1   any of those criteria.

2   So I think we are going to have --

3   I'm not sure if it's a surrogate as much as

4   it's just a -- it's a biomarker. It's the

5   resolution of an arrhythmia, or a resolution

6   of an EKG finding in some patients.

7   In others, it may be -- it may

8   fulfill the criteria that it is actually a

9   clinical endpoint. People feel bad, you take

10   them out of it, and they feel better. That,

11   to me, is an important clinical outcome.

12   CHAIR HIATT: Yes, that's a very

13   important interpretation.

14   Comments?

15   DR. LINCOFF: I think what makes it

16   a surrogate is the time point. So if you are

17   saying at one hour, then that is a surrogate.

18   I don't think there is any question that afib

19   is a disease. I mean, if we said we've got a

20   drug that converts diabetes to normal, no one

21   would question that diabetes is an endpoint,

22   even if it's asymptomatic in many cases. Or

1   maybe I should say hypertension.

2   Hypertension leads to --

3   CHAIR HIATT: Well, be careful,

4   Michael. There's a slippery slope there.

5   (Laughter)

6   DR. LINCOFF: Right. No, diabetes

7   is a poor analogy. But hypertension, because

8   hypertension is asymptomatic until it causes

9   a mortal and morbid -- a mortal or morbid

10   endpoint, like stroke.

11   Well, so atrial fibrillation may

12   be asymptomatic, even for the patients who

13   are not feeling it, until it causes a

14   embolization or a hemodynamic compromise.

15   So I don't think, at least from my

16   standpoint, atrial fibrillation is a

17   surrogate, but whether you've converted it in

18   an hour or two hours or 24 hours, I think

19   that could reasonably be considered a

20   surrogate.

21   CHAIR HIATT: Well, the question

22   begs truly the thing you just kind of hit on,

1   which is that, and again, this committee has

2   debated this. You know, we discussed, in a

3   couple of meetings, the fact that blood

4   pressure is a surrogate endpoint that is

5   directly linked to clinical outcome, as you

6   lower the blood pressure.

7   The same is true for LDL

8   cholesterol.

9   The question is, is that true for

10   atrial fibrillation. Yes, it's a disease,

11   it's an arrhythmia. But the question is, by

12   converting, you'll see the questions that

13   come up later today, are there clinical

14   consequences that are beneficial to that

15   conversion.

16   And we've discussed a fair amount

17   already this morning. There are symptomatic

18   benefits in certain patients, but are there

19   morbid, mortal benefits? Or are there

20   avoidance of harm benefits that occur by

21   conversion of that endpoint?

22   DR. CANNON: I think it depends on

1   the underlying heart disease. So we know

2   that, for many patients, lone atrial

3   fibrillation in relatively young people, it's

4   relatively benign if it's not causing

5   symptoms.

6   But for older people, or people

7   with serious structural heart disease, it can

8   be a big problem, particularly if weight

9   control is not well attended to. It can

10   exacerbate heart failure for patients who

11   have stiff hearts. It can obviously

12   contribute to symptoms.

13   And we know overall atrial

14   fibrillation has a mortality risk that is far

15   greater than people in sinus rhythm, no

16   question about that. But in large part,

17   that's because of the underlying structural

18   heart disease.

19   CHAIR HIATT: Okay, so two

20   comments.

21   One is, you brought up this

22   morning a lot of consideration for specific

1   subgroups. So that's a theme I think the

2   committee needs to continue to keep in mind,

3   that maybe not all AF is the same.

4   So let's be mindful of that. And

5   then I think the second thing is, remember,

6   the natural history of any risk factor

7   doesn't make it necessarily a viable

8   surrogate or not. So that maybe raising HDL

9   cholesterol is not a good thing with the

10   drug, though it's a huge risk factor for

11   events.

12   So the same is true for type II

13   diabetes. So I think we should be careful

14   that, if we are going to treat a surrogate,

15   we are assuming there is a relationship

16   between treating that endpoint, and a

17   clinically relevant outcome.

18   That's the question that was

19   posed.

20   DR. CANNON: But again, I think you

21   can't dissociate that from the underlying

22   heart disease, the context in which that

1   atrial fibrillation exists.

2   CHAIR HIATT: Exactly. So your

3   point then is to be retained is that there

4   may be very relevant subgroups under this

5   broad definition of atrial fibrillation.

6   DR. MASSIE: I took the surrogate a

7   little bit, maybe wrongly, as the particular

8   endpoint of demonstrating conversion for 60

9   seconds, and is a surrogate, for even knowing

10   whether they are in afib, very much down the

11   line.

12   So I think there are two levels.

13   The specific way in which it was defined

14   clearly is telling you something about the

15   effect of the acute therapy, but certainly

16   not even about the effect of the -- now on

17   the natural history of atrial fibrillation,

18   much less the complication stuff.

19   But I would say, another thing is

20   if you really could get somebody out of afib

21   and know they weren't going to get in, then

22   it would probably mean something. It's

1   probably related to the underlying condition

2   that would allow that or not.

3   I believe that the number of

4   medicines that are given for atrial fib,

5   avoiding them itself is a positive outcome.

6   So it's not -- so in a sense, it's a

7   surrogate for not taking dangerous drugs.

8   CHAIR HIATT: Okay, so keep in mind

9   what you think that endpoint means. Clearly,

10   is it a surrogate for a durable conversion at

11   24 hours seems to be very good. But the

12   question posed, is it a surrogate for

13   clinically meaningful endpoints, and I would

14   include those as symptomatic endpoints, and

15   as morbid mortal endpoints.

16   DR. HARRINGTON: And so could we

17   agree on the phrase that we are going to call

18   the resolution a biomarker, because it's not

19   yet proven to be a surrogate? The surrogate

20   thing bothers me.

21   CHAIR HIATT: Well, I think the

22   concepts are out there. So it's a little

 1   past the time for the discussion on the

 2   general topic.

 3   Norman, do you have any other

 4   issues you'd like us to clarify?

 5   DR. STOCKBRIDGE: No, I think

 6   that's been a very good thing to set the

 7   stage for what comes next.

 8   CHAIR HIATT: Steven Findlay, could

 9   you introduce yourself?

10   MR. FINDLAY: Yes, I'm Steven

11   Findlay. I'm the consumer representative on

12   this panel.

13   CHAIR HIATT: And I know it's a

14   mundane issue, but the committee has to

15   circle their menu for their lunch vote. We

16   remain anonymous until it's presented on the

17   projector up here. Put your name on, too, so

18   that way nothing is truly anonymous.

19   Before the sponsor starts, is

20   anyone needing of a break? Consensus? Want

21   to move on?

22   We're moving on.

1   So next we will have an

2   introduction about the development program.

3   Dr. Raineri.

4   ASTELLAS PHARMACY US, INC. PRESENTATION

5   INTRODUCTION

6   DR. RAINERI: Good morning, Dr.

7   Hiatt, committee members, FDA participants,

8   and guests.

9   My name is Don Raineri. I'm a

10   senior director of regulatory affairs for

11   Astellas Pharma US.

12   On behalf of Astellas and our

13   development partner, Cardiome, I'd like to

14   thank you for this opportunity to present and

15   discuss the data for vernakalant

16   hydrochloride injection, also known as

17   Kynapid, which is a novel intravenous anti-

18   rhythmic agent for the rapid conversion of

19   atrial fibrillation to sinus rhythm.

20   Based on the data that you will

21   see this morning, we have proposed the

22   following indication. Vernakalant injection

1   is indicated for the rapid conversion of

2   atrial fibrillation of less than or equal to

3   seven days duration to sinus rhythm.

4   The proposed dosing for

5   vernakalant injection is an initial infusion

6   of three milligrams per kilogram infused over

7   10 minutes.

8   If conversion to sinus rhythm does

9   not occur within 15 minutes after the end of

10   the initial infusion, then a second 10-minute

11   infusion of two milligrams per kilogram may

12   be administered.

13   This slide shows the key

14   attributes of vernakalant injection. You

15   will see data this morning which shows that

16   vernakalant provides for rapid conversion of

17   atrial fibrillation to sinus rhythm, as well

18   as effective reduction of the symptoms

19   associated with atrial fibrillation.

20   In addition, sinus rhythm is

21   maintained out to 24 hours.

22   Vernakalant injection can be used

1   with rate or rhythm control medication if

2   required without affecting safety or

3   efficacy.

4   In our presentation today, we'll

5   provide you with data which shows that

6   vernakalant injection has a well

7   characterized safety profile, as well as a

8   favorable risk-benefit profile.

9   When taken together, these data

10   show that vernakalant injection provides an

11   important treatment alternative for patients

12   with acute symptomatic atrial fibrillation.

13   This is our program for today.

14   Following my introduction, Dr. Edward

15   Pritchett, from Duke University, will present

16   a clinical overview of atrial fibrillation,

17   and the medical need for vernakalant

18   injection.

19   Dr. Greg Beatch, from Cardiome,

20   will then present the mechanism of action of

21   vernakalant.

22   Dr. James Kerns, from Astellas,

1   will follow with the toxicology and clinical

2   pharmacology of vernakalant. Dr. Therese

3   Kitt, from Astellas, will then present the

4   clinical efficacy and safety data for

5   vernakalant injection, as well as our

6   proposal for risk management.

7   And Dr. Jeremy Ruskin, from

8   Massachusetts General Hospital, will conclude

9   with a risk-benefit summary of vernakalant

10   injection.

11   These are the consultants who have

12   worked with us throughout the development

13   program for vernakalant injection, and we are

14   pleased to have them with us today to respond

15   to questions from the committee.

16   In addition to Dr. Pritchett and

17   Dr. Ruskin, we are pleased to have with us

18   today Dr. David Fedida, Dr. Peter Kowey, and

19   Dr. Craig Pratt.

20   In addition, we have the following

21   internal experts available from Astellas and

22   Cardiome to respond to questions.

 1   At this time, I'd like to turn the

 2   presentation over to Dr. Edward Pritchett to

 3   present the clinical overview of atrial

 4   fibrillation, and the medical need for

 5   vernakalant injection.

 6   CLINICAL OVERVIEW OF ATRIAL FIBRILLATION

 7   DR. PRITCHETT: Thank you, and good

 8   morning.

 9   My remarks will be very brief.

10   I just want to remind you that

11   atrial fibrillation is a big problem. It is

12   the most common sustained cardiac arrhythmia

13   in the United States, and it is the most

14   common diagnosis for arrhythmia-related

15   hospitalization in the United States.

16   There are about 2.3 million U.S.

17   adults who carry a diagnosis of atrial

18   fibrillation now, and that number will

19   increase as the population ages.

20   The clinical presentation of

21   atrial fibrillation is now largely with

22   symptoms. It is most commonly identified

1   because patients show up complaining about

2   symptoms. The cardiovascular health study is

3   a large, multi-center epidemiology study that

4   is looking at the incidence of heart disease.

5   And they have reported that 80 percent of the

6   patients with atrial fibrillation that they

7   identify are identified because they have

8   symptoms. So this is largely a discussion

9   about symptoms, as the committee has alluded

10   to.

11   In fact, the most appropriate use

12   of antiarrhythmic drugs in patients with

13   atrial fibrillation is for relief of

14   symptoms, as discussed in the guidelines and

15   in recent review articles.

16   And there are lots of symptoms

17   that are closely associated with the

18   occurrence of atrial fibrillation. And I've

19   listed in the third bullet the symptoms that

20   were collected in the flecainide atrial

21   fibrillation program almost 20 years ago, in

22   which over 3,000 patients, or over 3,000

1   episodes of atrial fibrillation were

2   documented by trans-telephonic monitoring,

3   and patients volunteered the symptoms that

4   they had.

5   And those symptoms were compiled

6   by Ani Bhandari after that program, and have

7   been published. And those symptoms have now

8   been reduced to a number of checklists that

9   have been used in antiarrhythmic drug

10   development programs, including the program

11   that you will see today.

12   Indeed, the history of all

13   antiarrhythmic drug development is largely a

14   symptom-driven history. Prior to 1986, most

15   drug development programs for antiarrhythmic

16   drugs concentrated on drugs for ventricular

17   arrhythmias, so we had drugs like

18   disopyramide, like the on 1C drugs,

19   flecainide and encainide, introduced in the

20   `70s and early `80s.

21   In the mid-`80s, there was sort of

22   a shift to interest in developing drugs for

1   supra-ventricular arrhythmias, including

2   atrial fibrillation, and those development

3   programs largely used symptomatic arrhythmia

4   recurrence as an outcome.

5   And these are FDA approval since

6   1986 for oral drugs for symptomatic

7   arrhythmic recurrence. The first of these is

8   the verapamil program presented to this

9   committee in 1984 led to labeling for

10   immediate release verapamil for PSVT in 1986.

11   That was followed by the first multi-center

12   clinical trial program that used symptomatic

13   arrhythmia outcomes, flecainide for PSVT and

14   atrial fibrillation that led to the symptom

15   checklists that are being used today.

16   Then in 1997, propafenone for PSVT

17   and AF, dofetilide in 1999, d.l. sotalol in

18   2000, and then in 2003, sustained release

19   propafenone. Dofetilide in 1999 was also

20   approved for oral use to convert atrial

21   fibrillation to sinus rhythm, but the speed

22   of that is magnitudes difference from an

1   intravenous drug.

2   The curious thing is that, during

3   this 20-year period, there has really been

4   nothing much done about intravenous therapies

5   for atrial fibrillation to restore sinus

6   rhythm.

7   There is, in fact, only one drug,

8   and that's ibutilide, which was approved and

9   labeled for this indication in 1996, the only

10   drug approved, in fact, in the last 40 years

11   for converting sinus -- atrial fibrillation

12   to sinus rhythm.

13   And this has been a very difficult

14   indication for the pharmaceutical industry to

15   crack. So there simply aren't very many

16   intravenous drugs. Drugs can be used off-

17   label. We've heard mention of intravenous

18   amiodarone this morning, it's off-label use.

19   And it's gotten mixed reviews in the

20   literature with respect to its success.

21   But the bottom line is that we

22   simply don't have a lot of drugs that we can

1   use intravenously for rapid restoration of

2   sinus rhythm.

3   So as I said, in summary then, few

4   choices of drugs that are approved and

5   labeled, and they all have imperfect

6   efficacy, and they all have adverse effects.

7   You all have discussed electrical

8   cardioversion this morning. It does require

9   conscious sedation, it has its own

10   complications, and there are some settings

11   where it is clearly inappropriate.

12   Therefore, what the cardiology

13   community and patients with atrial

14   fibrillation need is additional choices of

15   drugs that they can use, drugs with a high

16   rate of efficacy for restoring sinus rhythm

17   accompanied by relief of symptoms, and a

18   rapid onset of action, drugs with low rates

19   of adverse effects, a low incidence of drug

20   interactions, and a lack of interference with

21   electrical cardioversion.

22   That completes my remarks, and I

1   will be happy to turn the podium over to my

2   colleague, Dr. Beatch.

3   MECHANISM OF ACTION

4   DR. BEATCH: Thank you, Dr.

5   Pritchett.

6   Mr. Chairman, members of the

7   panel, it's my pleasure to present the

8   mechanism of action of vernakalant.

9   Vernakalant is a multi-ion channel

10   blocker, which blocks potassium channels and

11   sodium channels in a manner that is targeted

12   to atrial fibrillation.

13   Vernakalant produces relatively

14   atrial-selective increases in atrial

15   refractory periods, and rate dependent

16   slowing of conduction velocity, and rapidly

17   converts atrial fibrillation.

18   Vernakalant's efficacy and safety

19   profile are consistent with its ion-channel

20   blocking properties.

21   Vernakalant blocks potassium

22   channels important in control of atrial

1   repolarization at all phases of the atrial

2   action potential, including the transient

3   outward current, the alter-rapid delayed

4   rectifier, the rapid component of the delayed

5   rectifier, and the acetylcholine-dependent

6   potassium channel.

7   And it blocks these currents

8   within the therapeutic range of plasma

9   concentrations, which is 2-12 micromolar.

10   In contrast, it does not block the

11   slow component of the delayed rectifier, nor

12   the inward rectifier at therapeutic

13   concentrations.

14   Importantly, it does block the

15   ultra rapid component of the delayed

16   rectifier, and the acetylcholine dependent

17   current, which are atrial specific currents.

18   The block of these atrial

19   potassium channels is responsible for

20   vernakalant's ability to prolong the action

21   potential duration.

22   In this recent study of tissue

1   taken from patients with atrial fibrillation,

2   and presented at the European Society of

3   Cardiology by Dr. Ravens earlier this year,

4   vernakalant was shown to significantly

5   prolong the action potential duration at 20

6   percent and 90 percent repolarization. And

7   these effects led to increases in the

8   effective refractory period in these atrial

9   tissues, which were significant within the

10   therapeutic range of concentrations.

11   Increasing atrial refractoriness

12   has also been shown in the clinical study.

13   As shown here, vernakalant prolongs the

14   atrial refractory period much more markedly

15   than it does the ventricular refractory

16   period in man at a pacing rate of 100 beats

17   per minute, and a dose of four milligrams per

18   kilogram.

19   This clinical study shows that

20   vernakalant's ion channel blocking profile

21   produces relative, although not absolute,

22   atrial selective eletrophysiologic effects in

1   man.

2   Having discussed vernakalant's

3   mechanism of action referrable to its

4   potassium channel blocking, I would now like

5   to draw your attention to vernakalant's other

6   mode of action, namely, block of sodium

7   current.

8   As can be seen in this study

9   previously referred to, vernakalant produces

10   little effect on a measure of sodium current

11   block in these atrial tissues, and this was

12   the change in voltage over time for the

13   upstroke velocity in the atrial action

14   potentials.

15   A key feature of vernakalant's

16   mechanism of action in AF is its frequency

17   dependent block of sodium current. These are

18   concentration response relations for

19   vernakalant's block of human heart sodium

20   current under normal conditions, and under

21   the conditions of atrial fibrillation in the

22   atrium.

1   At therapeutic concentrations,

2   shown in the inset, vernakalant produced

3   little block of the sodium current at normal

4   heart rates. When the cells were rapidly

5   paced, vernakalant's potency increased

6   fivefold.

7   As further evidence of

8   vernakalant's potentiated sodium channel

9   block in atrial fibrillation, we studied

10   vernakalant's affects on atrial conduction

11   velocity in vivo.

12   Here vernakalant slowed atrial

13   conduction at fibrillatory rates in the dog

14   atria.

15   Shown on the Y axis is the

16   changing conduction time, and the increasing

17   pacing rates of simulation in the atria are

18   on the X axis.

19   Vernakalant, at four milligrams

20   per kilogram, produced little conduction

21   slowing at 200 beats per minute, with

22   progressive slowing seen as the pacing rate

1   increased to 400 beats per minute, which

2   mimics the activation times in AF.

3   This demonstrates that

4   vernakalant's frequency dependent sodium

5   channel block demonstrated in vitro readily

6   translates to conduction slowing in vivo.

7   Vernakalant rapidly and

8   effectively converts atrial fibrillation in a

9   dog model. Vernakalant's efficacy for

10   conversion of atrial fibrillation has been

11   confirmed in multiple nonclinical studies, as

12   well as clinical studies, which Dr. Kitt will

13   show.

14   And rapid conversion is one of the

15   clinical benefits of vernakalant.

16   I would now like to discuss the

17   safety implications of vernakalant's

18   mechanism of action. Since currently

19   available antiarrhythmic drugs such as

20   flecainide have been associated with pro-

21   arrhythmia under the conditions of ischemia,

22   we investigated vernakalant's effects in a

1   highly pro-fibrillatory model in pigs.

2   In this study, episodes of

3   ischemia, followed reperfusion, resulted in a

4   high incidence of ventrical fibrillation and

5   mortality in the control treated animals.

6   Flecainide resulted in a lethal VT

7   in all the pigs within five minutes of

8   ischemia. In contrast, vernakalant had a

9   lower incidence of ventricular arrhythmia and

10   mortality in this model.

11   And this suggests that vernakalant

12   does not have an increased risk of pro-

13   arrhythmia and mortality in this pig model.

14   Vernakalant did not show cardio-

15   depressant actions in conscious animals in an

16   ICH standard cardiovascular safety study.

17   Since there were, however, adverse events of

18   hypotension seen in our clinical trials, we

19   elected to study vernakalant in anaesthetized

20   dogs where we could increase the dose in

21   plasma concentrations higher than were

22   tolerated in conscious dogs.

1   As shown here, vernakalant did not

2   affect systolic nor diastolic blood pressures

3   at therapeutic plasma concentrations.

4   However, as we increased the dose,

5   which resulted in plasma concentrations

6   fivefold higher than the Cmax we saw in

7   patients, there were significant reductions

8   in systolic blood pressure.

9   In keeping with vernakalant's

10   atrial targeted actions, vernakalant has

11   minimal effects on the action potential

12   duration in rabbit Purkinje fibers. The

13   rabbit Purkinje fiber assay is an ICH

14   standard assay used to assess the potential

15   risk for torsades de pointes.

16   Drugs which prolong the Purkinje

17   fiber action potential duration have a risk

18   for prolonging QT intervals, and an increased

19   risk for torsades de pointes.

20   As shown here, dofetilide

21   produced concentration dependent increases in

22   the action potential duration, including

1   within its therapeutic range, and this is

2   consistent with its selective IKR blockade.

3   Vernakalant produced relatively

4   minor changes in the Purkinje fiber action

5   potential duration, which reached

6   significance at 10 to 30 micromolar.

7   And these more relatively minor

8   effects are consistent with vernakalant's

9   concomitant block of late sodium current.

10   And this suggests that vernakalant

11   may have a lower risk of pro-arrhythmia

12   compared to selective IKR blockers.

13   As further evidence of a reduced

14   potential for inducing torsades de pointes,

15   vernakalant suppressed dofetilide induced

16   early after depolarizations, in an in vitro

17   pro-arrhythmia model. Shown here, dofetilide

18   at a high concentration significantly

19   prolonged the action potential duration, and

20   elicited these instabilities of

21   repolarization, known as early-after

22   depolarizations.

1   These early-after depolarizations

2   are believed to trigger torsades de pointes.

3   In contrast, with the addition of

4   vernakalant, shown here, the early-after

5   depolarizations were abolished, and the

6   action potentials were normalized.

7   This again suggests that

8   vernakalant may have a lower pro-arrhythmic

9   risk than the specific IKR blocker

10   dofetalite.

11   In addition, vernakalant

12   suppressed torsades de pointes in an in vivo

13   model of torsades. Shown here in the control

14   conditions, infusions of methoxamine and

15   clofilium produced torsades de pointes in

16   seven of nine animals.

17   With the addition of vernakalant

18   infusion, there was a dose-dependent decrease

19   in the incidence and the duration of torsades

20   de pointes.

21   Vernakalant suppressed pro-

22   arrhythmia in this rabbit model of torsades

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1   de pointes, and this again suggests that

2   vernakalant may have less pro-arrhythmic risk

3   than drugs with more marked effects on

4   ventricular repolarization.

5   In summary, then, vernakalant is a

6   multi-ion channel blocker, with activity that

7   is potentiated in the atria during AF.

8   Vernakalant rapidly converts atrial

9   fibrillation, and appears to have a lower

10   pro-arrhythmic risk in animal models.

11   Vernakalant's safety and efficacy

12   are consistent with its unique ion channel

13   blocking properties.

14   Thank you. And Dr. Keirns will

15   now present vernakalant's toxicology and

16   pharmacokinetics.

17   TOXICOLOGY & CLINICAL PHARMACOLOGY

18   DR. KEIRNS: Thank you, Dr. Beatch,

19   Dr. Hiatt, and committee members. I'll

20   briefly describe the assessment of toxicology

21   and clinical pharmacology which we've carried

22   out for vernakalant.

1   Starting with the toxicology, we

2   conducted a customary program in rodents and

3   non-rodents, and I'll note that there is a

4   note at the bottom of the slide that shows

5   you the corresponding pages in your briefing

6   book.

7   In these studies, the dose

8   limiting toxicities were all transient and

9   spontaneously reversible. They were not

10   associated with any gross or microscopic

11   histological findings, and they were

12   consistent with the ion channel blockade that

13   Dr. Beatch just described.

14   The symptoms that were seen were

15   salivation, tremor, ataxia, and at the very

16   highest dose with repeat dosing, we saw

17   convulsions.

18   In terms of the therapeutic index

19   relative to the efficacious dose that Dr.

20   Beatch just described, these findings were

21   seen at a factor of 10 higher exposure.

22   The pharmacokinetics in metabolism

1   in dogs and humans have been assessed, and

2   showed rapid distribution, and a short

3   elimination half-life. In humans, the

4   metabolism of vernakalant is primarily by

5   cytochrome P450 2D6, and the systemic

6   exposure of parent compound at the maximum

7   concentration compared to the exposure in

8   dogs that I described on the slide before is

9   a factor of three.

10   Continuing to describe the

11   pharmacokinetics further, they are dose

12   proportional and linear. There is rapid

13   distribution with an alpha half-life of about

14   10 minutes, and a high volume of

15   distribution.

16   The terminal elimination half-life

17   is fairly short, three hours, but somewhat

18   longer, 5-1/2 hours in 2D6 poor metabolizers.

19   Vernakalant is not highly protein bound, and

20   the metabolic pathways have been well

21   characterized.

22   This slide illustrates the

1   pharmacokinetic profile with the phase III

2   clinical dosing that Dr. Kitt will describe,

3   and makes a couple of other points.

4   Just to orient you, Dr. Kitt will

5   describe two 10-minute infusions, one for the

6   first 10 minutes, and then an observation

7   period for 15 minutes, followed in those

8   patients who do not convert on the first

9   infusion, by another 10-minute infusion.

10   And the curves that are displayed

11   here are based on modeling of the phase III

12   clinical data, and we also looked

13   specifically at differences between normal

14   extensive metabolizers, and 2D6 poor

15   metabolizers.

16   You can see that, in the early

17   times, the concentrations are almost

18   identical, and then they diverge somewhat due

19   to the longer half-life in the poor

20   metabolizers.

21   But one of the more important

22   points is that there is a rapid drop in

1   concentrations at the end of each infusion,

2   which is actually driven by distribution, not

3   by the elimination.

4   We assessed a number of

5   demographic variables, as well as concomitant

6   medications, by using population

7   pharmacokinetics, and found that Cmax and

8   systemic exposure were not, over the first 90

9   minutes, were not significantly influenced by

10   age, sex, renal function, or 2D6 expression,

11   as I just showed you in the slide before.

12   In addition, we analyzed co-

13   administration of 2D6 inhibitors and beta

14   blockers, and did not see any difference in

15   the Cmax or early exposure of the compound in

16   the -- with these concomitant medications.

17   Finally, as Dr. Kitt will show

18   you, phase III studies indicated that there

19   were no safety implications with co-

20   administration of 2D6 inhibitors or

21   substrates.

22   I'd now like to turn the

1   presentation over to Dr. Kitt to describe

2   clinical efficacy and safety.

3   CLINICAL EFFICACY AND SAFETY

4   DR. KITT: Good morning, committee

5   members.

6   I am Therese Kitt, and it's my

7   pleasure to be able to present to you the

8   clinical data from our vernakalant clinical

9   trials.

10   Efficacy data will be presented

11   first, focusing on three studies: the two

12   primary registration studies, and a study

13   that we did in patients who developed atrial

14   fibrillation post cardiac surgery.

15   The efficacy presentation will be

16   followed then by the safety data

17   presentation.

18   There were nine clinical trials in

19   the vernakalant NDA as outlined on this

20   slide. There were two phase I clinical

21   studies, and electrophysiology study.

22   The CRAFT study was our phase II

1   dose ranging study.

2   The phase III studies were all

3   labeled ACT, which stands for atrial

4   arrhythmia conversion trial, or ACT.

5   The two registration trials are

6   ACT I and ACT III. These two studies are

7   considered the pooled primary population

8   during my efficacy discussion.

9   ACT II was a study in patients

10   post-cardiac surgery, and ACT IV was an open

11   labeled safety study.   Scene 2 was a study

12   done in patients with typical atrial flutter.

13   In this study, vernakalant was shown not to

14   be effective in converting atrial flutter to

15   sinus rhythm, and the efficacy data will not

16   be further discussed. However, the safety

17   data from these patients are included in our

18   safety analysis.

19   Eight hundred and twenty three

20   subjects were exposed to vernakalant, and

21   there were 773 patients exposed, and 335

22   patients received placebo.

 1   Once again, as Dr. Keirns had

 2   mentioned, I have source documents here, a

 3   source page and a table that you can find in

 4   your briefing document if you want further

 5   information on that particular slide.

 6   I will be discussing different

 7   patient numbers from different patient

 8   populations at different data sets. And this

 9   table lists the different efficacy and safety

10   populations.

11   The primary efficacy studies was

12   ACT I and ACT III, in which 575 patients with

13   atrial fibrillation received study drug, 236

14   patients received placebo, and 339 received

15   vernakalant.

16   Again, the term pooled primary

17   studies refers to the combined patients from

18   ACT I and ACT III with atrial fibrillation.

19   ACT III enrolled patients with

20   both atrial fibrillation and with flutter.

21   However, when the results of the Scene 2

22   study were known, the analysis plan was

1   changed to exclude patients with atrial

2   flutter. This was done before the database

3   was locked.

4   In the post-cardiac surgery study,

5   50 patients with atrial fibrillation received

6   placebo, and 100 patients received

7   vernakalant.

8   The Phase III database contains

9   737 patients who received vernakalant, and

10   the total number of patients who received

11   vernakalant in our phase II and III studies

12   was 773 patients.

13   I will now discuss the efficacy

14   data.

15   The phase II dose ranging study

16   enrolled patients with a duration of atrial

17   fibrillation of three hours to 72 hours.

18   This graph shows the cumulative efficacy

19   after one and two doses. There was no

20   difference between placebo and the low dose

21   vernakalant group.

22   Vernakalant was effective in the

1   higher dose group with 53 percent of the

2   patients converting to sinus rhythm, and the

3   median time to conversion in the patients who

4   responded to vernakalant was 14 minutes.

5   This study established the

6   minimally effective dose to be two milligrams

7   per kilogram. Based on these results, the

8   step dose design for phase three was three

9   milligrams per kilogram, and if no conversion

10   to sinus rhythm was seen, a second dose of

11   two milligrams per kilogram was administered.

12   The dosing regimen was reversed,

13   giving the three milligrams per kilogram

14   first, assuming more patients would convert,

15   following the higher initial dose.

16   This is the phase III design for

17   our pivotal studies. The phase III studies

18   were multi-center, randomized, double blind,

19   and placebo controlled, in patients with

20   atrial fibrillation with a duration of

21   greater than three hours, and less than or

22   equal to 45 days.

1   Patients were stratified based on

2   the duration of their atrial fibrillation.

3   Patients were allowed to have background use

4   of oral rate and rhythm control medications.

5   Patients were randomly assigned to

6   receive up to one of two infusions, the first

7   infusion of vernakalant of three milligrams

8   per kilogram given over 10 minutes, followed

9   by a 15-minute observation period, and if

10   they had not converted to sinus rhythm, the

11   second dose of two milligrams per kilogram

12   was administered.

13   In our studies, placebo was normal

14   saline.

15   Patients underwent continuous

16   halter monitoring, starting at screening, and

17   going up through 24 hours. They also were on

18   a telemetry, starting at randomization and up

19   to a minimum of two hours.

20   An atrial fibrillation symptom

21   checklist was done at screening, at baseline,

22   at 90 minutes, at 24 hours, seven days, and

1   also up to 30 days.

2   As noted on this slide, electrical

3   cardioversion and other treatments were

4   permitted after two hours. The patients were

5   seen for follow up visit on day seven, and

6   there was a phone call follow up on day 30.

7   These are the key inclusion and

8   exclusion criteria. Patients were eligible

9   for the studies if they had symptomatic

10   atrial fibrillation with a duration of

11   greater than three hours and less than 45

12   days, and they were receiving anticoagulants

13   therapy as per the guidelines.

14   As I had mentioned previously,

15   patients could be receiving oral

16   antiarrhythmic agents, but they could not

17   receive IV antiarrhythmics if they had been

18   given within the previous 24 hours.

19   Patients needed to be

20   hemodynamically -- patients who were

21   hemodynamically unstable, or who had an MI

22   acute coronary syndrome, or cardiac surgery

1   within the previous 30 days, were not

2   eligible for this study.

3   The primary endpoint was the

4   conversion of atrial fibrillation to sinus

5   rhythm within 90 minutes of study drug

6   initiation for a duration of one minute in

7   patients with an atrial fibrillation duration

8   of three hours to less than or equal to seven

9   days.

10   Secondary and exploratory

11   endpoints supported our primary endpoint, and

12   included the time to conversion to sinus

13   rhythm, conversion of atrial fibrillation to

14   sinus rhythm in patients who had an atrial

15   fibrillation duration of three hours to 45

16   days, a reduction in atrial fibrillation

17   symptoms, and maintenance of sinus rhythm

18   after conversion.

19   The phase III baseline

20   characteristics of patients are listed here,

21   and were balanced between the two treatment

22   groups. Patients in our studies had

1   histories of congestive heart failure,

2   ischemic heart disease, or hypertension,

3   which represents the real world population.

4   Efficacy is presented here. The

5   X-axis is the proportion of patients who

6   converted to sinus rhythm, and the Y-axis --

7   or the X axis is time. The little orange

8   bars are two infusions of vernakalant.

9   The gray dashed line is our

10   placebo group, and the green line is the

11   vernakalant group.

12   Efficacy was consistent in both of

13   our pivotal trials, with 51 percent of the

14   patients with recent onset atrial

15   fibrillation converting to sinus rhythm,

16   compared with 4 percent in the placebo group.

17   In patients who converted to sinus

18   rhythm in our responders, the time to

19   conversion was rapid. Median time to

20   conversion was 11 minutes in the ACT I study,

21   and the median time to conversion in

22   responders in ACT III was eight minutes.

1   The analysis I have presented here

2   is a modified intent to treat analysis, or an

3   as-treated analysis, which was discussed with

4   the FDA and agreed to prior to breaking the

5   study blind.

6   Patients who were randomized, but

7   did not receive the study drug, were excluded

8   from this analysis.

9   The intent to treat analysis,

10   imputing patients who spontaneously converted

11   to sinus rhythm as successes, and others were

12   imputed as failures, and in doing this

13   analysis, there was no difference in terms of

14   the modified intent to treat analysis, or the

15   intent to treat analysis.

16   These are the conversion rates for

17   the three subgroups of patients stratified by

18   the duration of atrial fibrillation, and to

19   the short duration atrial fibrillation group

20   which was our primary endpoint, the overall

21   population, and the long duration group.

22   As expected, patients with a

1   shorter duration of atrial fibrillation had a

2   higher rate of conversion.

3   One of the questions you have been

4   asked to address is the relationship between

5   time in atrial fibrillation, and conversion

6   after vernakalant.

7   In the ACT I and the ACT IV study,

8   which was the open label study, atrial

9   fibrillation duration was collected in a way

10   that allowed us to look at the relationship

11   between atrial fibrillation duration and

12   conversion.

13   The following graph shows the

14   observed, which are the bars, and the

15   modeled, which are the lines here with the 95

16   percent time for these intervals shown by the

17   dashed lines. The probably of conversion by

18   atrial fibrillation duration broken down by

19   days, which is given here on the X-axis.

20   As you can see by the model, which

21   is a generalized additive model, as atrial

22   fibrillation duration increases, the

1   probability of conversion decreases similar

2   to other conversion modalities.

3   There is a greater uncertainty

4   around the conversion rate for patients with

5   longer duration of atrial fibrillation as

6   indicated by the width of the 95 percent

7   confidence intervals in the longer durations.

8   This is, in part, an artifact of

9   the study design, stratified and randomized

10   by AF duration of our three hour to seven

11   day, and eight to 45 days. One can see that,

12   based on the 95 percent confidence interval,

13   patients with atrial fibrillation duration of

14   less than 48 hours have conversion rates that

15   range from 45 to 70 percent. And those with

16   atrial fibrillation duration of three hours

17   to seven days -- or excuse me, from three to

18   seven days, have conversion rates that range

19   from 15 to 40 percent.

20   The placebo subtractive efficacy

21   data, based on age, gender, and use of rate

22   or rhythm control medications is presented

1   here. Placebo is better if to this side of

2   zero, and vernakalant is better if this -- if

3   to this side of zero.

4   This point up here is our overall

5   treatment effect, and this is the 95 percent

6   confidence intervals.

7   Efficacy was not affected by age,

8   gender, or use of rate or rhythm control

9   medications. This slide is similar to the

10   previous slide. Again, the top category is

11   the overall treatment effect. There appears

12   to be a trend towards reduced efficacy in

13   patients with a history of congestive heart

14   failure based on a limited database, but no

15   effect of ischemic heart disease or

16   hypertension on efficacy.

17   A pre-specified endpoint in our

18   pivotal studies was relief of atrial

19   fibrillation symptoms, which was collected by

20   a symptom checklist. Vernakalant provided

21   relief of atrial fibrillation symptoms. At

22   minute 90, about 50 percent of our patients

1   who received vernakalant were asymptomatic,

2   compared with about 26 percent of the placebo

3   group.

4   And I know during the discussion

5   earlier this morning, the question had come

6   up about what was the percentage of patients

7   who were asymptomatic at hour 24, and there

8   was very little difference between the

9   placebo group and the vernakalant group, with

10   about 70 percent of the patients being

11   asymptomatic at hour 24. And when one looks

12   at the number of patients that were

13   asymptomatic at day seven, once again, there

14   was little difference between placebo and

15   vernakalant, with about 60 percent of the

16   patients being asymptomatic.

17   Symptom reduction was mediated by

18   the conversion to sinus rhythm as shown on

19   this slide. At minute 90, about 69 percent

20   of the patients who received vernakalant and

21   converted to sinus rhythm were symptom free.

22   Patients who received vernakalant, but

 1   remained in atrial fibrillation, about 29

 2   percent of those patients were symptom free.

 3   A life table estimate was used to

 4   determine the maintenance of sinus rhythm

 5   following the conversion to sinus rhythm. At

 6   24 hours, 97 percent of the patients who

 7   received vernakalant and converted to sinus

 8   rhythm remained in sinus rhythm, and patients

 9   who received placebo and spontaneously

10   converted, at 24 hours, 83 percent of those

11   placebo patients remained in sinus rhythm.

12   I have just covered the primary

13   efficacy studies in patients who presented

14   with atrial fibrillation, and will now go

15   over the study in patients who developed

16   atrial fibrillation post-cardiac surgery.

17   The baseline characteristics of

18   patients in this analysis did not differ, and

19   was balanced between the two treatment

20   groups.

21   This is the efficacy in the post

22   surgical patients. Again, the Y-axis is the

1   proportion of patients who had converted to

2   sinus rhythm, and this is the time from first

3   dose to conversion, with our two infusion

4   bars.

5   Again, placebo is shown as the

6   gray line, and patients who receive

7   vernakalant is shown as the green line.

8   The conversion rate and the post-

9   cardiac surgery atrial fibrillation study was

10   47 percent in the vernakalant group, compared

11   with 14 percent in the placebo group.

12   Conversion was rapid, with a median time to

13   conversion of 12 minutes in the responders.

14   Efficacy was robust and consistent

15   across all of our studies. Included in this

16   slide is the ACT IV study, which I had

17   mentioned was an open label safety study.

18   However, we did collect efficacy in that

19   study, and in the ACT IV study in patients

20   who had atrial fibrillation of three hours to

21   seven days in duration, 51 percent of those

22   patients converted to sinus rhythm.

1   So once again, efficacy was

2   consistent across all of our studies, ranging

3   from 47 percent in the post-surgical

4   population, to 53 percent in our phase II

5   study.

6   To summarize efficacy, vernakalant

7   was effective in converting atrial

8   fibrillation to sinus rhythm in patients who

9   spontaneously developed atrial fibrillation,

10   and in those post-cardiac surgery patients.

11   In the patients who converted, the

12   median time to conversion was 10 minutes.

13   Efficacy was not affected by age, gender,

14   rate, or rhythm control medications, or

15   concomitant illnesses such as congestive

16   heart failure or ischemic heart disease.

17   There was relief of atrial

18   fibrillation symptoms, and sinus rhythm was

19   maintained out to 24 hours.

20   The next series of slides will

21   cover safety. I will first discuss adverse

22   events, serious adverse events, including

1   deaths. Events of interest will then be

2   presented.

3   These events were identified

4   during the review of the safety data, and

5   based on other antiarrhythmic agents.

6   Events of interest include

7   ventricular arrhythmias, including effects on

8   the QT and torsades de pointes, bradycardia,

9   and hypotension.

10   Safety data collection was

11   comprehensive in our clinical studies, and

12   included adverse events, 12 with ECG and

13   vital signs which were collected every five

14   minutes from the start of the infusion up

15   through minute 50, and then as outlined here.

16   In addition, a 24 hour Holter was

17   recorded.

18   As you can see, the monitoring in

19   the first 24 hours was extensive and capable

20   of capturing asymptomatic and infrequent

21   events.

22   The safety database contains all

1   patients, and there were 773 patients who

2   received vernakalant, compared with 335 in

3   the placebo group.

4   Patients had concomitant

5   illnesses, such as congestive heart failure,

6   ischemic heart disease, and hypotension,

7   which are typically seen in patients seeking

8   treatment for atrial fibrillation.

9   The use of rate and rhythm control

10   medications during the seven days prior to

11   study drug administration did not differ

12   between placebo or the vernakalant groups.

13   Adverse events which occurred

14   within the first 24 hours are of particular

15   interest because of the short half-life of

16   vernakalant. This table summarizes the

17   adverse events occurring in more than 5

18   percent, and at a higher rate than in the

19   placebo group.

20   Table 16 in your briefing document

21   contains a more complete list of the adverse

22   events. The most common adverse events seen

1   in the vernakalant group were dysgeusia,

2   which was typically described as a metallic

3   taste, sneezing, parathesias, nausea, and

4   hypotension.

5   The median time to onset in

6   patients receiving vernakalant was seven to

7   35 minutes, and the median duration in the

8   patients who received vernakalant was eight

9   to 20 minutes.

10   Hypotension is the most clinically

11   important adverse event that is on this list,

12   and will be discussed in detail later.

13   The incidence of any serious

14   adverse event occurring within the first 24

15   hours was similar for placebo and

16   vernakalant, with 3.9 percent of the patients

17   who received placebo reporting any serious

18   adverse event, compared with 4.1 percent of

19   the vernakalant group.

20   Serious adverse events of complete

21   heart block, sinus arrest, sinus bradycardia

22   or bradycardia, ventricular fibrillation and

1   hypotension were the most common serious

2   adverse events occurring in the vernakalant

3   group in the first 24 hours.

4   The incidence of stroke is not

5   shown on this slide, since the incidence was

6   low in our clinical studies. But to help you

7   to address question number nine, which the

8   agency has asked you to address, the

9   incidence of stroke within the 30 days

10   following study drug administration in the

11   placebo group was 1.2 percent, and in the

12   vernakalant group, the incidence of stroke

13   was 0.4 percent.

14   There were five deaths in the

15   vernakalant studies. All deaths occurred in

16   patients receiving vernakalant. There was

17   one death within the first 24 hours that was

18   considered by the investigator to be related

19   to vernakalant, and that is this top patient

20   here.

21   The other four deaths were not

22   considered by the investigator to be related

1   to vernakalant, and one occurred on day two,

2   and the others occurred more than seven days

3   after receiving vernakalant.

4   I will now discuss the one related

5   death.

6   The patient was a 64-year-old man

7   with critical aortic stenosis, an injection

8   fraction of 40 percent, and New York Heart

9   Association Class II congestive heart

10   failure.

11   Serious protocol violations

12   occurred in this patient, including dosing a

13   patient who was hemodynamically unstable

14   during an acute myocardial infarction. He

15   became hypotensive following the

16   administration of metoprolol, and was give in

17   saline to restore his blood pressure.

18   The patient received two doses of

19   vernakalant, and became hypotensive after

20   both doses. Following the second infusion,

21   he developed ventricular fibrillation, and

22   resuscitation attempts were not successful.

1   Autopsy showed him to have aortic

2   stenosis and myocardial hypertrophy.

3   There were four unrelated deaths.

4   All these deaths occurred more than 24 hours

5   after receiving vernakalant. A 68-year-old

6   woman died during a gastroscopy procedure.

7   At autopsy, she was found to have a ruptured

8   dissecting aortic aneurysm.

9   A 67-year-old man with lung

10   cancer, pneumonia, suffered a respiratory

11   arrest, and was placed on life support. He

12   died following the family's decision to

13   remove life support eight days after

14   receiving vernakalant.

15   A 70-year-old woman with breast

16   cancer died from a gastrointestinal

17   hemorrhage 24 days after receiving

18   vernakalant, and a 90-year-old woman died of

19   congestive heart failure 26 days after

20   receiving vernakalant.

21   None of these deaths were

22   considered by the investigator to be related

1   to the administration of vernakalant.   None

2   had a common pharmacological cause which may

3   have contributed to their deaths.

4   Events of interest will now be

5   presented. Based on a safety profile of

6   other antiarrhythmic agents, and in reviewing

7   the safety data for vernakalant, three events

8   of interest were identified: ventricular

9   arrhythmia, bradycardia, and hypotension.

10   Incidence tables were created

11   using the phase III studies for these three

12   events using multiple data sources, such as

13   adverse events, 12 Lead ECGs, the 24 hour

14   Holter recordings, and vital signs.

15   There were no pre-specified

16   definitions for adverse events such as

17   bradycardia or hypotension, and so these

18   events were judged and classified by the

19   investigator.

20   A conservative definition of

21   ventricular tachycardia was used, and was

22   defined as at least three consecutive beats,

1   at a rate of 100 beats or more per minute.

2   Analyses were conducted for all

3   post dose, and for the two to 24 hour time

4   period. The zero to 24 hour time period is

5   the most informative, because it was the time

6   of intensive data collection, and because

7   most of vernakalant is cleared from the blood

8   within this period.

9   The zero to 24 hour time period

10   was divided into the zero to two, and two to

11   24 hour periods, since after two hours, other

12   treatments for atrial fibrillation were

13   allowed.

14   This table summarizes the

15   ventricular events during the zero to two and

16   two to 24 hour period. The incidence of

17   ventricular tachycardia was approximately

18   three percent in both the placebo and the

19   vernakalant group.

20   In the two to 24 hour time period,

21   the incidence of ventricular tachycardia was

22   8-1/2 to 12 percent, and essentially no

1   difference between placebo or the vernakalant

2   group.

3   There was one case of torsades de

4   pointes, which occurred in the two to 24 hour

5   time period, which is shown here.

6   There are two cases of ventricular

7   fibrillation during the zero to two hour time

8   period. One does not show up on this table,

9   since this table summarizes the phase III

10   data, and the one case occurred in the phase

11   II study.

12   The case that is shown here on

13   this slide is a case that resulted in the

14   fatal outcome which I had just discussed.

15   The second case of ventricular

16   fibrillation will now be discussed.

17   A 24-year-old female with atrial

18   fibrillation presented to the emergency room

19   with a rapid ventricular response. About two

20   hours following the initiation of vernakalant

21   infusion, electrical cardioversion was

22   attempted.

1   A non-synchronized cardioversion

2   shock was delivered, with ensuring

3   ventricular fibrillation. Immediate

4   defibrillation was successful. She was

5   discharged the next day.

6   The investigator determined that

7   the ventricular fibrillation was due to the

8   delivery of a non-synchronized electrical

9   shock, and not drug related.

10   This is a case of non-synchronized

11   electrical cardioversion due to a technical

12   malfunction, which is known to occur.

13   There are a total of four reports

14   of torsades de pointes in the 30-day follow

15   up period: one in a patient receiving

16   placebo, and three in patients receiving

17   vernakalant. Of the three patients receiving

18   vernakalant, one occurred, which is the top

19   case here, within the first 24 hours, and the

20   other two occurred more than 24 hours after

21   receiving vernakalant.

22   This is the ECG tracing of the

1   torsades which occurred within the first 24

2   hours after receiving vernakalant. A 51-

3   year-old man with atrial flutter did not

4   convert after receiving vernakalant.

5   Ibutilide was given two hours and 20 minutes

6   after the initiation of the vernakalant

7   infusion. He developed an asymptomatic,

8   nine-beat run of torsades, immediately

9   following the infusion of ibutilide.

10   The torsades is captured on the

11   Holter recording.

12   An association with vernakalant

13   cannot be excluded in this case, since it

14   occurred two hours and 20 minutes after the

15   initiation of the infusion of the

16   vernakalant.

17   The incidence of torsades de

18   pointes in our safety database, then, is one

19   out of 773 patients, or 0.13 percent.

20   Here are the other cases of the

21   torsades. A 90-year-old woman developed

22   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

1   gray bar shows when other therapies are

2   permitted.

3   QTCF was selected over QTCB, since

4   QTcF is not greatly affected by heart rate.

5   Baseline QTCF was similar for placebo and

6   vernakalant, and as you can see, the QTC

7   interval increases with each of the

8   infusions, and it starts returning to

9   baseline once the infusion is discontinued.

10   From 90 minutes out to follow up,

11   there is very little change in the QTCF

12   interval.

13   Shifts from baseline in the QTCF

14   were evaluated for patients in the phase III

15   studies. This slide summarizes the QTCF of

16   greater than 500 milliseconds, and greater

17   than 550 milliseconds.

18   The cumulative incidence of any

19   patient with a QTCF of greater than 550

20   milliseconds during the zero to two hour

21   post-dose period was 0.6 percent for

22   vernakalant, and 0.4 percent for placebo.

1   After minute 30, there was no

2   difference between placebo and the

3   vernakalant group. The incidence of any

4   patient with a QTCF of greater than 500

5   milliseconds during the zero to two hour time

6   period was 7.2 percent for vernakalant, and

7   2.8 percent for placebo. There was no

8   difference between placebo and vernakalant

9   after 90 minutes.

10   This graph shows the QTCF change

11   from baseline for the 2D6 poor and extensive

12   metabolizers. This shows change from baseline

13   for the QTCF. This shows time.

14   The extensive metabolizers are

15   shown by the yellow line here, the little

16   squares, and poor metabolizers are shown by

17   the green line with the triangles.

18   Although the number of poor

19   metabolizers is small, there appears to be no

20   difference between the poor and extensive

21   metabolizers in change from baseline in QTCF.

22   The incidence of bradycardia was

1   summarized using adverse events, 12 Lead ECG

2   data, and Holter data.

3   In the zero to two hour time

4   period, the Holter data showed no difference

5   between placebo or the vernakalant group.

6   Looking at adverse events in the

7   12 Lead ECG, there appears to be a higher

8   incidence of bradycardia during the zero to

9   two hour time period. The reverse is seen in

10   the two to 24 hour time period when other

11   therapies are allowed. You can see there is

12   a higher incidence of bradycardia in the

13   placebo group when compared to the

14   vernakalant group.

15   The higher incidence of

16   bradycardia is due to patients converting to

17   sinus rhythm following the administration of

18   vernakalant.

19   This slide shows the heart rate by

20   responder status. This is the heart rate on

21   the Y-axis, and time again is shown here on

22   the X-axis.

1   Patients who received vernakalant

2   and converted to sinus rhythm are shown by

3   the solid green line. Patients who received

4   vernakalant but remained in atrial

5   fibrillation are shown by the dashed green

6   line, and placebo is shown by the gray line.

7   Patients who converted to sinus

8   rhythm with vernakalant had a slowing of

9   their heart rates. And when other therapies

10   are allowed, as shown out here, you can see

11   their heart rates start to become similar.

12   Of particular interest are the

13   patients who had a serious adverse event, or

14   bradycardia during the first 24 hours post

15   infusion, or had study drug discontinued due

16   to bradycardia. Details of these cases can

17   be found in table 21 in your briefing

18   document.

19   There were 15 patients who met

20   this criteria: 13 in the vernakalant group,

21   for an incidence of 1.7 percent, and two

22   patients in the placebo group for an

1   incidence of 0.6 percent.

2   The onset of bradycardia occurred

3   either during one of the two infusions, or

4   within 10 minutes of the end of the infusion.

5   The duration was from less than a minute to

6   four days.

7   The bradycardia responded to

8   discontinuation of the infusion, or atropine,

9   and in one patient who was post-operative and

10   still had their epicardial wires in place,

11   the bradycardia was treated by pacing.

12   There were two patients in the

13   placebo group who had an event of

14   bradycardia. One occurred after electrical

15   cardioversion, and the second occurred 20

16   hours after received placebo.

17   The incidence of hypotension was

18   summarized using adverse events and blood

19   pressure. This slide presents the adverse

20   event and systolic blood pressure less than

21   90 millimeters of mercury data.

22   Further details are found in Table

1   22 in your briefing document.

2   The incidence of hypotension

3   reported as an adverse event, or systolic

4   blood pressure less than 90 millimeters of

5   mercury, was higher in the vernakalant group

6   compared to the placebo group in the zero to

7   two hour time period.

8   And once again as we saw for

9   bradycardia, the reverse is seen in the two

10   to 24 hour period.

11   Of particular interest again are

12   patients who had a serious adverse event of

13   hypotension during the first 24 hours, or who

14   had study drug discontinued due to

15   hypotension, and there were 12 patients who

16   met these criteria. There were two in the

17   placebo group for an incidence of 0.6

18   percent, and 10, or 1.3 percent, in the

19   vernakalant group.

20   Table 23 in your briefing document

21   provides detailed information on these

22   patients.

1   The onset of hypotension occurred

2   either during the two infusions, or within 15

3   minutes of the end of the infusion.

4   In one patient, the onset occurred

5   about seven hours after vernakalant, and was

6   associated with the diagnosis of

7   cholecystitis, and following the

8   administration of verapamil. The duration of

9   the hypotension was from two minutes to two

10   hours and 16 minutes.

11   The hypotension responded to

12   placing the patient in a Trendelenburg

13   position, stopping the infusion, and giving

14   saline if necessary.

15   One patient was treated with

16   norepinephrine, and one patient was treated

17   with phenylephrine.

18   There were two placebo patients

19   who developed hypotension. One event

20   occurred after electrical cardioversion, and

21   one event occurred five hours after receiving

22   placebo.

1   There are a total of 164 patients

2   in our phase III safety database with a

3   history of congestive heart failure. 110

4   patients received placebo, and 54 received --

5   excuse me, 110 patients received vernakalant,

6   and 54 received placebo.

7   During the zero to 24 hour time

8   period, a trend towards an increased

9   incidence of hypotension was observed in

10   patients receiving vernakalant. There was no

11   difference in the incidence of bradycardia or

12   ventricular arrhythmia.

13   The safety database in patients

14   with a history of congestive heart failure is

15   limited. Vernakalant should be administered

16   with caution in patients who have a history

17   of congestive heart failure, and further

18   studies are needed.

19   Electrical cardioversion was

20   allowed two hours after receiving study drug.

21   There was no difference in the vernakalant

22   group compared with placebo in the percentage

1   of successful cardioversions, the median

2   number of shocks, or the median joules.

3   To summarize the safety of

4   vernakalant, there was one vernakalant-

5   related death in a patient with critical

6   aortic stenosis, and an acute MI who

7   developed hypotension and ventricular

8   fibrillation following the administration of

9   metoprolol and vernakalant.

10   Transient increases were seen in

11   the QRS and QT intervals.

12   The incidence of torsades was 0.13

13   percent in the first 24 hours after

14   administration of vernakalant, and occurred

15   immediately following an infusion of

16   ibutilide.

17   Clinically important bradycardia,

18   defined as a serious adverse event within the

19   first 24 hours, or patients who required

20   discontinuation of study drug due to

21   bradycardia, occurred in 1.7 percent of the

22   vernakalant group, and 0.6 percent of the

1   placebo group, and was associated with

2   conversion to sinus rhythm.

3   Clinically important hypotension,

4   again defined as a serious adverse event

5   within the first 24 hours, or hypotension

6   requiring discontinuation of study drug,

7   occurred in 1.3 percent of the vernakalant

8   group compared with 0.6 percent of the

9   placebo group.

10   The hypotension was

11   periinfusional, transient, and responded to

12   saline. Two patients were treated with

13   pressors.

14   I would like to conclude my

15   presentation with a discussion of risk

16   management and post-marketing studies,

17   assuming that we would get approval, of

18   course.

19   We see four components to risk

20   management. The prescribing information,

21   health care provider education, pharmaco-

22   vigilance, and post-marketing studies.

1   The FDA approved label will be the

2   primary tool in risk management. The package

3   insert will identify the patient population

4   for which vernakalant should be used. This

5   includes patients with symptomatic, recent

6   onset atrial fibrillation, and who are

7   hemodynamically stable.

8   Patients with an acute MI, acute

9   coronary syndrome, symptomatic, or

10   decompensated congestive heart failure should

11   not receive vernakalant. And vernakalant

12   should be used with caution in patients who

13   have a history of congestive heart failure.

14   Vernakalant should be administered

15   in a monitored setting with a physician in

16   attendance during the infusion. Vital sign

17   measurements, and continuous cardiac rhythm

18   monitoring should be conducted for a minimum

19   of 90 minutes after the end of the infusion,

20   or until the ECG parameters have stabilized,

21   and the patient is clinically stable.

22   If hypotension, bradycardia, or

1   clinically significant changes are seen in

2   the ECG, vernakalant infusion should be

3   immediately discontinued, the second dose

4   should not be given, and the patient should

5   be treated symptomatically.

6   The education program will be

7   comprehensive and focused on a select target

8   audience. The prescribing information will

9   be the basis for our educational activities.

10   Routine pharmaco-vigilance

11   practices will be employed, including adverse

12   event reporting, with emphasis on ventricular

13   arrhythmia and deaths, reviewing the

14   literature for adverse event reports, data

15   mining, and the use of signal detection

16   programming.

17   Additional studies are ongoing or

18   planned. These include a study on

19   ventricular defibrillation threshold, and the

20   effect of vernakalant on key glycoprotein

21   transporters.

22   PK studies in hepatically or

1   renally impaired patients are ongoing.

2   A safety and efficacy study will

3   be initiated in the near future in Europe.

4   We are also planning a post

5   marketing observational study, which is

6   discussed on the next slide.

7   Safety has been well characterized

8   in the development program, and we recognize

9   if vernakalant is approved, the incidence of

10   low frequency adverse events should be

11   addressed in the real world setting.

12   Therefore, we propose a post

13   marketing study to assess adverse events,

14   focusing on torsades de pointes, ventricular

15   arrhythmias, bradycardia, hypotension, and

16   deaths.

17   Design options for this study may

18   include a registry and/or mining of managed

19   health care databases.

20   The details of these studies will

21   be worked out with the FDA, and experts in

22   the field.

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1   Based on the observed event rates,

2   we believe a sample size of approximately

3   2,000 patients will provide additional

4   information on the safety profile of

5   vernakalant in the treatment of atrial

6   fibrillation.

7   I thank you for your attention,

8   and I now turn the podium over to Dr. Jeremy

9   Ruskin, who will now discuss the risks and

10   benefits of vernakalant.

11   RISK/BENEFIT SUMMARY

12   DR. RUSKIN: Thank you, Dr. Kitt.

13   Dr. Hiatt, committee members, FDA

14   members, guests, I appreciate the opportunity

15   to offer some comments on the benefits and

16   risks of vernakalant injection.

17   Just to get at a point that Dr.

18   Harrington raised earlier, this is an attempt

19   to map the patients in the vernakalant trials

20   in relation to the AFFIRM study, which has

21   been discussed this morning, and also a large

22   European survey of patients with atrial

1   fibrillation. And there are some demographics

2   and relevant medical history presented here

3   for each of the populations.

4   You can see that there is an age

5   difference, not a huge one, but an age

6   difference between AFFIRM and the vernakalant

7   studies, based on the fact that, as we heard

8   this morning, the AFFIRM trial entered

9   patients age 65 or older, largely directed at

10   an older population, with a small subset who

11   had major risk factors that allowed them to

12   enter at a younger age.

13   The other difference is that there

14   is less congestive heart failure in the

15   vernakalant studies than AFFIRM. But in

16   terms of valvular disease, coronary heart

17   disease and hypertension, the trials or the

18   populations are essentially

19   indistinguishable.

20   And I think that this indicates

21   that the trials were done in a clinically

22   relevant population, not solely restricted to

1   young patients without structural heart

2   disease.

3   The major risks of vernakalant are

4   listed here, and you have heard about these

5   in detail from Dr. Kitt, and they include

6   torsades, hypotension and bradycardia, and

7   what are listed here are hypotension and

8   bradycardia that were reported either as

9   SAEs, or required drug discontinuation.

10   The point estimates are listed

11   here, and in order to model a worst case

12   scenario, the upper bound of the 95 percent

13   confidence limits are listed here. And you

14   can see that, for torsades, the point

15   estimate is 0.13 percent, the upper 95

16   percent confidence bound is 0.6 percent.

17   For serious hypotension, the point

18   estimate is 1.3 percent, with an upper 95

19   percent confidence bound of 2.2 percent, and

20   for bradycardia, the point estimate is 1.7,

21   with an upper confidence bound of 2.7

22   percent.

1   The QT prolongation, as you've

2   heard from Dr. Kitt, is moderate, and

3   transient. There was one case of torsades de

4   pointes which occurred during the first 24

5   hours after administration of vernakalant,

6   and immediately following an infusion of

7   ibutilide, and I'll offer an additional

8   comment on that towards the end.

9   The hypotension associated with

10   the drug is peri-infusional and generally

11   transient, and in almost all cases responded

12   to conservative measures.

13   The bradycardia, as you also

14   heard, is largely associated with conversion

15   of atrial fibrillation to sinus rhythm.

16   A couple of words about congestive

17   heart failure, another area of concern for

18   two reasons. One, the experience is

19   relatively limited, and two, there appears to

20   be somewhat lower efficacy, and perhaps more

21   in the way of hypotension.

22   And what's listed here are

1   efficacy and hypotension AEs as a function of

2   placebo patients with a history of failure,

3   vernakalant patients with a history of

4   congestive failure, and vernakalant patients

5   with no history of heart failure.

6   And you can see the lower efficacy

7   rate, small numbers, but at least a

8   suggestion of a lower efficacy rate, and

9   likely more hypotension in vernakalant

10   treated patients with a history of heart

11   failure compared to those without.

12   The next two slides summarize the

13   benefits of vernakalant injection, and as you

14   also heard from Dr. Kitt, the drug

15   effectively converts atrial fibrillation to

16   sinus rhythm in about 50 percent of patients.

17   This effect is highly consistent

18   across studies. The onset of action of the

19   drug is rapid, with a median time to

20   conversion of approximately 10 minutes, and

21   conversion from atrial fib to sinus rhythm by

22   treatment strategy, that is, vernakalant

1   versus placebo, results in a highly

2   significant reduction in symptoms.

3   This symptom reduction is mediated

4   by conversion of atrial fibrillation to sinus

5   rhythm.

6   In addition, the effect of the

7   drug is durable, with 97 percent of

8   converters remaining in sinus rhythm at 24

9   hours. Vernakalant can be administered with

10   background rate or rhythm control

11   medications, which were present in 72 percent

12   and 20 percent of patients, respectively.

13   Electrical cardioversion remains

14   an option, because it is as effective in

15   vernakalant non-responders as it is in

16   placebo patients. And the drug is safe and

17   effective in patients with common

18   comorbidities, including hypertension, which

19   was present in 52 percent of patients, and

20   ischemic heart disease, which was present in

21   24 percent of patients.

22   This slide provides a profile of

1   all serious ventricular arrhythmias observed

2   during treatment with vernakalant during the

3   first 24 hours.

4   You have heard that there were two

5   cases of ventricular fibrillation, one

6   clearly associated with drug administration

7   involving a major protocol violation in a

8   patient with critical aortic stenosis, and

9   likely global ischemia.

10   The second case involved the

11   induction of ventricular fibrillation by a

12   non-synchronized DC shock in a young female

13   patient who had received vernakalant a few

14   hours prior.

15   In that patient, the ECG intervals

16   showed no evidence of QT or QRS widening

17   prior to the event, and a 12 Lead ECG

18   immediately after conversion showed normal

19   QRS and QT intervals, again suggesting that

20   this was not a pharmacologic pro-arrhythmic

21   event.

22   The one case of torsades de

1   pointes which was reported was an

2   asymptomatic, 9-beat run of polymorphic

3   ventricular tachycardia that occurred

4   immediately after administration of ibutilide

5   in a patient who had received two doses of

6   vernakalant about two hours earlier.

7   While the temporal association

8   with ibutilide is compelling in this case, a

9   possible contribution of vernakalant to the

10   occurrence of torsades cannot be excluded.

11   All the remaining arrhythmias were

12   non-sustained ventricular tachycardias, both

13   monomorphic and polymorphic, and as you can

14   see, these occurred with a frequency that was

15   slightly lower, but statistically

16   indistinguishable on vernakalant compared to

17   placebo.

18   In summary, vernakalant is

19   effective for the rapid conversion of atrial

20   fibrillation to sinus rhythm, with an

21   accompanying reduction in atrial fibrillation

22   associated symptoms.

1   Clearly, more experience is needed

2   in congestive heart failure, and the drug is

3   associated with risks, predominantly

4   hypotension, bradycardia, and a very low pro-

5   arrhythmic risk.

6   For me as a clinician, these risks

7   are favorably balanced by the benefits of the

8   drug, and are manageable.

9   And for that reason, I believe

10   that vernakalant injection provides an

11   important treatment alternative for patients

12   with acute symptomatic atrial fibrillation.

13   Thank you.

14   CHAIR HIATT: Thank you all very

15   much.

16   I think given the time of the

17   morning we should take a break, and then

18   reconvene and pose our questions to the

19   sponsor and their presentations.

20   So maybe 15 minutes.

21   (Whereupon at 10:57 a.m.

22   the proceeding in the

 1   above-entitled matter

 2   went off the record to

 3   return on the record at

 4   11:20 a.m.)

 5   QUESTIONS/DISCUSSION FROM THE COMMITTEE

 6   CHAIR HIATT: We're slightly off

 7   schedule, but I think we can make that up

 8   fairly easily. No one is scheduled for the

 9   public commentary part of this.

10   So I think the morning session has

11   been quite helpful. And we did really begin

12   with a general discussion as well. So now is

13   the time for the Committee specifically to

14   address any questions to the sponsor or

15   perhaps Dr. Granger about any of the things

16   we have seen so far this morning.

17   As everyone is getting set up, I

18   would like to lead off with a couple of

19   things. I have some specific questions. The

20   one that kind struck me initially was that I

21   think 20 percent of the patients that came

22   into these trials were asymptomatic. And, as

1   we heard today, one of the sort of compelling

2   reasons to convert people is because they

3   have sort of drive you in that direction. So

4   I would like to know why that occurred.

5   I think the thing that I have a

6   bigger issue with is sort of the absence of

7   data that I think the sponsor must have, some

8   of which we heard about just a minute ago

9   about the symptomatic status of patients at

10   24 hours.

11   I have in my mind a table that has

12   these three windows: zero to 2, 2 to 24, and

13   24 hours to 7 days. And then I have a list

14   of variables split by drug and placebo. You

15   know, those converted to atrial fibrillation,

16   Cardioversion, those who took other

17   antiarrhythmic drugs, symptom score, adverse

18   events, deaths, and other kinds of serious

19   safety concerns.

20   And I realized that things changed

21   after two hours, that patients were then

22   allowed to take sort of standard therapies,

1   which included both perhaps chemical and, as

2   we saw in the briefing document, electrical

3   Cardioversion, which occurred in 37 percent

4   of patients randomized to drug and 58 percent

5   of patients randomized to placebo. So

6   clearly more patients on placebo had to

7   undergo electrical Cardioversion.

8   But in terms of getting at the

9   overall risk-benefit of this development

10   program, I think at least understanding those

11   endpoints at 24 hours is extremely important

12   and not just narrowing our window to the

13   two-hour time frame.

14   We heard a little bit, again, that

15   symptomatic differences were not seen at 24

16   hours or later. And if you look at the heart

17   rate status by responders' group, slide 74,

18   clearly when you evoke other therapies, there

19   really doesn't appear to be any difference

20   between drug responders and drug

21   nonresponders, or placebo, at least in terms

22   of heart rate. And if heart rate is a

1   reflection of symptoms, there was no

2   difference in symptoms either.

3   So is there some way we could fill

4   out a table that kind of completed that

5   missing data? We have complete data to two

6   hours. I think a lot of things were not

7   presented at 24 hours. We have adverse

8   events that we don't have the symptoms for.

9   And so I guess I would like to see that.

10   DR. MASSIE: Can I just add one

11   request, which I think is embedded in yours,

12   which is of those that didn't get

13   electrically converted, what the spontaneous

14   conversion rate is at that 24-hour time since

15   we have the Holters? Because I have to plead

16   stupidity. In some of my earlier comments, I

17   really read this booklet as you had to be 72

18   hours, 3 days, out, not 3 hours.

19   And so we're clearly right in the

20   middle of the window when we would expect

21   perhaps 25 to 30 percent of these people to

22   convert spontaneously over that period of

1   time that I misrepresented.

2   CHAIR HIATT: Yes.

3   DR. MASSIE: At least for 24

4   hours, we should get that.

5   CHAIR HIATT: So before we go much

6   further into perhaps dozens of specific

7   questions that we would like to have

8   addressed, I don't wonder if the sponsor will

9   be prepared to provide us with that

10   additional information, those missing data

11   cells, particularly at 24 hours, you know,

12   the numbers of patients converted at 24

13   hours; the number of patients undergoing

14   electrical Cardioversion, which we did get in

15   the briefing document; use of other

16   antiarrhythmic drugs; the actual symptom

17   scores at 24 hours.

18   We have adverse events I think

19   pretty well described out that far. And then

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

21   perhaps we could circle back to that

22   question, even later, early in the afternoon,

1   if necessary.

2   MEMBER HARRINGTON: Could I just

3   get a little more information? If that table

4   is going to be constructed, Bill, I would

5   like a safety composite. We are seeing

6   things, you know, low-frequency events. But

7   I would like to know what happens when you

8   add everything up and in the same issue at 24

9   hours for both arms.

10   CHAIR HIATT: I see Dr. Kitt

11   standing at the microphone.

12   DR. KITT: Okay. There are quite

13   a few questions in there. And I will try to

14   go through them as best as I can remember

15   them. And please if I forget something, let

16   me know.

17   CHAIR HIATT: And sorry to

18   interrupt you, but verbally would be nice.

19   But I might forget some of the numbers. If

20   it's possible to prepare a slide that has the

21   primary data out to two hours, which we have

22   all seen and read before the meeting, you all

1   nicely presented, but then carrying those

2   things forward to 24 hours on the safety side

3   is mostly done, but on the efficacy side and

4   perhaps the add out the bad stuff and if it's

5   possible out to seven days. We might

6   visually look at that because I think it

7   gives us a more complete picture of risk and

8   benefit.

9   DR. KITT: Okay. I think one of

10   your questions you had asked was why were

11   people at baseline asymptomatic. And I think

12   that refers to figure 5 in your briefing

13   document.

14   Between screening and baseline,

15   other therapies were allowed. So somebody

16   had come in with a very rapid heart rate.

17   They could have received a dose of

18   Metoprolol. And so some of those patients

19   had a reduction in their symptoms. So that's

20   why at baseline some of our patients were

21   asymptomatic because we did allow the

22   treatment before baseline.

1   Slide up. I think this slide may

2   address some of your other questions. This

3   is our three hours to seven-day group,

4   patients who had converted to sinus rhythm

5   and those who had remained in atrial

6   fibrillation. So here at baseline are

7   percentage of patients without symptoms. And

8   then the data had shown at 90 minutes.

9   And here at 24 hours, I think

10   patients became asymptomatic due to the

11   conversion to sinus rhythm. Those who

12   remained in atrial fibrillation less than 40

13   percent were asymptomatic, whether that be at

14   24 hours or 7 days.

15   CHAIR HIATT: Thanks. Just before

16   you walk off with that one, then, so that you

17   clearly have a symptomatic advantage out to 2

18   hours, but then as other therapies are

19   employed, you lose that advantage at 24 hours

20   and 7 days. Is that correct, then?

21   DR. KITT: That's right. The

22   patients that we studied in our studies, the

1   patients we studied, were those I think where

2   clearly the physician felt that they needed

3   to be converted to sinus rhythm. And if they

4   did not convert with vernakalant, they went

5   out to have other therapies.

6   CHAIR HIATT: So all of this

7   discussion will acknowledge clearly that

8   other therapies were employed after two

9   hours. And clearly there is a relationship

10   between going back into sinus rhythm and

11   relief of atrial fibrillation symptoms. So

12   we understand that. But I guess it is just

13   good to see the data.

14   DR. KITT: Okay. Slide up. Maybe

15   this will help. So the majority of the

16   patients that remained in atrial fibrillation

17   after study treatment received either

18   electrical Cardioversion or other

19   antiarrhythmic agents within the first 24

20   hours. So the top line here is other

21   spontaneous converters from placebo and the

22   vernakalant converters. And here are the

1   non-converters.

2   And you can see that the

3   non-converters, about 80 percent of those, in

4   our study went on to get treated with either

5   electrical Cardioversion and/or

6   antiarrhythmic agents. And a majority of

7   those patients actually had electrical

8   Cardioversion. I don't think there were very

9   many that received antiarrhythmics.

10   DR. MASSIE: Do you know anything

11   about the spontaneous conversion in the

12   people who were not treated, the 20 percent?

13   DR. KITT: Just a minute.

14   (Pause.)

15   DR. KITT: No. I'm afraid we

16   don't have that analysis.

17   DR. CANNON: I believe you or

18   someone presented that there was a follow-up

19   contact at 7 days and at 30 days. Maybe it's

20   7 days EKG or Holter and 30 days telephone

21   contact.

22   My specific question is about the

1   durability. So I know that at 90 minutes,

2   the people who converted at 24 hours, the

3   majority, 90-something percent, were still in

4   sinus rhythm. So my question is, what about

5   at 7 days and at 30 days?

6   What percent of people who are

7   successfully cardioverted with the drug

8   vernakalant and who were in sinus rhythm at

9   24 hours remained in sinus rhythm at 7 days

10   and 30 days? Do you have those data?

11   DR. KITT: Just a minute, please.

12   (Pause.)

13   DR. CANNON: So this follows on

14   figure 53, where you show the data, the

15   durability, at 90 minutes. So I am asking

16   for an extension of durability.

17   DR. KITT: Right. We did do

18   12-Lead ECG on day seven.

19   DR. CANNON: Okay.

20   DR. KITT: The day 30 was just a

21   telephone telephone call. I don't recall

22   offhand what the percentage --

1   CHAIR HIATT: So what about day

2   seven?

3   DR. KITT: We're trying to get

4   that data for you. What is it? Ninety-three

5   to 94 percent remained in sinus rhythm at day

6   seven.

7   CHAIR HIATT: And tell us about

8   both groups. I'm sorry. So at day seven,

9   what percent of both groups were in sinus?

10   DR. KITT: Placebo and

11   vernakalant?

12   DR. CANNON: And while you're

13   looking that up, what about the symptoms at

14   day seven for both groups as well because it

15   was indicated you did the symptom checklist

16   at both time points.

17   DR. KITT: Okay. Slide up,

18   please. This shows if they were in sinus

19   rhythm. This shows how many were

20   symptom-free at day seven. So if they were

21   in sinus rhythm and they received placebo, 67

22   percent were symptom-free, 65 percent in the

1   vernakalant group if they were in sinus

2   rhythm on day 7.

3   DR. CANNON: But, of course, the

4   placebo patients by then, many would have

5   received something. They would have been

6   electrically cardioverted or --

7   DR. KITT: Right. Those are

8   people --

9   DR. CANNON: -- ibutilide or

10   whatever. So that's a tough comparison, I

11   think.

12   MEMBER HARRINGTON: Well, I think

13   what you're saying, Richard, is you're

14   embarking upon a strategy here. So the

15   strategy is pharmacologic Cardioversion from

16   the outset in the half of the people that it

17   fails in. They also undergo electrical

18   Cardioversion or a period of two hours of

19   observation followed by electrical

20   Cardioversion.

21   So I think from the clinician's

22   perspective at seven days, what you are

1   seeing is the strategy comparison. And at

2   the strategy, there is no difference.

3   DR. CANNON: So along that

4   thinking, though, we need to know what the

5   placebo patients actually got, how many

6   converted spontaneously, how many got

7   electrical -- well, she actually presented

8   those data -- how many got ibutilide or

9   something else. I mean, additively, it may

10   be that similar numbers of people got similar

11   kinds of similar treatments of one sort or

12   another.

13   CHAIR HIATT: Well, remember at 24

14   hours, 58 percent of placebo patients had to

15   be cardioverted versus 37 percent. Because I

16   think Dr. Harrington actually said what I

17   think is running through my mind, it's a

18   treatment strategy for comparing drug to

19   placebo, but that's over a very short

20   interval.

21   And so the issue is, what does

22   that look like at a relatively short interval

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1   of 24 hours or 7 days?

2   MEMBER LINCOFF: But not entirely

3   because, I mean, no one is suggesting here

4   that the drug is better than just electrical

5   Cardioversion. If the idea was just a

6   strategy, then we would do a drug-based

7   strategy versus an electrical cardio-based

8   strategy.

9   I mean, the purpose of these

10   studies was to determine if the drug could

11   eliminate the need for the electrical

12   Cardioversion, recognizing that if it didn't,

13   then one would go on. I mean, in practice,

14   the idea would be that fewer patients

15   ultimately would have to have electrical

16   Cardioversion because we believe that there

17   are some disadvantages to Cardioversion. If

18   it was simply a strategy approach, then it

19   would be start off with electricity or start

20   off with drug and default to electricity.

21   And that really isn't the idea

22   here. The idea is if we can convert