any of those criteria.

So I think we are going to have --

I'm not sure if it's a surrogate as much as
it's just a -- it's a biomarker. It's the
resolution of an arrhythmia, or a resolution
of an EKG finding in some patients.

In others, it may be -- it may
fulfill the criteria that it is actually a
clinical endpoint. People feel bad, you take
them out of it, and they feel better. That,
to me, is an important clinical outcome.

CHAIR HIATT: Yes, that's a very
important interpretation.

Comments?

DR. LINCOFF: I think what makes it
a surrogate is the time point. So if you are
saying at one hour, then that is a surrogate.
I don't think there is any question that afib
is a disease. I mean, if we said we've got a
drug that converts diabetes to normal, no one
would question that diabetes is an endpoint,
even if it's asymptomatic in many cases. Or
maybe I should say hypertension.

Hypertension leads to --

CHAIR HIATT: Well, be careful, Michael. There's a slippery slope there.

(Laughter)

DR. LINCOFF: Right. No, diabetes is a poor analogy. But hypertension, because hypertension is asymptomatic until it causes a mortal and morbid -- a mortal or morbid endpoint, like stroke.

Well, so atrial fibrillation may be asymptomatic, even for the patients who are not feeling it, until it causes a embolization or a hemodynamic compromise.

So I don't think, at least from my standpoint, atrial fibrillation is a surrogate, but whether you've converted it in an hour or two hours or 24 hours, I think that could reasonably be considered a surrogate.

CHAIR HIATT: Well, the question begs truly the thing you just kind of hit on,
which is that, and again, this committee has debated this. You know, we discussed, in a couple of meetings, the fact that blood pressure is a surrogate endpoint that is directly linked to clinical outcome, as you lower the blood pressure.

The same is true for LDL cholesterol.

The question is, is that true for atrial fibrillation. Yes, it's a disease, it's an arrhythmia. But the question is, by converting, you'll see the questions that come up later today, are there clinical consequences that are beneficial to that conversion.

And we've discussed a fair amount already this morning. There are symptomatic benefits in certain patients, but are there morbid, mortal benefits? Or are there avoidance of harm benefits that occur by conversion of that endpoint?

DR. CANNON: I think it depends on
the underlying heart disease. So we know that, for many patients, lone atrial fibrillation in relatively young people, it's relatively benign if it's not causing symptoms.

But for older people, or people with serious structural heart disease, it can be a big problem, particularly if weight control is not well attended to. It can exacerbate heart failure for patients who have stiff hearts. It can obviously contribute to symptoms.

And we know overall atrial fibrillation has a mortality risk that is far greater than people in sinus rhythm, no question about that. But in large part, that's because of the underlying structural heart disease.

CHAIR HIATT: Okay, so two comments.

One is, you brought up this morning a lot of consideration for specific
subgroups. So that's a theme I think the committee needs to continue to keep in mind, that maybe not all AF is the same.

So let's be mindful of that. And then I think the second thing is, remember, the natural history of any risk factor doesn't make it necessarily a viable surrogate or not. So that maybe raising HDL cholesterol is not a good thing with the drug, though it's a huge risk factor for events.

So the same is true for type II diabetes. So I think we should be careful that, if we are going to treat a surrogate, we are assuming there is a relationship between treating that endpoint, and a clinically relevant outcome.

That's the question that was posed.

DR. CANNON: But again, I think you can't dissociate that from the underlying heart disease, the context in which that
atrial fibrillation exists.

CHAIR HIATT: Exactly. So your point then is to be retained is that there may be very relevant subgroups under this broad definition of atrial fibrillation.

DR. MASSIE: I took the surrogate a little bit, maybe wrongly, as the particular endpoint of demonstrating conversion for 60 seconds, and is a surrogate, for even knowing whether they are in afib, very much down the line.

So I think there are two levels. The specific way in which it was defined clearly is telling you something about the effect of the acute therapy, but certainly not even about the effect of the -- now on the natural history of atrial fibrillation, much less the complication stuff.

But I would say, another thing is if you really could get somebody out of afib and know they weren't going to get in, then it would probably mean something. It's
probably related to the underlying condition
that would allow that or not.

I believe that the number of
medicines that are given for atrial fib,
avoiding them itself is a positive outcome.
So it's not -- so in a sense, it's a
surrogate for not taking dangerous drugs.

CHAIR HIATT: Okay, so keep in mind
what you think that endpoint means. Clearly,
is it a surrogate for a durable conversion at
24 hours seems to be very good. But the
question posed, is it a surrogate for
clinically meaningful endpoints, and I would
include those as symptomatic endpoints, and
as morbid mortal endpoints.

DR. HARRINGTON: And so could we
agree on the phrase that we are going to call
the resolution a biomarker, because it's not
yet proven to be a surrogate? The surrogate
thing bothers me.

CHAIR HIATT: Well, I think the
concepts are out there. So it's a little
past the time for the discussion on the general topic.

Norman, do you have any other issues you'd like us to clarify?

DR. STOCKBRIDGE: No, I think that's been a very good thing to set the stage for what comes next.

CHAIR HIATT: Steven Findlay, could you introduce yourself?

MR. FINDLAY: Yes, I'm Steven Findlay. I'm the consumer representative on this panel.

CHAIR HIATT: And I know it's a mundane issue, but the committee has to circle their menu for their lunch vote. We remain anonymous until it's presented on the projector up here. Put your name on, too, so that way nothing is truly anonymous.

Before the sponsor starts, is anyone needing of a break? Consensus? Want to move on?

We're moving on.
So next we will have an introduction about the development program.

Dr. Raineri.

ASTELLAS PHARMACY US, INC. PRESENTATION

INTRODUCTION

DR. RAINERI: Good morning, Dr. Hiatt, committee members, FDA participants, and guests.

My name is Don Raineri. I'm a senior director of regulatory affairs for Astellas Pharma US.

On behalf of Astellas and our development partner, Cardiome, I'd like to thank you for this opportunity to present and discuss the data for vernakalant hydrochloride injection, also known as Kynapid, which is a novel intravenous anti-rhythmic agent for the rapid conversion of atrial fibrillation to sinus rhythm.

Based on the data that you will see this morning, we have proposed the following indication. Vernakalant injection


is indicated for the rapid conversion of atrial fibrillation of less than or equal to seven days duration to sinus rhythm.

The proposed dosing for vernakalant injection is an initial infusion of three milligrams per kilogram infused over 10 minutes.

If conversion to sinus rhythm does not occur within 15 minutes after the end of the initial infusion, then a second 10-minute infusion of two milligrams per kilogram may be administered.

This slide shows the key attributes of vernakalant injection. You will see data this morning which shows that vernakalant provides for rapid conversion of atrial fibrillation to sinus rhythm, as well as effective reduction of the symptoms associated with atrial fibrillation.

In addition, sinus rhythm is maintained out to 24 hours.

Vernakalant injection can be used
with rate or rhythm control medication if required without affecting safety or efficacy.

In our presentation today, we'll provide you with data which shows that vernakalant injection has a well characterized safety profile, as well as a favorable risk-benefit profile.

When taken together, these data show that vernakalant injection provides an important treatment alternative for patients with acute symptomatic atrial fibrillation.

This is our program for today.

Following my introduction, Dr. Edward Pritchett, from Duke University, will present a clinical overview of atrial fibrillation, and the medical need for vernakalant injection.

Dr. Greg Beatch, from Cardiome, will then present the mechanism of action of vernakalant.

Dr. James Kerns, from Astellas,
will follow with the toxicology and clinical pharmacology of vernakalant. Dr. Therese Kitt, from Astellas, will then present the clinical efficacy and safety data for vernakalant injection, as well as our proposal for risk management.

And Dr. Jeremy Ruskin, from Massachusetts General Hospital, will conclude with a risk-benefit summary of vernakalant injection.

These are the consultants who have worked with us throughout the development program for vernakalant injection, and we are pleased to have them with us today to respond to questions from the committee.

In addition to Dr. Pritchett and Dr. Ruskin, we are pleased to have with us today Dr. David Fedida, Dr. Peter Kowey, and Dr. Craig Pratt.

In addition, we have the following internal experts available from Astellas and Cardiome to respond to questions.
At this time, I'd like to turn the presentation over to Dr. Edward Pritchett to present the clinical overview of atrial fibrillation, and the medical need for vernakalant injection.

CLINICAL OVERVIEW OF ATRIAL FIBRILLATION

DR. PRITCHETT: Thank you, and good morning.

My remarks will be very brief.

I just want to remind you that atrial fibrillation is a big problem. It is the most common sustained cardiac arrhythmia in the United States, and it is the most common diagnosis for arrhythmia-related hospitalization in the United States.

There are about 2.3 million U.S. adults who carry a diagnosis of atrial fibrillation now, and that number will increase as the population ages.

The clinical presentation of atrial fibrillation is now largely with symptoms. It is most commonly identified
because patients show up complaining about symptoms. The cardiovascular health study is a large, multi-center epidemiology study that is looking at the incidence of heart disease. And they have reported that 80 percent of the patients with atrial fibrillation that they identify are identified because they have symptoms. So this is largely a discussion about symptoms, as the committee has alluded to.

In fact, the most appropriate use of antiarrhythmic drugs in patients with atrial fibrillation is for relief of symptoms, as discussed in the guidelines and in recent review articles.

And there are lots of symptoms that are closely associated with the occurrence of atrial fibrillation. And I've listed in the third bullet the symptoms that were collected in the flecainide atrial fibrillation program almost 20 years ago, in which over 3,000 patients, or over 3,000
episodes of atrial fibrillation were
documented by trans-telephonic monitoring,
and patients volunteered the symptoms that
they had.

And those symptoms were compiled
by Ani Bhandari after that program, and have
been published. And those symptoms have now
been reduced to a number of checklists that
have been used in antiarrhythmic drug
development programs, including the program
that you will see today.

Indeed, the history of all
antiarrhythmic drug development is largely a
symptom-driven history. Prior to 1986, most
drug development programs for antiarrhythmic
drugs concentrated on drugs for ventricular
arrhythmias, so we had drugs like
disopyramide, like the on 1C drugs,
flecainide and encainide, introduced in the
`70s and early `80s.

In the mid-`80s, there was sort of
a shift to interest in developing drugs for
supra-ventricular arrhythmias, including atrial fibrillation, and those development programs largely used symptomatic arrhythmia recurrence as an outcome.

And these are FDA approval since 1986 for oral drugs for symptomatic arrhythmic recurrence. The first of these is the verapamil program presented to this committee in 1984 led to labeling for immediate release verapamil for PSVT in 1986. That was followed by the first multi-center clinical trial program that used symptomatic arrhythmia outcomes, flecainide for PSVT and atrial fibrillation that led to the symptom checklists that are being used today.

Then in 1997, propafenone for PSVT and AF, dofetilide in 1999, d.l. sotalol in 2000, and then in 2003, sustained release propafenone. Dofetilide in 1999 was also approved for oral use to convert atrial fibrillation to sinus rhythm, but the speed of that is magnitudes difference from an
intravenous drug.

The curious thing is that, during this 20-year period, there has really been nothing much done about intravenous therapies for atrial fibrillation to restore sinus rhythm.

There is, in fact, only one drug, and that's ibutilide, which was approved and labeled for this indication in 1996, the only drug approved, in fact, in the last 40 years for converting sinus -- atrial fibrillation to sinus rhythm.

And this has been a very difficult indication for the pharmaceutical industry to crack. So there simply aren't very many intravenous drugs. Drugs can be used off-label. We've heard mention of intravenous amiodarone this morning, it's off-label use. And it's gotten mixed reviews in the literature with respect to its success.

But the bottom line is that we simply don't have a lot of drugs that we can
use intravenously for rapid restoration of
sinus rhythm.

So as I said, in summary then, few
choices of drugs that are approved and
labeled, and they all have imperfect
efficacy, and they all have adverse effects.

You all have discussed electrical
cardioversion this morning. It does require
conscious sedation, it has its own
complications, and there are some settings
where it is clearly inappropriate.

Therefore, what the cardiology
community and patients with atrial
fibrillation need is additional choices of
drugs that they can use, drugs with a high
rate of efficacy for restoring sinus rhythm
accompanied by relief of symptoms, and a
rapid onset of action, drugs with low rates
of adverse effects, a low incidence of drug
interactions, and a lack of interference with
electrical cardioversion.

That completes my remarks, and I
will be happy to turn the podium over to my
colleague, Dr. Beatch.

MECHANISM OF ACTION

DR. BEATCH: Thank you, Dr. Pritchett.

Mr. Chairman, members of the panel, it's my pleasure to present the
mechanism of action of vernakalant.

Vernakalant is a multi-ion channel blocker, which blocks potassium channels and
sodium channels in a manner that is targeted to atrial fibrillation.

Vernakalant produces relatively atrial-selective increases in atrial refractory periods, and rate dependent slowing of conduction velocity, and rapidly converts atrial fibrillation.

Vernakalant's efficacy and safety profile are consistent with its ion-channel blocking properties.

Vernakalant blocks potassium channels important in control of atrial
repolarization at all phases of the atrial action potential, including the transient outward current, the alter-rapid delayed rectifier, the rapid component of the delayed rectifier, and the acetylcholine-dependent potassium channel.

And it blocks these currents within the therapeutic range of plasma concentrations, which is 2-12 micromolar.

In contrast, it does not block the slow component of the delayed rectifier, nor the inward rectifier at therapeutic concentrations.

Importantly, it does block the ultra rapid component of the delayed rectifier, and the acetylcholine dependent current, which are atrial specific currents.

The block of these atrial potassium channels is responsible for vernakalant's ability to prolong the action potential duration.

In this recent study of tissue
taken from patients with atrial fibrillation, and presented at the European Society of Cardiology by Dr. Ravens earlier this year, vernakalant was shown to significantly prolong the action potential duration at 20 percent and 90 percent repolarization. And these effects led to increases in the effective refractory period in these atrial tissues, which were significant within the therapeutic range of concentrations.

Increasing atrial refractoriness has also been shown in the clinical study. As shown here, vernakalant prolongs the atrial refractory period much more markedly than it does the ventricular refractory period in man at a pacing rate of 100 beats per minute, and a dose of four milligrams per kilogram.

This clinical study shows that vernakalant's ion channel blocking profile produces relative, although not absolute, atrial selective electrophysiologic effects in
Having discussed vernakalant's mechanism of action referrable to its potassium channel blocking, I would now like to draw your attention to vernakalant's other mode of action, namely, block of sodium current.

As can be seen in this study previously referred to, vernakalant produces little effect on a measure of sodium current block in these atrial tissues, and this was the change in voltage over time for the upstroke velocity in the atrial action potentials.

A key feature of vernakalant's mechanism of action in AF is its frequency dependent block of sodium current. These are concentration response relations for vernakalant's block of human heart sodium current under normal conditions, and under the conditions of atrial fibrillation in the atrium.
At therapeutic concentrations, shown in the inset, vernakalant produced little block of the sodium current at normal heart rates. When the cells were rapidly paced, vernakalant's potency increased fivefold.

As further evidence of vernakalant's potentiated sodium channel block in atrial fibrillation, we studied vernakalant's affects on atrial conduction velocity in vivo.

Here vernakalant slowed atrial conduction at fibrillatory rates in the dog atria.

Shown on the Y axis is the changing conduction time, and the increasing pacing rates of simulation in the atria are on the X axis.

Vernakalant, at four milligrams per kilogram, produced little conduction slowing at 200 beats per minute, with progressive slowing seen as the pacing rate...
increased to 400 beats per minute, which mimics the activation times in AF.

This demonstrates that vernakalant's frequency dependent sodium channel block demonstrated in vitro readily translates to conduction slowing in vivo.

Vernakalant rapidly and effectively converts atrial fibrillation in a dog model. Vernakalant's efficacy for conversion of atrial fibrillation has been confirmed in multiple nonclinical studies, as well as clinical studies, which Dr. Kitt will show.

And rapid conversion is one of the clinical benefits of vernakalant.

I would now like to discuss the safety implications of vernakalant's mechanism of action. Since currently available antiarrhythmic drugs such as flecainide have been associated with pro-arrhythmia under the conditions of ischemia, we investigated vernakalant's effects in a
highly pro-fibrillatory model in pigs.

In this study, episodes of ischemia, followed reperfusion, resulted in a high incidence of ventrical fibrillation and mortality in the control treated animals.

Flecainide resulted in a lethal VT in all the pigs within five minutes of ischemia. In contrast, vernakalant had a lower incidence of ventricular arrhythmia and mortality in this model.

And this suggests that vernakalant does not have an increased risk of pro-arrhythmia and mortality in this pig model.

Vernakalant did not show cardio-depressant actions in conscious animals in an ICH standard cardiovascular safety study. Since there were, however, adverse events of hypotension seen in our clinical trials, we elected to study vernakalant in anaesthetized dogs where we could increase the dose in plasma concentrations higher than were tolerated in conscious dogs.
As shown here, vernakalant did not affect systolic nor diastolic blood pressures at therapeutic plasma concentrations. However, as we increased the dose, which resulted in plasma concentrations fivefold higher than the Cmax we saw in patients, there were significant reductions in systolic blood pressure.

In keeping with vernakalant's atrial targeted actions, vernakalant has minimal effects on the action potential duration in rabbit Purkinje fibers. The rabbit Purkinje fiber assay is an ICH standard assay used to assess the potential risk for torsades de pointes.

Drugs which prolong the Purkinje fiber action potential duration have a risk for prolonging QT intervals, and an increased risk for torsades de pointes.

As shown here, dofetilide produced concentration dependent increases in the action potential duration, including
within its therapeutic range, and this is consistent with its selective IKR blockade.

Vernakalant produced relatively minor changes in the Purkinje fiber action potential duration, which reached significance at 10 to 30 micromolar.

And these more relatively minor effects are consistent with vernakalant's concomitant block of late sodium current.

And this suggests that vernakalant may have a lower risk of pro-arrhythmia compared to selective IKR blockers.

As further evidence of a reduced potential for inducing torsades de pointes, vernakalant suppressed dofetilide induced early after depolarizations, in an in vitro pro-arrhythmia model. Shown here, dofetilide at a high concentration significantly prolonged the action potential duration, and elicited these instabilities of repolarization, known as early-after depolarizations.
These early-after depolarizations are believed to trigger torsades de pointes. In contrast, with the addition of vernakalant, shown here, the early-after depolarizations were abolished, and the action potentials were normalized. This again suggests that vernakalant may have a lower pro-arrhythmic risk than the specific IKR blocker dofetalite.

In addition, vernakalant suppressed torsades de pointes in an in vivo model of torsades. Shown here in the control conditions, infusions of methoxamine and clofilium produced torsades de pointes in seven of nine animals. With the addition of vernakalant infusion, there was a dose-dependent decrease in the incidence and the duration of torsades de pointes. Vernakalant suppressed pro-arrhythmia in this rabbit model of torsades.
de pointes, and this again suggests that vernakalant may have less pro-arrhythmic risk than drugs with more marked effects on ventricular repolarization.

In summary, then, vernakalant is a multi-ion channel blocker, with activity that is potentiated in the atria during AF. Vernakalant rapidly converts atrial fibrillation, and appears to have a lower pro-arrhythmic risk in animal models.

Vernakalant's safety and efficacy are consistent with its unique ion channel blocking properties.

Thank you. And Dr. Keirns will now present vernakalant's toxicology and pharmacokinetics.

TOXICOLOGY & CLINICAL PHARMACOLOGY

DR. KEIRNS: Thank you, Dr. Beatch, Dr. Hiatt, and committee members. I'll briefly describe the assessment of toxicology and clinical pharmacology which we've carried out for vernakalant.
Starting with the toxicology, we conducted a customary program in rodents and non-rodents, and I'll note that there is a note at the bottom of the slide that shows you the corresponding pages in your briefing book.

In these studies, the dose limiting toxicities were all transient and spontaneously reversible. They were not associated with any gross or microscopic histological findings, and they were consistent with the ion channel blockade that Dr. Beatch just described.

The symptoms that were seen were salivation, tremor, ataxia, and at the very highest dose with repeat dosing, we saw convulsions.

In terms of the therapeutic index relative to the efficacious dose that Dr. Beatch just described, these findings were seen at a factor of 10 higher exposure.

The pharmacokinetics in metabolism
in dogs and humans have been assessed, and showed rapid distribution, and a short elimination half-life. In humans, the metabolism of vernakalant is primarily by cytochrome P450 2D6, and the systemic exposure of parent compound at the maximum concentration compared to the exposure in dogs that I described on the slide before is a factor of three.

Continuing to describe the pharmacokinetics further, they are dose proportional and linear. There is rapid distribution with an alpha half-life of about 10 minutes, and a high volume of distribution.

The terminal elimination half-life is fairly short, three hours, but somewhat longer, 5-1/2 hours in 2D6 poor metabolizers. Vernakalant is not highly protein bound, and the metabolic pathways have been well characterized.

This slide illustrates the
pharmacokinetic profile with the phase III clinical dosing that Dr. Kitt will describe, and makes a couple of other points.

Just to orient you, Dr. Kitt will describe two 10-minute infusions, one for the first 10 minutes, and then an observation period for 15 minutes, followed in those patients who do not convert on the first infusion, by another 10-minute infusion.

And the curves that are displayed here are based on modeling of the phase III clinical data, and we also looked specifically at differences between normal extensive metabolizers, and 2D6 poor metabolizers.

You can see that, in the early times, the concentrations are almost identical, and then they diverge somewhat due to the longer half-life in the poor metabolizers.

But one of the more important points is that there is a rapid drop in
concentrations at the end of each infusion, which is actually driven by distribution, not by the elimination.

We assessed a number of demographic variables, as well as concomitant medications, by using population pharmacokinetics, and found that Cmax and systemic exposure were not, over the first 90 minutes, were not significantly influenced by age, sex, renal function, or 2D6 expression, as I just showed you in the slide before.

In addition, we analyzed co-administration of 2D6 inhibitors and beta blockers, and did not see any difference in the Cmax or early exposure of the compound in the -- with these concomitant medications.

Finally, as Dr. Kitt will show you, phase III studies indicated that there were no safety implications with co-administration of 2D6 inhibitors or substrates.

I'd now like to turn the
presentation over to Dr. Kitt to describe clinical efficacy and safety.

CLINICAL EFFICACY AND SAFETY

DR. KITT: Good morning, committee members.

I am Therese Kitt, and it's my pleasure to be able to present to you the clinical data from our vernakalant clinical trials.

Efficacy data will be presented first, focusing on three studies: the two primary registration studies, and a study that we did in patients who developed atrial fibrillation post cardiac surgery.

The efficacy presentation will be followed then by the safety data presentation.

There were nine clinical trials in the vernakalant NDA as outlined on this slide. There were two phase I clinical studies, and electrophysiology study.

The CRAFT study was our phase II
dose ranging study.

The phase III studies were all labeled ACT, which stands for atrial arrhythmia conversion trial, or ACT.

The two registration trials are ACT I and ACT III. These two studies are considered the pooled primary population during my efficacy discussion.

ACT II was a study in patients post-cardiac surgery, and ACT IV was an open labeled safety study. Scene 2 was a study done in patients with typical atrial flutter. In this study, vernakalant was shown not to be effective in converting atrial flutter to sinus rhythm, and the efficacy data will not be further discussed. However, the safety data from these patients are included in our safety analysis.

Eight hundred and twenty three subjects were exposed to vernakalant, and there were 773 patients exposed, and 335 patients received placebo.
Once again, as Dr. Keirns had mentioned, I have source documents here, a source page and a table that you can find in your briefing document if you want further information on that particular slide.

I will be discussing different patient numbers from different patient populations at different data sets. And this table lists the different efficacy and safety populations.

The primary efficacy studies was ACT I and ACT III, in which 575 patients with atrial fibrillation received study drug, 236 patients received placebo, and 339 received vernakalant.

Again, the term pooled primary studies refers to the combined patients from ACT I and ACT III with atrial fibrillation. ACT III enrolled patients with both atrial fibrillation and with flutter. However, when the results of the Scene 2 study were known, the analysis plan was
changed to exclude patients with atrial flutter. This was done before the database was locked.

In the post-cardiac surgery study, 50 patients with atrial fibrillation received placebo, and 100 patients received vernakalant.

The Phase III database contains 737 patients who received vernakalant, and the total number of patients who received vernakalant in our phase II and III studies was 773 patients.

I will now discuss the efficacy data.

The phase II dose ranging study enrolled patients with a duration of atrial fibrillation of three hours to 72 hours. This graph shows the cumulative efficacy after one and two doses. There was no difference between placebo and the low dose vernakalant group.

Vernakalant was effective in the
higher dose group with 53 percent of the
patients converting to sinus rhythm, and the
median time to conversion in the patients who
responded to vernakalant was 14 minutes.

This study established the
minimally effective dose to be two milligrams
per kilogram. Based on these results, the
step dose design for phase three was three
milligrams per kilogram, and if no conversion
to sinus rhythm was seen, a second dose of
two milligrams per kilogram was administered.

The dosing regimen was reversed,
giving the three milligrams per kilogram
first, assuming more patients would convert,
following the higher initial dose.

This is the phase III design for
our pivotal studies. The phase III studies
were multi-center, randomized, double blind,
and placebo controlled, in patients with
atrial fibrillation with a duration of
greater than three hours, and less than or
equal to 45 days.
Patients were stratified based on the duration of their atrial fibrillation. Patients were allowed to have background use of oral rate and rhythm control medications. Patients were randomly assigned to receive up to one of two infusions, the first infusion of vernakalant of three milligrams per kilogram given over 10 minutes, followed by a 15-minute observation period, and if they had not converted to sinus rhythm, the second dose of two milligrams per kilogram was administered.

In our studies, placebo was normal saline.

Patients underwent continuous halter monitoring, starting at screening, and going up through 24 hours. They also were on a telemetry, starting at randomization and up to a minimum of two hours.

An atrial fibrillation symptom checklist was done at screening, at baseline, at 90 minutes, at 24 hours, seven days, and
also up to 30 days.

As noted on this slide, electrical cardioversion and other treatments were permitted after two hours. The patients were seen for follow up visit on day seven, and there was a phone call follow up on day 30.

These are the key inclusion and exclusion criteria. Patients were eligible for the studies if they had symptomatic atrial fibrillation with a duration of greater than three hours and less than 45 days, and they were receiving anticoagulants therapy as per the guidelines.

As I had mentioned previously, patients could be receiving oral antiarrhythmic agents, but they could not receive IV antiarrhythmics if they had been given within the previous 24 hours.

Patients needed to be hemodynamically -- patients who were hemodynamically unstable, or who had an MI acute coronary syndrome, or cardiac surgery
within the previous 30 days, were not eligible for this study.

The primary endpoint was the conversion of atrial fibrillation to sinus rhythm within 90 minutes of study drug initiation for a duration of one minute in patients with an atrial fibrillation duration of three hours to less than or equal to seven days.

Secondary and exploratory endpoints supported our primary endpoint, and included the time to conversion to sinus rhythm, conversion of atrial fibrillation to sinus rhythm in patients who had an atrial fibrillation duration of three hours to 45 days, a reduction in atrial fibrillation symptoms, and maintenance of sinus rhythm after conversion.

The phase III baseline characteristics of patients are listed here, and were balanced between the two treatment groups. Patients in our studies had
histories of congestive heart failure, ischemic heart disease, or hypertension, which represents the real world population.

Efficacy is presented here. The X-axis is the proportion of patients who converted to sinus rhythm, and the Y-axis -- or the X axis is time. The little orange bars are two infusions of vernakalant.

The gray dashed line is our placebo group, and the green line is the vernakalant group.

Efficacy was consistent in both of our pivotal trials, with 51 percent of the patients with recent onset atrial fibrillation converting to sinus rhythm, compared with 4 percent in the placebo group.

In patients who converted to sinus rhythm in our responders, the time to conversion was rapid. Median time to conversion was 11 minutes in the ACT I study, and the median time to conversion in responders in ACT III was eight minutes.
The analysis I have presented here is a modified intent to treat analysis, or an as-treated analysis, which was discussed with the FDA and agreed to prior to breaking the study blind.

Patients who were randomized, but did not receive the study drug, were excluded from this analysis.

The intent to treat analysis, imputing patients who spontaneously converted to sinus rhythm as successes, and others were imputed as failures, and in doing this analysis, there was no difference in terms of the modified intent to treat analysis, or the intent to treat analysis.

These are the conversion rates for the three subgroups of patients stratified by the duration of atrial fibrillation, and to the short duration atrial fibrillation group which was our primary endpoint, the overall population, and the long duration group.

As expected, patients with a
shorter duration of atrial fibrillation had a higher rate of conversion.

One of the questions you have been asked to address is the relationship between time in atrial fibrillation, and conversion after vernakalant.

In the ACT I and the ACT IV study, which was the open label study, atrial fibrillation duration was collected in a way that allowed us to look at the relationship between atrial fibrillation duration and conversion.

The following graph shows the observed, which are the bars, and the modeled, which are the lines here with the 95 percent time for these intervals shown by the dashed lines. The probably of conversion by atrial fibrillation duration broken down by days, which is given here on the X-axis.

As you can see by the model, which is a generalized additive model, as atrial fibrillation duration increases, the
probability of conversion decreases similar
to other conversion modalities.

There is a greater uncertainty
around the conversion rate for patients with
longer duration of atrial fibrillation as
indicated by the width of the 95 percent
confidence intervals in the longer durations.

This is, in part, an artifact of
the study design, stratified and randomized
by AF duration of our three hour to seven
day, and eight to 45 days. One can see that,
based on the 95 percent confidence interval,
patients with atrial fibrillation duration of
less than 48 hours have conversion rates that
range from 45 to 70 percent. And those with
atrial fibrillation duration of three hours
to seven days -- or excuse me, from three to
seven days, have conversion rates that range
from 15 to 40 percent.

The placebo subtractive efficacy
data, based on age, gender, and use of rate
or rhythm control medications is presented
here. Placebo is better if to this side of zero, and vernakalant is better if this -- if to this side of zero.

This point up here is our overall treatment effect, and this is the 95 percent confidence intervals.

Efficacy was not affected by age, gender, or use of rate or rhythm control medications. This slide is similar to the previous slide. Again, the top category is the overall treatment effect. There appears to be a trend towards reduced efficacy in patients with a history of congestive heart failure based on a limited database, but no effect of ischemic heart disease or hypertension on efficacy.

A pre-specified endpoint in our pivotal studies was relief of atrial fibrillation symptoms, which was collected by a symptom checklist. Vernakalant provided relief of atrial fibrillation symptoms. At minute 90, about 50 percent of our patients
who received vernakalant were asymptomatic, compared with about 26 percent of the placebo group.

And I know during the discussion earlier this morning, the question had come up about what was the percentage of patients who were asymptomatic at hour 24, and there was very little difference between the placebo group and the vernakalant group, with about 70 percent of the patients being asymptomatic at hour 24. And when one looks at the number of patients that were asymptomatic at day seven, once again, there was little difference between placebo and vernakalant, with about 60 percent of the patients being asymptomatic.

Symptom reduction was mediated by the conversion to sinus rhythm as shown on this slide. At minute 90, about 69 percent of the patients who received vernakalant and converted to sinus rhythm were symptom free.

Patients who received vernakalant, but
remained in atrial fibrillation, about 29 percent of those patients were symptom free.

A life table estimate was used to determine the maintenance of sinus rhythm following the conversion to sinus rhythm. At 24 hours, 97 percent of the patients who received vernakalant and converted to sinus rhythm remained in sinus rhythm, and patients who received placebo and spontaneously converted, at 24 hours, 83 percent of those placebo patients remained in sinus rhythm.

I have just covered the primary efficacy studies in patients who presented with atrial fibrillation, and will now go over the study in patients who developed atrial fibrillation post-cardiac surgery.

The baseline characteristics of patients in this analysis did not differ, and was balanced between the two treatment groups.

This is the efficacy in the post surgical patients. Again, the Y-axis is the
proportion of patients who had converted to sinus rhythm, and this is the time from first dose to conversion, with our two infusion bars.

Again, placebo is shown as the gray line, and patients who receive vernakalant is shown as the green line.

The conversion rate and the post-cardiac surgery atrial fibrillation study was 47 percent in the vernakalant group, compared with 14 percent in the placebo group. Conversion was rapid, with a median time to conversion of 12 minutes in the responders.

Efficacy was robust and consistent across all of our studies. Included in this slide is the ACT IV study, which I had mentioned was an open label safety study. However, we did collect efficacy in that study, and in the ACT IV study in patients who had atrial fibrillation of three hours to seven days in duration, 51 percent of those patients converted to sinus rhythm.
So once again, efficacy was consistent across all of our studies, ranging from 47 percent in the post-surgical population, to 53 percent in our phase II study.

To summarize efficacy, vernakalant was effective in converting atrial fibrillation to sinus rhythm in patients who spontaneously developed atrial fibrillation, and in those post-cardiac surgery patients.

In the patients who converted, the median time to conversion was 10 minutes. Efficacy was not affected by age, gender, rate, or rhythm control medications, or concomitant illnesses such as congestive heart failure or ischemic heart disease.

There was relief of atrial fibrillation symptoms, and sinus rhythm was maintained out to 24 hours.

The next series of slides will cover safety. I will first discuss adverse events, serious adverse events, including
1 deaths. Events of interest will then be
2 presented.
3
4 These events were identified
5 during the review of the safety data, and
6 based on other antiarrhythmic agents.
7
8 Events of interest include
9 ventricular arrhythmias, including effects on
10 the QT and torsades de pointes, bradycardia,
11 and hypotension.
12
13 Safety data collection was
14 comprehensive in our clinical studies, and
15 included adverse events, 12 with ECG and
16 vital signs which were collected every five
17 minutes from the start of the infusion up
18 through minute 50, and then as outlined here.
19
20 In addition, a 24 hour Holter was
21 recorded.
22
23 As you can see, the monitoring in
24 the first 24 hours was extensive and capable
25 of capturing asymptomatic and infrequent
26 events.
27
28 The safety database contains all
patients, and there were 773 patients who received vernakalant, compared with 335 in the placebo group.

Patients had concomitant illnesses, such as congestive heart failure, ischemic heart disease, and hypotension, which are typically seen in patients seeking treatment for atrial fibrillation.

The use of rate and rhythm control medications during the seven days prior to study drug administration did not differ between placebo or the vernakalant groups.

Adverse events which occurred within the first 24 hours are of particular interest because of the short half-life of vernakalant. This table summarizes the adverse events occurring in more than 5 percent, and at a higher rate than in the placebo group.

Table 16 in your briefing document contains a more complete list of the adverse events. The most common adverse events seen
in the vernakalant group were dysgeusia, which was typically described as a metallic taste, sneezing, parathesias, nausea, and hypotension.

The median time to onset in patients receiving vernakalant was seven to 35 minutes, and the median duration in the patients who received vernakalant was eight to 20 minutes.

Hypotension is the most clinically important adverse event that is on this list, and will be discussed in detail later.

The incidence of any serious adverse event occurring within the first 24 hours was similar for placebo and vernakalant, with 3.9 percent of the patients who received placebo reporting any serious adverse event, compared with 4.1 percent of the vernakalant group.

Serious adverse events of complete heart block, sinus arrest, sinus bradycardia or bradycardia, ventricular fibrillation and
hypotension were the most common serious adverse events occurring in the vernakalant group in the first 24 hours.

The incidence of stroke is not shown on this slide, since the incidence was low in our clinical studies. But to help you to address question number nine, which the agency has asked you to address, the incidence of stroke within the 30 days following study drug administration in the placebo group was 1.2 percent, and in the vernakalant group, the incidence of stroke was 0.4 percent.

There were five deaths in the vernakalant studies. All deaths occurred in patients receiving vernakalant. There was one death within the first 24 hours that was considered by the investigator to be related to vernakalant, and that is this top patient here.

The other four deaths were not considered by the investigator to be related
to vernakalant, and one occurred on day two, and the others occurred more than seven days after receiving vernakalant.

I will now discuss the one related death.

The patient was a 64-year-old man with critical aortic stenosis, an injection fraction of 40 percent, and New York Heart Association Class II congestive heart failure.

Serious protocol violations occurred in this patient, including dosing a patient who was hemodynamically unstable during an acute myocardial infarction. He became hypotensive following the administration of metoprolol, and was given saline to restore his blood pressure.

The patient received two doses of vernakalant, and became hypotensive after both doses. Following the second infusion, he developed ventricular fibrillation, and resuscitation attempts were not successful.
Autopsy showed him to have aortic stenosis and myocardial hypertrophy.

There were four unrelated deaths.

All these deaths occurred more than 24 hours after receiving vernakalant. A 68-year-old woman died during a gastroscopy procedure. At autopsy, she was found to have a ruptured dissecting aortic aneurysm.

A 67-year-old man with lung cancer, pneumonia, suffered a respiratory arrest, and was placed on life support. He died following the family's decision to remove life support eight days after receiving vernakalant.

A 70-year-old woman with breast cancer died from a gastrointestinal hemorrhage 24 days after receiving vernakalant, and a 90-year-old woman died of congestive heart failure 26 days after receiving vernakalant.

None of these deaths were considered by the investigator to be related
to the administration of vernakalant. None
had a common pharmacological cause which may
have contributed to their deaths.

Events of interest will now be
presented. Based on a safety profile of
other antiarrhythmic agents, and in reviewing
the safety data for vernakalant, three events
of interest were identified: ventricular
arrhythmia, bradycardia, and hypotension.

Incidence tables were created
using the phase III studies for these three
events using multiple data sources, such as
adverse events, 12 Lead ECGs, the 24 hour
Holter recordings, and vital signs.

There were no pre-specified
definitions for adverse events such as
bradycardia or hypotension, and so these
events were judged and classified by the
investigator.

A conservative definition of
ventricular tachycardia was used, and was
defined as at least three consecutive beats,
at a rate of 100 beats or more per minute.

Analyses were conducted for all post dose, and for the two to 24 hour time period. The zero to 24 hour time period is the most informative, because it was the time of intensive data collection, and because most of vernakalant is cleared from the blood within this period.

The zero to 24 hour time period was divided into the zero to two, and two to 24 hour periods, since after two hours, other treatments for atrial fibrillation were allowed.

This table summarizes the ventricular events during the zero to two and two to 24 hour period. The incidence of ventricular tachycardia was approximately three percent in both the placebo and the vernakalant group.

In the two to 24 hour time period, the incidence of ventricular tachycardia was 8-1/2 to 12 percent, and essentially no
difference between placebo or the vernakalant group.

There was one case of torsades de pointes, which occurred in the two to 24 hour time period, which is shown here.

There are two cases of ventricular fibrillation during the zero to two hour time period. One does not show up on this table, since this table summarizes the phase III data, and the one case occurred in the phase II study.

The case that is shown here on this slide is a case that resulted in the fatal outcome which I had just discussed.

The second case of ventricular fibrillation will now be discussed.

A 24-year-old female with atrial fibrillation presented to the emergency room with a rapid ventricular response. About two hours following the initiation of vernakalant infusion, electrical cardioversion was attempted.
A non-synchronized cardioversion shock was delivered, with ensuring ventricular fibrillation. Immediate defibrillation was successful. She was discharged the next day.

The investigator determined that the ventricular fibrillation was due to the delivery of a non-synchronized electrical shock, and not drug related.

This is a case of non-synchronized electrical cardioversion due to a technical malfunction, which is known to occur.

There are a total of four reports of torsades de pointes in the 30-day follow up period: one in a patient receiving placebo, and three in patients receiving vernakalant. Of the three patients receiving vernakalant, one occurred, which is the top case here, within the first 24 hours, and the other two occurred more than 24 hours after receiving vernakalant.

This is the ECG tracing of the
torsades which occurred within the first 24 hours after receiving vernakalant. A 51-year-old man with atrial flutter did not convert after receiving vernakalant. Ibutilide was given two hours and 20 minutes after the initiation of the vernakalant infusion. He developed an asymptomatic, nine-beat run of torsades, immediately following the infusion of ibutilide.

The torsades is captured on the Holter recording.

An association with vernakalant cannot be excluded in this case, since it occurred two hours and 20 minutes after the initiation of the infusion of the vernakalant.

The incidence of torsades de pointes in our safety database, then, is one out of 773 patients, or 0.13 percent.

Here are the other cases of the torsades. A 90-year-old woman developed torsades 32 hours after receiving
1 vernakalant.
2  The third case was a 69-year-old
3 man who developed torsades de pointes on day
4 17 and 18 after receiving vernakalant, and
5 three days after aortic and tricuspid valve
6 surgery.
7  The fourth case was a 53-year-old
8 man who did not convert after receiving
9 placebo. He developed torsades de pointes
10 after receiving increasing doses of sotalol,
11 and about an hour after electrical
12 cardioversion.
13  None of these cases were
14 considered related to study drug by the
15 investigator.
16  The QT interval data that I am
17 showing you on this slide includes patients
18 who are in sinus rhythm, as well as those who
19 have remained in atrial fibrillation.
20  QTCF is shown here on the Y-axis,
21 and time is shown on the X-axis. Once again,
22 our orange bars are two infusions, and this
gray bar shows when other therapies are permitted.

QTcF was selected over QTcB, since QTcF is not greatly affected by heart rate.

Baseline QTcF was similar for placebo and vernakalant, and as you can see, the QTc interval increases with each of the infusions, and it starts returning to baseline once the infusion is discontinued.

From 90 minutes out to follow up, there is very little change in the QTcF interval.

Shifts from baseline in the QTcF were evaluated for patients in the phase III studies. This slide summarizes the QTcF of greater than 500 milliseconds, and greater than 550 milliseconds.

The cumulative incidence of any patient with a QTcF of greater than 550 milliseconds during the zero to two hour post-dose period was 0.6 percent for vernakalant, and 0.4 percent for placebo.
After minute 30, there was no difference between placebo and the vernakalant group. The incidence of any patient with a QTCF of greater than 500 milliseconds during the zero to two hour time period was 7.2 percent for vernakalant, and 2.8 percent for placebo. There was no difference between placebo and vernakalant after 90 minutes.

This graph shows the QTCF change from baseline for the 2D6 poor and extensive metabolizers. This shows change from baseline for the QTCF. This shows time.

The extensive metabolizers are shown by the yellow line here, the little squares, and poor metabolizers are shown by the green line with the triangles.

Although the number of poor metabolizers is small, there appears to be no difference between the poor and extensive metabolizers in change from baseline in QTCF.

The incidence of bradycardia was
summarized using adverse events, 12 Lead ECG data, and Holter data.

In the zero to two hour time period, the Holter data showed no difference between placebo or the vernakalant group.

Looking at adverse events in the 12 Lead ECG, there appears to be a higher incidence of bradycardia during the zero to two hour time period. The reverse is seen in the two to 24 hour time period when other therapies are allowed. You can see there is a higher incidence of bradycardia in the placebo group when compared to the vernakalant group.

The higher incidence of bradycardia is due to patients converting to sinus rhythm following the administration of vernakalant.

This slide shows the heart rate by responder status. This is the heart rate on the Y-axis, and time again is shown here on the X-axis.
Patients who received vernakalant and converted to sinus rhythm are shown by the solid green line. Patients who received vernakalant but remained in atrial fibrillation are shown by the dashed green line, and placebo is shown by the gray line.

Patients who converted to sinus rhythm with vernakalant had a slowing of their heart rates. And when other therapies are allowed, as shown out here, you can see their heart rates start to become similar.

Of particular interest are the patients who had a serious adverse event, or bradycardia during the first 24 hours post infusion, or had study drug discontinued due to bradycardia. Details of these cases can be found in table 21 in your briefing document.

There were 15 patients who met this criteria: 13 in the vernakalant group, for an incidence of 1.7 percent, and two patients in the placebo group for an
incidence of 0.6 percent.

The onset of bradycardia occurred either during one of the two infusions, or within 10 minutes of the end of the infusion. The duration was from less than a minute to four days.

The bradycardia responded to discontinuation of the infusion, or atropine, and in one patient who was post-operative and still had their epicardial wires in place, the bradycardia was treated by pacing.

There were two patients in the placebo group who had an event of bradycardia. One occurred after electrical cardioversion, and the second occurred 20 hours after received placebo.

The incidence of hypotension was summarized using adverse events and blood pressure. This slide presents the adverse event and systolic blood pressure less than 90 millimeters of mercury data.

Further details are found in Table
The incidence of hypotension reported as an adverse event, or systolic blood pressure less than 90 millimeters of mercury, was higher in the vernakalant group compared to the placebo group in the zero to two hour time period.

And once again as we saw for bradycardia, the reverse is seen in the two to 24 hour period.

Of particular interest again are patients who had a serious adverse event of hypotension during the first 24 hours, or who had study drug discontinued due to hypotension, and there were 12 patients who met these criteria. There were two in the placebo group for an incidence of 0.6 percent, and 10, or 1.3 percent, in the vernakalant group.

Table 23 in your briefing document provides detailed information on these patients.
The onset of hypotension occurred either during the two infusions, or within 15 minutes of the end of the infusion.

In one patient, the onset occurred about seven hours after vernakalant, and was associated with the diagnosis of cholecystitis, and following the administration of verapamil. The duration of the hypotension was from two minutes to two hours and 16 minutes.

The hypotension responded to placing the patient in a Trendelenburg position, stopping the infusion, and giving saline if necessary.

One patient was treated with norepinephrine, and one patient was treated with phenylephrine.

There were two placebo patients who developed hypotension. One event occurred after electrical cardioversion, and one event occurred five hours after receiving placebo.
There are a total of 164 patients in our phase III safety database with a history of congestive heart failure. 110 patients received placebo, and 54 received Vernakalant, and 54 received placebo.

During the zero to 24 hour time period, a trend towards an increased incidence of hypotension was observed in patients receiving vernakalant. There was no difference in the incidence of bradycardia or ventricular arrhythmia.

The safety database in patients with a history of congestive heart failure is limited. Vernakalant should be administered with caution in patients who have a history of congestive heart failure, and further studies are needed.

Electrical cardioversion was allowed two hours after receiving study drug. There was no difference in the vernakalant group compared with placebo in the percentage
of successful cardioversions, the median number of shocks, or the median joules.

To summarize the safety of vernakalant, there was one vernakalant-related death in a patient with critical aortic stenosis, and an acute MI who developed hypotension and ventricular fibrillation following the administration of metoprolol and vernakalant.

Transient increases were seen in the QRS and QT intervals.

The incidence of torsades was 0.13 percent in the first 24 hours after administration of vernakalant, and occurred immediately following an infusion of ibutilide.

Clinically important bradycardia, defined as a serious adverse event within the first 24 hours, or patients who required discontinuation of study drug due to bradycardia, occurred in 1.7 percent of the vernakalant group, and 0.6 percent of the
placebo group, and was associated with conversion to sinus rhythm.

Clinically important hypotension, again defined as a serious adverse event within the first 24 hours, or hypotension requiring discontinuation of study drug, occurred in 1.3 percent of the vernakalant group compared with 0.6 percent of the placebo group.

The hypotension was periinfusional, transient, and responded to saline. Two patients were treated with pressors.

I would like to conclude my presentation with a discussion of risk management and post-marketing studies, assuming that we would get approval, of course.

We see four components to risk management. The prescribing information, health care provider education, pharmacovigilance, and post-marketing studies.
The FDA approved label will be the primary tool in risk management. The package insert will identify the patient population for which vernakalant should be used. This includes patients with symptomatic, recent onset atrial fibrillation, and who are hemodynamically stable.

Patients with an acute MI, acute coronary syndrome, symptomatic, or decompensated congestive heart failure should not receive vernakalant. And vernakalant should be used with caution in patients who have a history of congestive heart failure.

Vernakalant should be administered in a monitored setting with a physician in attendance during the infusion. Vital sign measurements, and continuous cardiac rhythm monitoring should be conducted for a minimum of 90 minutes after the end of the infusion, or until the ECG parameters have stabilized, and the patient is clinically stable.

If hypotension, bradycardia, or
clinically significant changes are seen in
the ECG, vernakalant infusion should be
immediately discontinued, the second dose
should not be given, and the patient should
be treated symptomatically.

The education program will be
comprehensive and focused on a select target
audience. The prescribing information will
be the basis for our educational activities.

Routine pharmaco-vigilance
practices will be employed, including adverse
event reporting, with emphasis on ventricular
arrhythmia and deaths, reviewing the
literature for adverse event reports, data
mining, and the use of signal detection
programming.

Additional studies are ongoing or
planned. These include a study on
ventricular defibrillation threshold, and the
effect of vernakalant on key glycoprotein
transporters.

PK studies in hepatically or
renally impaired patients are ongoing.

A safety and efficacy study will be initiated in the near future in Europe.

We are also planning a post marketing observational study, which is discussed on the next slide.

Safety has been well characterized in the development program, and we recognize if vernakalant is approved, the incidence of low frequency adverse events should be addressed in the real world setting.

Therefore, we propose a post marketing study to assess adverse events, focusing on torsades de pointes, ventricular arrhythmias, bradycardia, hypotension, and deaths.

Design options for this study may include a registry and/or mining of managed health care databases.

The details of these studies will be worked out with the FDA, and experts in the field.
Based on the observed event rates, we believe a sample size of approximately 2,000 patients will provide additional information on the safety profile of vernakalant in the treatment of atrial fibrillation.

I thank you for your attention, and I now turn the podium over to Dr. Jeremy Ruskin, who will now discuss the risks and benefits of vernakalant.

RISK/BENEFIT SUMMARY

DR. RUSKIN: Thank you, Dr. Kitt.

Dr. Hiatt, committee members, FDA members, guests, I appreciate the opportunity to offer some comments on the benefits and risks of vernakalant injection.

Just to get at a point that Dr. Harrington raised earlier, this is an attempt to map the patients in the vernakalant trials in relation to the AFFIRM study, which has been discussed this morning, and also a large European survey of patients with atrial
fibrillation. And there are some demographics
and relevant medical history presented here
for each of the populations.

You can see that there is an age
difference, not a huge one, but an age
difference between AFFIRM and the vernakalant
studies, based on the fact that, as we heard
this morning, the AFFIRM trial entered
patients age 65 or older, largely directed at
an older population, with a small subset who
had major risk factors that allowed them to
enter at a younger age.

The other difference is that there
is less congestive heart failure in the
vernakalant studies than AFFIRM. But in
terms of valvular disease, coronary heart
disease and hypertension, the trials or the
populations are essentially
indistinguishable.

And I think that this indicates
that the trials were done in a clinically
relevant population, not solely restricted to
young patients without structural heart disease.

The major risks of vernakalant are listed here, and you have heard about these in detail from Dr. Kitt, and they include torsades, hypotension and bradycardia, and what are listed here are hypotension and bradycardia that were reported either as SAEs, or required drug discontinuation.

The point estimates are listed here, and in order to model a worst case scenario, the upper bound of the 95 percent confidence limits are listed here. And you can see that, for torsades, the point estimate is 0.13 percent, the upper 95 percent confidence bound is 0.6 percent.

For serious hypotension, the point estimate is 1.3 percent, with an upper 95 percent confidence bound of 2.2 percent, and for bradycardia, the point estimate is 1.7, with an upper confidence bound of 2.7 percent.
The QT prolongation, as you've heard from Dr. Kitt, is moderate, and transient. There was one case of torsades de pointes which occurred during the first 24 hours after administration of vernakalant, and immediately following an infusion of ibutilide, and I'll offer an additional comment on that towards the end.

The hypotension associated with the drug is peri-infusional and generally transient, and in almost all cases responded to conservative measures.

The bradycardia, as you also heard, is largely associated with conversion of atrial fibrillation to sinus rhythm.

A couple of words about congestive heart failure, another area of concern for two reasons. One, the experience is relatively limited, and two, there appears to be somewhat lower efficacy, and perhaps more in the way of hypotension.

And what's listed here are
efficacy and hypotension AEs as a function of placebo patients with a history of failure, vernakalant patients with a history of congestive failure, and vernakalant patients with no history of heart failure.

And you can see the lower efficacy rate, small numbers, but at least a suggestion of a lower efficacy rate, and likely more hypotension in vernakalant treated patients with a history of heart failure compared to those without.

The next two slides summarize the benefits of vernakalant injection, and as you also heard from Dr. Kitt, the drug effectively converts atrial fibrillation to sinus rhythm in about 50 percent of patients.

This effect is highly consistent across studies. The onset of action of the drug is rapid, with a median time to conversion of approximately 10 minutes, and conversion from atrial fibrillation to sinus rhythm by treatment strategy, that is, vernakalant.
versus placebo, results in a highly significant reduction in symptoms.

This symptom reduction is mediated by conversion of atrial fibrillation to sinus rhythm.

In addition, the effect of the drug is durable, with 97 percent of converters remaining in sinus rhythm at 24 hours. Vernakalant can be administered with background rate or rhythm control medications, which were present in 72 percent and 20 percent of patients, respectively.

Electrical cardioversion remains an option, because it is as effective in vernakalant non-responders as it is in placebo patients. And the drug is safe and effective in patients with common comorbidities, including hypertension, which was present in 52 percent of patients, and ischemic heart disease, which was present in 24 percent of patients.

This slide provides a profile of
all serious ventricular arrhythmias observed
during treatment with vernakalant during the
first 24 hours.

You have heard that there were two
cases of ventricular fibrillation, one
clearly associated with drug administration
involving a major protocol violation in a.patient with critical aortic stenosis, and
likely global ischemia.

The second case involved the
induction of ventricular fibrillation by a
non-synchronized DC shock in a young female
patient who had received vernakalant a few
hours prior.

In that patient, the ECG intervals
showed no evidence of QT or QRS widening
prior to the event, and a 12 Lead ECG
immediately after conversion showed normal
QRS and QT intervals, again suggesting that
this was not a pharmacologic pro-arrhythmie
event.

The one case of torsades de
pointes which was reported was an asymptomatic, 9-beat run of polymorphic ventricular tachycardia that occurred immediately after administration of ibutilide in a patient who had received two doses of vernakalant about two hours earlier.

While the temporal association with ibutilide is compelling in this case, a possible contribution of vernakalant to the occurrence of torsades cannot be excluded.

All the remaining arrhythmias were non-sustained ventricular tachycardias, both monomorphic and polymorphic, and as you can see, these occurred with a frequency that was slightly lower, but statistically indistinguishable on vernakalant compared to placebo.

In summary, vernakalant is effective for the rapid conversion of atrial fibrillation to sinus rhythm, with an accompanying reduction in atrial fibrillation associated symptoms.
Clearly, more experience is needed in congestive heart failure, and the drug is associated with risks, predominantly hypotension, bradycardia, and a very low pro-arrhythmic risk.

For me as a clinician, these risks are favorably balanced by the benefits of the drug, and are manageable.

And for that reason, I believe that vernakalant injection provides an important treatment alternative for patients with acute symptomatic atrial fibrillation.

Thank you.

CHAIR HIATT: Thank you all very much.

I think given the time of the morning we should take a break, and then reconvene and pose our questions to the sponsor and their presentations.

So maybe 15 minutes.

(Whereupon at 10:57 a.m. the proceeding in the
above-entitled matter
went off the record to
return on the record at
11:20 a.m.)

QUESTIONS/DISCUSSION FROM THE COMMITTEE

CHAIR HIATT: We're slightly off
schedule, but I think we can make that up
fairly easily. No one is scheduled for the
public commentary part of this.

So I think the morning session has
been quite helpful. And we did really begin
with a general discussion as well. So now is
the time for the Committee specifically to
address any questions to the sponsor or
perhaps Dr. Granger about any of the things
we have seen so far this morning.

As everyone is getting set up, I
would like to lead off with a couple of
things. I have some specific questions. The
one that kind struck me initially was that I
think 20 percent of the patients that came
into these trials were asymptomatic. And, as
we heard today, one of the sort of compelling reasons to convert people is because they have sort of drive you in that direction. So I would like to know why that occurred.

I think the thing that I have a bigger issue with is sort of the absence of data that I think the sponsor must have, some of which we heard about just a minute ago about the symptomatic status of patients at 24 hours.

I have in my mind a table that has these three windows: zero to 2, 2 to 24, and 24 hours to 7 days. And then I have a list of variables split by drug and placebo. You know, those converted to atrial fibrillation, Cardioversion, those who took other antiarrhythmic drugs, symptom score, adverse events, deaths, and other kinds of serious safety concerns.

And I realized that things changed after two hours, that patients were then allowed to take sort of standard therapies,
which included both perhaps chemical and, as we saw in the briefing document, electrical Cardioversion, which occurred in 37 percent of patients randomized to drug and 58 percent of patients randomized to placebo. So clearly more patients on placebo had to undergo electrical Cardioversion.

But in terms of getting at the overall risk-benefit of this development program, I think at least understanding those endpoints at 24 hours is extremely important and not just narrowing our window to the two-hour time frame.

We heard a little bit, again, that symptomatic differences were not seen at 24 hours or later. And if you look at the heart rate status by responders' group, slide 74, clearly when you evoke other therapies, there really doesn't appear to be any difference between drug responders and drug nonresponders, or placebo, at least in terms of heart rate. And if heart rate is a
reflection of symptoms, there was no
difference in symptoms either.

So is there some way we could fill
out a table that kind of completed that
missing data? We have complete data to two
hours. I think a lot of things were not
presented at 24 hours. We have adverse
events that we don't have the symptoms for.
And so I guess I would like to see that.

DR. MASSIE: Can I just add one
request, which I think is embedded in yours,
which is of those that didn't get
electrically converted, what the spontaneous
conversion rate is at that 24-hour time since
we have the Holters? Because I have to plead
stupidity. In some of my earlier comments, I
really read this booklet as you had to be 72
hours, 3 days, out, not 3 hours.

And so we're clearly right in the
middle of the window when we would expect
perhaps 25 to 30 percent of these people to
convert spontaneously over that period of
time that I misrepresented.

     CHAIR HIATT: Yes.

     DR. MASSIE: At least for 24

     hours, we should get that.

     CHAIR HIATT: So before we go much

     further into perhaps dozens of specific

     questions that we would like to have

     addressed, I don't wonder if the sponsor will

     be prepared to provide us with that

     additional information, those missing data

     cells, particularly at 24 hours, you know,

     the numbers of patients converted at 24

     hours; the number of patients undergoing

     electrical Cardioversion, which we did get in

     the briefing document; use of other

     antiarrhythmic drugs; the actual symptom

     scores at 24 hours.

     We have adverse events I think

     pretty well described out that far. And then

     maybe we'll take some time to do that. And

     perhaps we could circle back to that

     question, even later, early in the afternoon,
if necessary.

MEMBER HARRINGTON: Could I just get a little more information? If that table is going to be constructed, Bill, I would like a safety composite. We are seeing things, you know, low-frequency events. But I would like to know what happens when you add everything up and in the same issue at 24 hours for both arms.

CHAIR HIATT: I see Dr. Kitt standing at the microphone.

DR. KITT: Okay. There are quite a few questions in there. And I will try to go through them as best as I can remember them. And please if I forget something, let me know.

CHAIR HIATT: And sorry to interrupt you, but verbally would be nice. But I might forget some of the numbers. If it's possible to prepare a slide that has the primary data out to two hours, which we have all seen and read before the meeting, you all
nicely presented, but then carrying those
things forward to 24 hours on the safety side
is mostly done, but on the efficacy side and
perhaps the add out the bad stuff and if it's
possible out to seven days. We might
visually look at that because I think it
gives us a more complete picture of risk and
benefit.

DR. KITT: Okay. I think one of
your questions you had asked was why were
people at baseline asymptomatic. And I think
that refers to figure 5 in your briefing
document.

Between screening and baseline,
other therapies were allowed. So somebody
had come in with a very rapid heart rate.
They could have received a dose of
Metoprolol. And so some of those patients
had a reduction in their symptoms. So that's
why at baseline some of our patients were
asymptomatic because we did allow the
treatment before baseline.
Slide up. I think this slide may address some of your other questions. This is our three hours to seven-day group, patients who had converted to sinus rhythm and those who had remained in atrial fibrillation. So here at baseline are percentage of patients without symptoms. And then the data had shown at 90 minutes.

And here at 24 hours, I think patients became asymptomatic due to the conversion to sinus rhythm. Those who remained in atrial fibrillation less than 40 percent were asymptomatic, whether that be at 24 hours or 7 days.

CHAIR HIATT: Thanks. Just before you walk off with that one, then, so that you clearly have a symptomatic advantage out to 2 hours, but then as other therapies are employed, you lose that advantage at 24 hours and 7 days. Is that correct, then?

DR. KITT: That's right. The patients that we studied in our studies, the
patients we studied, were those I think where clearly the physician felt that they needed to be converted to sinus rhythm. And if they did not convert with vernakalant, they went out to have other therapies.

CHAIR HIATT: So all of this discussion will acknowledge clearly that other therapies were employed after two hours. And clearly there is a relationship between going back into sinus rhythm and relief of atrial fibrillation symptoms. So we understand that. But I guess it is just good to see the data.

DR. KITT: Okay. Slide up. Maybe this will help. So the majority of the patients that remained in atrial fibrillation after study treatment received either electrical Cardioversion or other antiarrhythmic agents within the first 24 hours. So the top line here is other spontaneous converters from placebo and the vernakalant converters. And here are the
non-converters.

And you can see that the non-converters, about 80 percent of those, in our study went on to get treated with either electrical Cardioversion and/or antiarrhythmic agents. And a majority of those patients actually had electrical Cardioversion. I don't think there were very many that received antiarrhythmics.

DR. MASSIE: Do you know anything about the spontaneous conversion in the people who were not treated, the 20 percent?

DR. KITT: Just a minute.

(Pause.)

DR. KITT: No. I'm afraid we don't have that analysis.

DR. CANNON: I believe you or someone presented that there was a follow-up contact at 7 days and at 30 days. Maybe it's 7 days EKG or Holter and 30 days telephone contact.

My specific question is about the
durability. So I know that at 90 minutes, the people who converted at 24 hours, the majority, 90-something percent, were still in sinus rhythm. So my question is, what about at 7 days and at 30 days? What percent of people who are successfully cardioverted with the drug vernakalant and who were in sinus rhythm at 24 hours remained in sinus rhythm at 7 days and 30 days? Do you have those data?

DR. KITT: Just a minute, please.

(Pause.)

DR. CANNON: So this follows on figure 53, where you show the data, the durability, at 90 minutes. So I am asking for an extension of durability.

DR. KITT: Right. We did do 12-Lead ECG on day seven.

DR. CANNON: Okay.

DR. KITT: The day 30 was just a telephone telephone call. I don't recall offhand what the percentage --
CHAIR HIATT: So what about day seven?

DR. KITT: We're trying to get that data for you. What is it? Ninety-three to 94 percent remained in sinus rhythm at day seven.

CHAIR HIATT: And tell us about both groups. I'm sorry. So at day seven, what percent of both groups were in sinus?

DR. KITT: Placebo and vernakalant?

DR. CANNON: And while you're looking that up, what about the symptoms at day seven for both groups as well because it was indicated you did the symptom checklist at both time points.

DR. KITT: Okay. Slide up, please. This shows if they were in sinus rhythm. This shows how many were symptom-free at day seven. So if they were in sinus rhythm and they received placebo, 67 percent were symptom-free, 65 percent in the
vernakalant group if they were in sinus rhythm on day 7.

DR. CANNON: But, of course, the placebo patients by then, many would have received something. They would have been electrically cardioverted or --

DR. KITT: Right. Those are people --

DR. CANNON: -- ibutilide or whatever. So that's a tough comparison, I think.

MEMBER HARRINGTON: Well, I think what you're saying, Richard, is you're embarking upon a strategy here. So the strategy is pharmacologic Cardioversion from the outset in the half of the people that it fails in. They also undergo electrical Cardioversion or a period of two hours of observation followed by electrical Cardioversion.

So I think from the clinician's perspective at seven days, what you are
seeing is the strategy comparison. And at
the strategy, there is no difference.

DR. CANNON: So along that
thinking, though, we need to know what the
placebo patients actually got, how many
converted spontaneously, how many got
electrical -- well, she actually presented
those data -- how many got ibutilide or
something else. I mean, additively, it may
be that similar numbers of people got similar
kinds of similar treatments of one sort or
another.

CHAIR HIATT: Well, remember at 24
hours, 58 percent of placebo patients had to
be cardioverted versus 37 percent. Because I
think Dr. Harrington actually said what I
think is running through my mind, it's a
treatment strategy for comparing drug to
placebo, but that's over a very short
interval.

And so the issue is, what does
that look like at a relatively short interval
of 24 hours or 7 days?

MEMBER LINCOFF: But not entirely because, I mean, no one is suggesting here that the drug is better than just electrical Cardioversion. If the idea was just a strategy, then we would do a drug-based strategy versus an electrical cardio-based strategy.

I mean, the purpose of these studies was to determine if the drug could eliminate the need for the electrical Cardioversion, recognizing that if it didn't, then one would go on. I mean, in practice, the idea would be that fewer patients ultimately would have to have electrical Cardioversion because we believe that there are some disadvantages to Cardioversion. If it was simply a strategy approach, then it would be start off with electricity or start off with drug and default to electricity.

And that really isn't the idea here. The idea is if we can convert