use, that would involve other drugs, not so much from the drug interaction issue at the metabolic level, but at the pharmacodynamic level, that would -- I'll mention my three questions, and then I'd raised the question about obstructive sleep apnea before with Dr. Casey, and I agree with his assessment that, you

know, that's not likely to be higher in the schizophrenia population, other than related to weight gain, but we also heard from him impressive data about, I think, 42 percent being significantly obese, and I think we can appreciate that that will often be a specific reason why patients on another atypical antipsychotic would choose to switch to ziprasidone.

So I guess my question is, would a drug with this profile, would that population, obstructive sleep apnea, since, to my understanding, that's a population that's more susceptible to cardiovascular and especially arrhythmia problems, and the third question, which again we just slightly got into, bradycardia, I think Dr. Lindenfeld mentioned as an important issue, and one predictable time of a slowing down of heart is during sleep, especially in slow-wave sleep, and since this drug, I guess, will be dosed twice a day and with meals and has a Cmax about six hours, I can imagine it peaking at a time when people would be falling asleep.

So these are some of the kind of, you know, real-life practical situations that I can easily envision, you know, a lot of patients being exposed to, and I'd just be interested in how our cardiology experts feel about any or several of these.

DR. LINDENFELD: Well, I think there will be

several opinions. I think I would guess that as you add more of these drugs, some of which have independent effects on the QT interval, you're going to see substantially more problems, and I'm still a little bit concerned, as I was this morning, that although I understand the reason that people were withdrawn from their other drugs, as we've heard, these patients are apparently on a number of other drugs, many of which independently affect the QT interval, even to a small degree, but I don't think in these studies, we have any idea what that's likely to be in a large population. So that concerns me.

We heard that sleep apnea is not common in this population. So I can't comment on that, and I think that the bradycardia issue is a separate issue, and I'd have to let Dr. Califf or Moss describe that.

But I am a little bit concerned about, as we get into more discussion, the variability in QTc intervals that we see with multiple measurements, and how we see a large number, and how many is enough to actually check the safety of these drugs? That would be something to come back to, I think.

DR. TAMMINGA: Could you be more specific about your last comment? The variability in QTc measurements?

DR. LINDENFELD: Well, we saw some data that the more times you measure it, the larger difference there

is in inter-individual difference, and so the question would be, if it goes from if you measure it 20 times, it goes from 68 up to a 98 difference among people, how many times is enough to be sure that you have reached some cut-off that's reasonably safe? That's an issue, a safety issue, I think, when we come back to that.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: As the pedantic statistician, may I comment on the fact that the larger the sample size gets, the larger the range gets, because the higher the probability is that you'll encounter some extreme value on one end or the other?

So it's not surprising that the more times we measure it, the more extreme values we find, just in a purely statistical sense.

DR. LINDENFELD: But I don't think that was the extreme value. Wasn't that the mean value that went up? Maybe I misinterpreted that slide, but I think it was the mean value that went up, not the range. Was it the range?

DR. HARRIGAN: No.

DR. TAMMINGA: Dr. Harrigan.

DR. HARRIGAN: The three values for those three studies were the means of that collection of individuals. So the various sample sizes, the mean of each individual's range. Does that make sense? No?

Each individual had a range, 20 individuals with a range, added those up and divided by 20, I believe, would be a reasonable summary of how those three studies did it.

DR. TAMMINGA: Dr. Marder.

DR. MARDER: While Dr. Harrigan's up, I'm wondering if I could ask him a question, and then perhaps the cardiologists would have an answer as well.

What about the experience of ziprasidone in the elderly? What kind of experience have you had, and did you measure QTc, and then I'd also like to hear from the cardiologists about what the risk is likely to be in an elderly population, and the drug is likely to be, if it's approved, to be used in some elderly individuals.

DR. HARRIGAN: Can we look at G4? Look at the distribution of patients in the Phase II/III database by decade.

So here we have basically a distribution, each row representing a decade, the age distribution of patients in the ziprasidone database. It's about 5 percent of patients over age 60, 217 people over age 60. This is fairly comparable with the Antipsychotic Drug Development Database, as I mentioned earlier. Patients tend to enroll at a slightly younger age, and there's very little specific dementia development in this program.

Now, let's look at M65 for QTc change by age. Taking the individuals who are age 65 and older, here's the mean change in each of the four treatment groups, and, of course, the sample sizes are directly underneath the mean with the confidence intervals.

So 76 individuals with a baseline/post-baseline ECG who are over age 65 years. As you can see, no particular suggestion in the mean of increased susceptibility to QTc prolongation in the elderly.

DR. TAMMINGA: Dr. Califf.

DR. CALIFF: Well, I mean, of course, one of the difficulties with the elderly -- I want to press Dr. Lindenfeld a little bit on this because she was wise enough with another drug, mebaformil, to look into this and see a problem down the road, which did occur.

One of the problems with the elderly, of course, is they're on a lot of other drugs, and the average person over age 65 is on 11, I think. Commonly, 15 percent of these people have atrial fibrillation, and they're likely to be treated with some of the other drugs we've talked about that also cause significant QT prolongation.

So unfortunately, a lot of this is all tied together. I think if we could be assured that people would take drugs or the doctors would prescribe the drugs purely by what the label says, you could potentially write

labeling that would prevent these interactions, but, unfortunately, our national track record here is not looking very good.

I think we have very good documentation now from a different studies that "Dear Doctor" letters don't work, and that writing labeling doesn't necessarily work. So I'm concerned about this, but again we're talking about a hypothetical risk, you know.

At least my judgment right now, based on the data we've seen, is that the risk is relatively low compared to some other drugs in the absence of interactions, but I'm also a little -- I just want to check out one thing, which is that it seemed from the measurements that were made in this most recent study, that the older atypical antipsychotics also cause QT prolongation, is that correct?

It seemed like there might have even been a little disagreement about the interpretation of the comparative data.

DR. TAMMINGA: Would you like Dr. Harrigan to put up that slide again with all the data on it? Maybe the one with the multiple different ways of calculating it with and without the inhibitors?

DR. CALIFF: It seemed that the Haldol didn't, but that the others may have.

So one thing we want to avoid here, I think, is excluding a new drug when the old drugs have the same problem.

DR. TAMMINGA: Well, the oldest of the drugs, of course, is thioridazine.

DR. HARRIGAN: The slide that Dr. Tamminga requested, we're putting up right now.

We'll look at mean change from baseline. So this has both its steady state and the presence of metabolic inhibitor. Again, the Bazett correction formula here on the left, baseline correction formula, derived from the Study 054 population at baseline, and the Framingham correction formula.

Your interpretation of the effects of other drugs depends partly on your selection of correction formula. With the Bazett formula, as I mentioned before, all of these drugs, with the exception of haloperidol, have changes from baseline with confidence intervals that do not overlap zero.

Now, if you flee from the Bazett formula to a formula which uses a different calculation for heart rate, then some of the drugs that cause more profound tachycardia will reduce their QTc effect over here. Ziprasidone is reduced a bit as well.

On the other hand, haloperidol, which did not

appear to have an effect potentially, its steady state with the Bazett formula, seems pretty clearly to have an effect over here, particularly with metabolic inhibitor.

DR. TAMMINGA: So the old drugs in that slide, Dr. Harrigan, are red for thioridazine and blue for Haldol, and all of the yellow to greenish dots would be the new antipsychotics, relatively recently approved?

DR. HARRIGAN: Yes, and white.

DR. TAMMINGA: And white. Excuse me. White.

DR. CALIFF: So it looks like we can be relatively certain from the confidence intervals there that ziprasidone prolongs the QT more than risperidone, but risperidone may also prolong the QT, just not as much.

DR. HARRIGAN: Well, the confidence intervals with the Bazett formula overlap between ziprasidone and risperidone and quetiapine. Now, I'm not sure what you mean by "more," but the point estimate for ziprasidone was 20 with the Bazett, and for risperidone, I think it was 11.6. Of course, then you have your choice of other formula.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: Again, as the pedantic statistician, there are 42 confidence intervals on there. If you attempted to correct those for multiple comparisons, the number that overlapped zero and overlapped with each