FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Cardiovascular and Renal Drugs Advisory Committee

NDA 22-425, dronedarone 400 milligrams

oral tablets

Wednesday, March 18, 2009

7:59 a.m.

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3501 University Boulevard East

Adelphi, Maryland

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I N D E X

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P R O C E E D I N G S

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DR. HARRINGTON: If people could take their seats, why don't we go ahead and get started.

My name is Bob Harrington. I'm a cardiologist at Duke University. And it's my privilege to chair today's meeting of the Cardio and Renal Vascular Drugs Advisory Committee. I'm going to read a brief statement and then I'll ask the committee to go around and introduce themselves, specifically listing your institution and your area of expertise so that people can put your remarks in context.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if either Elaine or I recognize you. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from

discussing the details of the meeting with the media until the meeting's conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or during lunch.

So, Dr. Fox, why don't we start with you and go around the room and make sure that people introduce themselves.

DR. FOX: My name is Jonathan Fox. I serve as the industry representative to the committee. I am a cardiologist in clinical development at AstraZeneca.

DR. KRANTZ: Good morning. Mori Krantz. I am a general cardiologist in Denver, Colorado.

DR. McGUIRE: Darren McGuire, general cardiology, UT Southwestern in Dallas.

DR. WOLFE: Sid Wolfe. I'm a general internist. I am, for this meeting, serving as the consumer representative.

DR. NELSON: Lewis Nelson. I'm an emergency physician and a medical toxicologist at New York University School of Medicine.

DR. SWENSON: Erik Swenson. I'm in pulmonary and critical care medicine at the University of Washington in Seattle.

DR. LINCOFF: Mike Lincoff. I'm an interventional cardiologist and director of clinical research at the Cleveland Clinic in Cleveland.

MS. FERGUSON: Elaine Ferguson, designated federal official.

DR. PAGANINI: Emil Paganini, critical care nephrologist, Cleveland, Ohio.

DR. BLACK: I'm Henry Black of New York University School of Medicine. My expertise is in hypertension and preventive cardiology.

MR. DUBBS: Bob Dubbs. I'm an interventional patient consultant.

DR. CALHOUN: I'm Bill Calhoun, pulmonary critical care and allergy/immunology, University of Texas in Galveston.

DR. KAUL: Sanjay Kaul, general and critical care cardiologist at Cedars-Sinai Heart Institute in Los Angeles.

DR. NEATON: Jim Neaton, University of Minnesota, professor of biostatistics.

DR. STOCKBRIDGE: I'm Norman Stockbridge. I'm the director of the division of cardiovascular and renal products at FDA.

MS. FERGUSON: The Food and Drug Administration is convening today's meeting of the Cardiovascular and Renal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members are special government employees, SGEs or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC 208 and 712 of the Food -- Federal Food,

Drug and Cosmetic Act, FD&C Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with the federal ethics and conflict of interest laws under 18 USC 208.

Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts of interest when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Under 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee's essential expertise.

Related to the discussions of today's meeting, the members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teachings, speaking, writing, patents and royalties and primary employment.

Today's agenda involves discussions of new drug application NDA 22-

425, dronedarone 400-milligram oral tablet sponsored by Sanofi-aventis for the proposed indication in patients with a history of or current atrial fibrillation or atrial flutter for the reduction of the risk of cardiovascular hospitalization or death.

This issue is a particular matters meeting during which specific matters related to dronedarone will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Jonathan Fox is serving as the non-voting industry representative acting on behalf of regulated industry. Dr. Fox's role at this meeting is to represent industry in general and not any one particular company. Dr. Fox is employed by AstraZeneca.

We would like to remind members and temporary voting members that if the discussion involves any other products or firms not already on the agenda for which a FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusions will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firm at issue.

And for right now I'd like to recognize the press contacts for this

meeting, Sandy Walsh and Karen Riley. Will you please stand if you are present.

Thank you, Karen.

DR. HARRINGTON: Great. The first order is to hear from Dr. Stockbridge to provide any opening remarks on behalf of the FDA.

DR. STOCKBRIDGE: I want to thank the permanent and temporary members of the committee for coming here today. The case before you today is going to be pretty interesting. No one seems to dispute that the drug delays the recurrence of atrial fibrillation, but we have two studies of morbidity and mortality that give persuasively and directionally different results.

You'll be asked to consider those results in terms of some logical sequence. We got result A, thought we understood it, then we did something different and got result B. Along the way, we discover that the hypothesis that led to study number 2 was flawed. So a new hypothesis had to be crafted to explain the difference between the outcomes.

You, on the committee, have to help us decide whether the new story is more than plausible; you have to help us decide whether you find it compelling. And if it is compelling, we need your help in drawing a line that identifies patients very likely to get result B.

Looking forward to the discussion, and thanks, everybody, for coming.

DR. HARRINGTON: Thanks, Norm.

For the panel members, the schedule of the day is going to shift approximately 15 minutes. The sponsor requires approximately an hour and 45 minutes for their presentation. We'll allow them to do that presentation without questions, and then approximately 10:00 we'll have 15 or so minutes for questions directly to the sponsor.

If we don't get everything in, we have plenty of time, particularly this afternoon, to have additional questions. So I'll ask the sponsor to try to keep on time so that we can get to the panel's questions. So I'll turn it over to the sponsor representatives to lead us through their presentations.

DR. GURAL: Good morning, Mr. Chairman, advisory committee, Food and Drug Administration and members of the public. My name is Richard Gural. I'm head of regulatory affairs for Sanofi-aventis.

During today's presentation, we will cover many different topics, as identified by Dr. Stockbridge. A lot of the information is contained within the briefing book for your reference. We will be covering a majority of it, but for the details, please refer to the briefing book if you have any questions.

Today we would like to address the unmet medical need for the treatment of patients with atrial fibrillation, which is a very complex and common form of cardiac arrhythmia in the United States population.

Current treatment options treat symptoms, but do not address the risk of the mortality and morbidity and cardiovascular hospitalization. There

is an unmet medical need for these drugs to improve morbidity and mortality beyond reducing the recurrence of afib. We will hear more about this later from Dr. Naccarelli.

I'd like to briefly overview for you some of the characteristics of dronedarone. Dronedarone is a multi-channel blocker. It possesses class I to IV Vaughan-Williams properties. Dronedarone is an analog of amiodarone.

As you can see in the structure below, the iodine portion of the molecule, which was contained within amiodarone, has been removed to improve thyroid safety. And you can also see that the methylsulfonamide group has been added to the dronedarone molecule to reduce its lipophilicity.

How does this translate into the pharmacokinetics of the drug? Following the well-absorbed -- dronedarone is well absorbed following oral administration, approximately 15 percent bioavailable following an extensive first pass metabolism.

There is a significant food effect. There is an increase in the area under the curve approximately two- to three-fold, which is therefore recommended that dronedarone be administered with meals.

The excretion and elimination of dronedarone has been characterized. It is extensively metabolized, predominantly through the CYP3A4 mechanism. There is minimal renal excretion. The approximate half-life is around 30 hours.

Intrinsic factors that influence the exposure to dronedarone include

age, body weight and gender of the patients being treated.

Extrinsic factors that influence the exposure are inhibitors and inducers of CYP3A4.

Dronedarone has been extensively studied through a number of phase 2 and phase 3 programs. I remind the committee that the -- again, the designs of the study are contained within the briefing book. We won't detail them today, with the exception of the ANDROMEDA and the ATHENA trial that Dr. Packer will review.

Briefly, the program contained a dose-ranging study called DAFNE, as well as a study of -- named EURIDIS and ADONIS. These three trials involved patients with known AF/AFL. ERATO was a study in patients with permanent AF. And DIONYSOS, which will be covered by Dr. Naccarelli was a competitive trial of dronedarone versus amiodarone.

I will remind the committee the agency has just received this information in February, and they have not completed their review on it.

Two studies were conducted, one in a special population called ANDROMEDA -- and we will hear about this more from Dr. Packer -- as well as the outcome study, ATHENA, in which we have demonstrated a significant reduction in cardiovascular hospitalization or mortality.

The dose selection for dronedarone followed first a study in normal volunteers in which the 400-milligram BID dose was demonstrated to be the lowest dose associated with a significant change in ECGs.

A dose of 400, 600 or 800 milligrams BID was then studied in patients with AF/AFL in a study called DAFNE. In this study, it was demonstrated that dronedarone 400 milligrams was associated with a significant reduction in the risk of recurrent AFL.

Doses of dronedarone at 600 and 800 milligrams were poorly tolerated and, therefore, were not recommended for further development. Thus, for all future clinical trials, 400 milligrams BID administered with food was the recommended dose.

Let me briefly review with you the regulatory history for dronedarone. Dronedarone was originally filed in June of 2005. The weight of evidence was based on the benefit of the studies in the maintenance of sinus rhythm and ventricular rate control, and was based on the studies DAFNE, EURIDIS, ADONIS, ERATO and ANDROMEDA. The studies EURIDIS and ADONIS will be covered this morning by Dr. Naccarelli.

The NDA was deemed non-approvable by the FDA in August 2006. In their non-approvable letter they did recognize that the 400-milligram BID dose did delay the time to the first recurrence of arrhythmia and also decreased symptomatic recurrence.

There was noted to be an unfavorable benefit risk largely because of the adverse outcomes in the ANDROMEDA trial -- again, something to be discussed by Dr. Packer this morning.

A new drug application was filed in July of 2008. This application

included reference to all the previously conducted trials and based the new application on the results of the ATHENA trial. And the -- a priority review was granted by the FDA for the unmet medical need and the significance of the findings.

As I mentioned previously, the DIONYSOS study, which was a comparative study against dronedarone to amiodarone was just recently filed to the FDA in February of this year, and they have not had yet a chance to review that.

The indication for discussion today is that Multaq is indicated in patients with either a recent history of or current non-permanent atrial fibrillation or flutter with associated risk factors. Multaq has been shown to decrease the combined risk of cardiovascular hospitalization or death.

As mentioned by Dr. Stockbridge, one of our major discussion points today will involve who is the appropriate patient and inappropriate patient to be treated with dronedarone.

The appropriate patient is a patient with recent history of or current non-permanent AF or AF flutter with associated risk factors. The inappropriate patient is a patient with symptoms of heart failure at rest with minimal exertion within the last month, or a patient hospitalized for heart failure within the last month. These, again, will be discussed by Dr. Packer and by Dr. Camm as well.

A brief outline of our presentation today. We will start with Dr.

Naccarelli from Hershey Medical Center who will discuss the unmet medical need for dronedarone in rate and rhythm studies. We will have Dr. Packer from the University of Texas Southwestern Medical Center at Dallas who will discuss the effects of dronedarone and major cardiovascular events from the ATHENA and the Administration. Dr. Chew of Sanofi then will review the safety profile of dronedarone in the AF/AFL population. And, lastly, we will have Dr. Camm from St. George's University of London review the benefit risk of dronedarone in the treatment of atrial fibrillation or flutter.

We have with us today a number of external experts who can address questions that you may have, as well as a number of internal experts who are familiar with all the data.

With that, I would like to turn the presentation over to Dr. Naccarelli.

DR. NACCARELLI: Mr. Chairman, members of the panel, my name is Jerry Naccarelli. I am chief of cardiology at the Penn State University College of Medicine at the Milton S. Hershey Medical Center. I'm a heart rhythm specialist and have a very active practice, heavily treating patients with atrial fibrillation and flutter.

Over the next ten minutes or so I would like to briefly give you a feel for where we are in the treatment of atrial fibrillation and flutter, identify some of the unmet needs and also introduce and highlight some of the studies that have been done with this compound.

As you know, atrial fibrillation and flutter is associated with increased morbidity and mortality, is a two-fold risk in death, a two- to three-fold risk in cardiovascular hospitalization, a four-and-a-half-fold risk in thromboembolism and stroke. Tachycardia can worsen, associated myocardial ischemia or heart failure, and adverse effects can occur on the atrium and ventricle, including remodeling, including with rapid, uncontrolled rates, the occurrence of tachycardia-induced cardiomyopathy.

This disease is a chronic recurrent disease. And recurrences and/or persistence of the arrhythmia in patients with both atrial fibrillation and atrial flutter is associated with an impaired quality of life secondary to their recurrent symptoms and reduced exercise tolerance. And there's an increased risk of cardiovascular death and cardiovascular hospitalization.

Some of this may be due to the effects of both arrhythmias on cardiocirculatory function, and some of this secondary to the associated conditions that are common co-morbid conditions associated with this arrhythmic disease.

There are millions of people in the United States that have this disease, and with the aging of the population in co-morbid conditions, this continues to grow. This is data from the NIH showing in magenta on the bottom younger patients, of 45 to 64 years old, and in the older population of 65 years or older in yellow you can see the growth in hospitalization rates per 10,000 population, and this continues to grow.

Most recent data that is available is up to 2006, and on the left of the slide shows atrial fibrillation in yellow, atrial flutter which you can see represents, as a solo disease, a much smaller percentage of patients and, in combination, when you add these are in green -- I would point out that these arrhythmias coexist commonly, that the incidence of atrial flutter as a lone arrhythmia is probably about 5 percent, that many patients with atrial flutter will have recurrences of atrial fib, and patients with atrial fib with have recurrences of atrial flutter.

But you can see on the left of this slide that in 2006 combined there were over 400,000 admissions as the primary diagnosis. On the right, the curve is a little bit different. You can see this is actually over 3-1/2 million, if you look at all the discharge diagnoses. So this is a real problem in our emergency rooms and in our wards at all the hospitals.

The long-term effects of these type of drugs in patients with non-permanent atrial fibrillation and flutter has not been well-defined. The development of drugs for the treatment of patients with atrial fibrillation and flutter have often focused on recurrence of the arrhythmia. Drug development programs have also focused on mortality and high-risk non-atrial fibrillation patients, to exclude possible pro-arrhythmic effects and points such as the time the first recurrence of atrial flutter, ignored the possible effects of treatment on morbidity and mortality.

This is a retrospective post-hoc study from the AFFIRM trial which,

prior to ATHENA, was the largest trial that had been on atrial fibrillation. As you remember, this compared rate control to rhythm control. And what is plotted here is the cumulative number of events -- that being death and cardiovascular hospitalization -- over the time of this trial, which was several years.

And the points that I would like to make on this is that whether one is a rate control advocate or a rhythm control advocate, you can see the frequency of these recurrent morbid events of death and cardiovascular hospitalization. And although there is no prospective data for amiodarone, which is the number one drug that is prescribed in the United States for atrial fibrillation, two-thirds of the patients in this study were on amiodarone and, if anything, you can see the rhythm control group did worse than the rate control group. And in the recent AFCHF trial, which was 82 percent amiodarone, there were similar findings.

Now, when we look at current treatment strategies for patients, the triad is rate control, rhythm control and prevention of stroke. Almost all patients have an attempted rate control as part of their therapy, usually pharmacologically with the drugs listed. Patients are identified for high risk for stroke, and appropriate patients are usually put on warfarin to achieve a therapeutic level, and this has a major role in reducing stroke.

Rhythm control, whether acutely or chronically, then is added to this, based on a case-per-case basis.

However, all of these treatments have excluded the major point that we're discussing today of can we reduce death or cardiovascular hospitalization.

As we look today on this therapy or, frankly, any other therapy, on how these treatments can affect morbidity and mortality, but specific to atrial fibrillation and flutter, we can look at the effect of this therapy resulting on the control of atrial fibrillation and flutter fitting -- feeding into a net effect, but we also have to weigh the favorable or unfavorable effects of this therapy on associated cardiac conditions or extra cardiac effects that could have either a positive or negative effect -- and this would lead us to the net effect of any therapy, specifically this drug, on morbidity and mortality in the patients with atrial fibrillation and flutter.

Now, as you know, dronedarone has some properties similar to amiodarone -- and this was shown by Richard earlier. It's a multi-channel blocker, and this slide -- if we could just concentrate on the top -- shows that this drug has some L-calcium channel blocking abilities, beta-adrenergic inhibition, potassium and sodium channel inhibition. These properties can be very favorable for rate control, for blocking -- prolonging refractoriness and slowing conduction at the AV node, and also atrial rhythm control could result, as I will show you in several studies in the reduction of atrial fibrillation and flutter.

Dr. Gural showed you some of the trials that were done to evaluate

the efficacy of dronedarone in the prevention of recurrence of atrial fibrillation and flutter, and I will highlight those very briefly since the majority of this data is in your briefing document.

The DAFNE trial was a phase 2 trial which showed that the 400-milligram twice-a-day dose of the compound statistically prevented recurrences while the higher doses were associated with gastrointestinal side effects and inefficacy, and this is why the 400-milligram dose was used for further studies.

The EURIDIS and ADONIS studies had a 2-to-1 ratio of randomization and were sister studies that went on in parallel, looking at atrial fibrillation and flutter within three months -- and the patients were in sinus rhythm at randomization.

And as mentioned briefly, the DIONYSOS trial was performed as an active comparator trial, compared to amiodarone, and this was part of the European regulatory pathway.

This slide shows the Kaplan Meier curves for the primary end point of first recurrence of atrial fibrillation and flutter from both the EURIDIS and ADONIS trials. One can see in EURIDIS there was a 22 percent reduction in the primary end point; in ADONIS a 27 percent reduction. This was statistically and clinically meaningful.

I should also mention that the patients who did have recurrences had a 12 to 14 beat-per-minute reduction in their heart rates during recurrences

due to the AV node blocking properties of the drug. And this was consistent through all the trials that looked at rate control as part of their analysis.

On one slide I will highlight the primary end point of DIONYSOS, which was to look and compare amiodarone and dronedarone -- dronedarone is in blue, amiodarone in orange -- and the primary end point being atrial fibrillation recurrence or premature drug discontinuation for whatever reason.

You can see in this trial that amiodarone was superior to dronedarone on that end point, but if one looks at the recurrence of atrial fibrillation -- this was the main driver of that end point -- with amiodarone having a statistically reduced reduction in recurrence of atrial fibrillation.

There was a trend in more patients with amiodarone over the short course of this study, which was only six month, having premature drug discontinuation because of adverse events.

This analysis is very similar to other published trials comparing amiodarone to, for example, sotalol and propathanone in the Canadian trial on atrial fibrillation where amiodarone was shown to have more efficacy in reducing atrial fibrillation recurrence, but a higher number of patients discontinuing because of adverse effects.

Now, getting back to the earlier cartoon, I wanted to just make the point that blocking all the channels we discussed earlier also have effects outside of the atrium and the AV node. These have beneficial effects in the ventricle, which could result in ventricular rhythm control. There is the

antiadrenergic effects which obviously have multiple possibilities, including effects on acute coronary syndrome, sudden death, reducing stroke and heart failure, and the calcium inhibition and NO liberation may also have effects on coronary and systemic vasodilation and lowering blood pressure.

So as we look at this drug, it may be more complicated than just looking at atrial fibrillation and flutter recurrence in looking at the net effects of what this drug may do on a given patient.

If we go back to the EURIDIS and ADONIS trial, there was a post-hoc analysis looking at the effect of the compound on death or cardiovascular hospitalization. In blue is the dronedarone 400 milligrams twice a day and in gray is placebo. You can see there was a favorable trend that just missed statistical significance with a hazard ratio of 0.8, giving a signal and generating a hypothesis that this drug, in a prospective large randomized trial, might meet this end point -- and you will hear more about that end point in the ATHENA presentation by Dr. Packer.

So, in summary, patients with atrial fibrillation and atrial flutter have an increased risk of death and cardiovascular hospitalization. Current anti-arrhythmic drugs for the suppression of both arrhythmias have not demonstrated reduction in the risk of death and cardiovascular hospitalization to date.

Randomized placebo-controlled clinical trials have shown that dronedarone prevents the recurrence of atrial fibrillation and atrial flutter.

Dronedarone has properties that can be expected to reduce the risk of death and cardiovascular hospitalization. A reduction in such risk was observed in the post-hoc analysis of EURIDIS and ADONIS.

So I'd like to introduce the next speaker, Dr. Packer, who will discuss the ANDROMEDA and ATHENA trials.

DR. PACKER: Thank you, Jerry. Mr. Chairman, members of the advisory committee, representatives of FDA, what I would like to do in the time allotted to me is to review the primary results of the ANDROMEDA and ATHENA trials. These were the trials specifically designed to look at the long-term effects of treatment with dronedarone on the risk of major cardiovascular events. I am going to organize my presentation in three modules, each of which is designed to address the questions that the FDA has directed to the committee about the ANDROMEDA and ATHENA trials.

The first module will review the background and results of ANDROMEDA and ATHENA. The second module will examine the internal consistency of these results. And the third module will focus on the reconciliation of the results of the ATHENA and ANDROMEDA trials.

First let's go into the background of these studies. As you have already heard, dronedarone was designed as an amiodarone analog and, therefore, it is relevant to begin with a review of what we know about the effect of amiodarone on morbidity and mortality in large-scale trials. This slide shows the six -- all six large-scale trials that have compared

amiodarone to placebo either in post-infarction patients or in patients with congestive heart failure. As you can see, these trials, in the four heart failure trials, they all had patients with low ejection fractions. Substantial proportion had patients with class III and IV heart failure.

If you look at the effect on cardiovascular events, you can see that, in general, there is no favorable or unfavorable effect of amiodarone in these studies. So, overall, what is considered to be a neutral effect on morbidity and mortality, and that includes the heart failure trials.

Now, this is important because, because it's not been associated with an increased risk of death, amiodarone is currently regarded as a first-choice anti-arrhythmic drug in the management of non-permanent atrial fibrillation in patients with heart failure. Those who manage heart failure really don't have too many other drugs that we can use in patients with non-permanent atrial fibrillation, and this is particularly true in patients with class III and IV heart failure. Ironically, mad is not approved by the FDA for this indication.

I do want to mention one thing about these four heart failure trials. All four heart failure trials with amiodarone enrolled patients who were clinically stable. They were all either outpatients or specifically excluded patients who were clinically unstable or had recent decompensation.

Now, with that in mind, let me emphasize that amiodarone and dronedarone are not necessarily drugs that had the same effects on the risk of

cardiovascular events, and I want to focus on one difference between the two drugs which has been highlighted in the FDA review. This is the effect of these drugs on blood pressure.

Amiodarone has been evaluated in a significant number of trials that have evaluated its effects on blood pressure. And when amiodarone is compared with placebo, there is no effect on blood pressure. But as you can see on this slide, when dronedarone is compared with placebo, in every single study that has been done with this drug, there is a reduction in systolic and in diastolic blood pressure that is generally seen starting about the first week in therapy, is maintained throughout the period of follow-up. The magnitude of this effect is also consistent across the studies and varies between around 2 to 3, 3-1/2 millimeters of mercury.

Of note, in the DIONYSOS trial, which directly compared dronedarone to amiodarone, again, the same 2, 3, 3-1/2 millimeter difference in blood pressure. The reason that this is important is that this magnitude of blood pressure in trials of antihypertensive drugs has been associated with a meaningful reduction in the risk of cardiovascular events. So something to keep in mind as we go forward.

This may or may not have anything to do with the driver to looking at outcomes which Dr. Naccarelli has already reviewed for you, which is the results of the EURIDIS and ADONIS trials. Now, let me just say that what you've already seen from Dr. Naccarelli is, when you combine these two trials,

there is a reduction in the risk of death or cardiovascular hospitalization of about 20 percent.

Now, this would be true if you put together all of the placebo control trials in atrial fibrillation. We show you EURIDIS and ADONIS because it had more events than any of the other trials, but those results would be the same if you put together all the trials.

And I do also want to just hasten to add that this analysis does not include stroke, does not include cerebrovascular events. And if you included stroke and cerebrovascular events -- the results are at the bottom of the slide -- they're not meaningfully difference -- perhaps a little bit better.

So with that background in mind, I want to first begin with a focus on the ANDROMEDA trial, and this trial focused on patients hospitalized for decompensated heart failure. Now, I have to remind the committee that these patients have the highest possible risk of a major cardiovascular event, which is exactly why they were selected for this study.

It is of note, however, the patients hospitalized for decompensated heart failure have generally not been enrolled in survivor trials designed to evaluate the safety of anti-arrhythmic drugs. Almost all of the studies that have been carried out to look at the safety of anti-arrhythmic drugs have focused on stable, post-infarction patients or patients with stable heart failure. Also important to note that ANDROMEDA was a heart failure trial, not an atrial fibrillation trial. Patients could be enrolled whether or not they

had a history of atrial fibrillation, and the atrial fibrillation may have been long-standing or of recent onset.

The main entry criteria for ANDROMEDA are reviewed on this slide. Let me just focus on the fact that in order to get into ANDROMEDA, you had to be hospitalized for worsening heart failure at the time of randomization. You had to have dyspnea or fatigue at rest or on slight exertion within a month prior to randomization. At the time of randomization, the patients had class II, III or IV heart failure and they all had signs of left ventricular systolic dysfunction as reflected by a wall motion index less than 1.2 -- approximately equal to a left ventricular ejection fraction of less than 35 percent.

I'm not going to review the exclusion criteria. They're in the briefing document, and they're summarized on this slide.

Here are the actual characteristics of the patients who were enrolled in ANDROMEDA. They look like patients with decompensated heart failure. Most of them are elderly men. They all are receiving appropriate therapy with ACE inhibitors and beta blockers and spironolactone. I want to also note that about 50 percent had evidence of decompensation by fluid retention, peripheral edema.

and what is of note is the history of atrial fibrillation and atrial flutter in the trial. Now, although it is true that about 35, 40 percent of the patients had a history of atrial fibrillation, in the vast majority of

cases, this was permanent atrial fibrillation, characteristic of patients with heart failure, long-standing heart failure. Only about 7 percent of the patients had recent onset atrial fibrillation or flutter that was terminated and was of recent onset and was not permanent in nature.

Now, these patients were randomly assigned, 1 to 1 ratio, to either double-blind treatment with dronedarone, 400 milligrams twice a day, or placebo, for a planned duration of at least 12 months. The primary end point was the combined risk of all-cause mortality or hospitalization for heart failure.

The original protocol projected a sample size of 1,000 patients, based on the assumption that there would be an event rate of 50 percent in the placebo group, a relative risk reduction of 20 percent in the dronedarone group, and a power of 90 percent to detect a treatment difference.

A total of 653 patients were enrolled in the dronedarone -- the primary analysis prospectively focused on 627 patients, half of whom were treated with placebo, half with dronedarone, and all patients had complete data with respect to vital status.

An independent data safety monitoring board was constituted prior to the start of the study to periodically review the results of the trial. The board identified all-cause mortality as the primary safety measure and prespecified in its charter early termination if the nominal P-value was less than .05 between the two groups in the risk of death at any time during

follow-up.

The board did not specify intervals for intramonitoring and, instead, compared differences in mortality rates in the two treatment groups after every one to two deaths.

Seven months into the study the board recommended early termination of enrollment and study treatment because of an increased risk of death in the dronedarone group and recommended all patients then be followed for six months.

I'm going to show you the mortality results at the time of the recommendation of the data safety monitoring board for termination of enrollment and treatment. As you can see, there were 12 deaths in the placebo group, 25 deaths in the dronedarone group -- this translates into a little bit over a two-fold increase in the risk of death. You can see the Kaplan Meier curves below. Almost all of the data is in the first two months of this study. The median follow-up was two months.

The number of deaths after two, three months is very, very small. And you can see within that two- to three-month period of time, there was an early separation with worse outcomes in the dronedarone group than in the placebo group.

Here's the breakdown on the mode of death. 20 -- almost all of the deaths, all but one, was deemed to be cardiovascular. And you can see regardless of how these deaths are classified, there were more deaths in the

dronedarone group than in the placebo group across all categories.

There were also more hospitalizations for cardiovascular reasons. You can see that, regardless of whether one looks at atrial fibrillation or worsening heart failure, myocardial ischemia, stroke, more events, more cardiovascular hospitalizations on dronedarone than on placebo.

So why? There are three possibilities that have been given considerable consideration. And I'm going to review each of these and focus on their merits and considerations.

First, it is possible that the results of ANDROMEDA represent a chance finding related to the uncertainty associated with frequent intramonitoring of small numbers of events in a trial that was terminated early. Those of us who have been involved in heart failure research for years are well aware of the fact that it is not uncommon in the area of heart failure to carry out a small intermediate-term study which records a number -- relatively small number of major cardiovascular events, for there to be a marked difference between the two treatment groups in this early study, for everyone to get excited about this difference, and then for a definitive study to fail to confirm and often reverse the findings of the initial study.

I know it would be hard to believe, but this is actually a partial list of these studies. I point out five of them. Some of these have dramatic effects, 62 percent reduction in risk, 46 percent reduction in the risk of death, 80 to 90 percent reduction in the risk of death -- all based on less

than 50 events, all statistically significant. And yet when a second study was carried out, a definitive study, often recording 10 to 20 times more events, these early results were not confirmed. And in one particular case, the results of the definitive study were directly opposite the results of the early study -- and I point out the vesnarinone study by Feldman.

Now, is it possible that the mortality difference in ANDROMEDA may have been a false positive result? Statistical simulations -- 10,000 such simulations of the conditions that characterize the conduct of the ANDROMEDA trial, based on the number of patients enrolled, the number of deaths, the frequency of interim analyses indicate that the false positive error rate for concluding the existence of a difference in mortality between the placebo and dronedarone group was not 5 percent, but it was 18 percent. So it's something to consider as we go forward and review additional data.

Second possibility. Second possibility is that the results of ANDROMEDA represent a true finding related to differences in the use of certain background medications following the randomization. This is reviewed in your briefing document. I don't want to spend a lot of time on this, but you've already learned, in reading the document that dronedarone is associated with an increase in serum creatinine which is related to inhibition of renal tubular secretion of creatinine so that the creatinine, after an implementation of therapy, rises slightly. A heart failure physician, seeing the increase in serum creatinine then gets, perhaps understandably, a bit

distressed, thinks it's due to the ACE inhibitor or angiotensin receptor blocker that the patient is receiving and, therefore, pulls away the ACE inhibitor and angiotensin receptor blocker.

And in this study, the number of people who discontinued the angiotensin receptor blocker or ACE inhibitor was greater in the dronedarone group than in the placebo group, and the number who were started on these drugs was lower in the dronedarone group than in the placebo group.

Let me just say for the record I don't think this is the explanation. If one does a multivariate analysis and factors in the differential use of ACE inhibitors or angiotensin receptor blockers and then looks at what the effect of dronedarone is versus placebo -- and that's summarized in the last row -- there is still an increase in risk, and the magnitude of the increase in risk is just about the same as it is in the unadjusted analysis.

So although there is a part of the briefing document that raises this question, I don't think this is a credible explanation for the findings of dronedarone in the ANDROMEDA trial.

Third possibility. Third possibility is that this represents a true finding that can be explained by the deleterious effect of dronedarone in recently unstable patients who are hospitalized for decompensated heart failure and who did not have non-permanent atrial fibrillation. I want to just call your attention to a subgroup analysis of the ANDROMEDA trial based

on heart class. The vast majority of patients were in class II and III at the time of randomization. You can see that most of the increase here is in the class III patients, not in the class II patients, raising the possibility that patients who are severely ill and clinically unstable are at increase in risk.

There is also another factor, and that is that, in general, patients in the ANDROMEDA trial did not have non-permanent atrial fibrillation. This is a pie chart showing the breakdown of the type of rhythm at the time of randomization. You can see the vast majority of patients had no atrial fibrillation or flutter at all, no history of it. Another sizable proportion had permanent atrial fibrillation. Only about 6 to 7 percent of the patients in the study had recent onset atrial fibrillation or flutter that was considered to be non-permanent and, therefore, would have been candidates for treatment with dronedarone according to the indication under discussion.

Now, interesting, if you look at the mortality rates in this study, almost all of the mortality increase is seen in the patients who either didn't have atrial fibrillation or flutter or had permanent atrial fibrillation and flutter. I want to focus on the bottom row here. These are the patients who had non-permanent atrial fibrillation in the study. You can see there were only two such events, one in the placebo group and one in the dronedarone group.

So with that in mind, the sponsor decided to move forward with a major outcome trial, considerably larger than the ANDROMEDA trial, and with a

different focus than the ANDROMEDA trial. Let me emphasize the difference in focus. ANDROMEDA was a heart failure trial where patients with atrial fibrillation may or may not have been enrolled. ATHENA was an atrial fibrillation trial that may or may not have had patients with heart failure. So it's important to look at these studies as having different objectives.

Now, here are the inclusion criteria for the ATHENA trial. Two primary qualifications for getting into the study. First is that you had to have atrial fibrillation and be at risk of recurrence. So you either had to be in sinus rhythm but had had atrial fibrillation or flutter within six months, or you had to be in atrial fibrillation or flutter with the likelihood of being converted to sinus rhythm. In any case, you had non-permanent atrial fibrillation, and if you had permanent atrial fibrillation, you weren't enrolled in the trial.

Second major criteria. Remember, this is an outcomes trial, and in order to make the trial feasible and doable within a reasonable period of time, patients who were enrolled, if they were at increased cardiovascular risk -- remember, as you saw from Dr. Naccarelli, that atrial fibrillation, non-permanent atrial fibrillation, is a disease of the elderly, usually elderly with lots of cardiovascular risk factors and, therefore, these were required for entry into the ATHENA trial.

Specifically, initially at the time when this protocol was first developed, you either had to be 70 years old or greater and, if you weren't 70

years old or greater, you had to have an additional risk factor, either hypertension or prior stroke, TIA or systemic embolism, or diabetes, or a left atrial diameter greater than 50 or a left ventricular ejection fraction of less than 40 percent. So left ventricular dysfunction was a qualifying criteria for the ATHENA trial.

Now, during the course of the study, the event rates were not meeting expectations, particularly for purposes of mortality. So the sponsor decided to further enrich the likelihood of getting a cardiovascular event by moving the age bar from 70 to 75 and did so by requiring that everyone in the study had to be at least 70 years old. And if you had no additional cardiovascular risk factors, you had to be at least 75 years old.

Now, the exclusion criteria listed on this slide -- they are identical to the exclusion criteria in the ANDROMEDA trial, with two exceptions. First is that if you had class IV heart failure within the prior four weeks, you were not in ATHENA. Remember, this was a qualifying criteria for ANDROMEDA. So class IV heart failure within four weeks got you into ANDROMEDA and excluded you from ATHENA. And if you had a GFR that was very low, you weren't in ATHENA.

So it was the class IV patients within the last four weeks, the patient hospitalized for decompensated heart failure that was the major distinction between the ATHENA and the ANDROMEDA trials because, otherwise, the exclusion criteria for the two studies were similar.

Here are the baseline characteristics of the patients. Again, a typical group of patients with non-permanent atrial fibrillation. Notice about an equal proportion of men and women here. Again, an elderly population, a lot of patients getting ACE inhibitors and beta blockers and oral anticoagulants. And you can see about 30 percent of the patients had heart failure.

Now, these patients were randomized 1 to 1 to either double-blind treatment with dronedarone, 400 milligrams twice a day, or placebo. Primary prespecified end point was the combined risk of all-cause mortality or cardiovascular hospitalization.

The secondary end points included all-cause mortality, cardiovascular hospitalization and cardiovascular death, and right before the blind was broken, the step-wise rejection procedure was implemented in order to guide FDA decisions about a claim.

Investigator determinations were used to analyze prespecified primary or secondary end points. There was no central adjudication procedure in this study, so all the analyses that you are going to see are based on investigator determinations.

Now, the original sample size for this study specified in the original protocol was a sample size of 3700 patients, 1 to 1 randomization, based on an expected 20 percent rate of the primary event in the placebo group and a 15 percent reduction in risk. This would translate the expectation of a

total of 970 primary events, and if these were observed, it would provide 80 percent power to test the primary hypothesis.

Now, during the course of the study, it was noted that mortality rates were lower than anticipated, and a major reason this trial was done was to get more precise estimates about the effect of this drug on mortality. And with a lower mortality rate, those estimates would be less precise than had been agreed with with the FDA.

Prior to the start of the study, discussions between the sponsor and the FDA said, look, if you're going to do this study, we're worried about mortality, and you have to be able to exclude a certain magnitude of increase in mortality. And the agreement was that the study, in order to provide reassurance about mortality, had to exclude a 50 percent increase in the risk of death and, therefore, at the time of the protocol amendment, the sample size was increased from 3700 to 4300 patients. The whole purpose here, as stated in the amendment, was to achieve a total of 260 deaths.

260 deaths was not the number that would be needed to look for a mortality advantage. It was the number needed to rule out a 50 percent increase in the risk of death. So just to keep that in perspective.

Altogether, there were 4,630 patients enrolled in ATHENA, randomized about 1 to 1, and, in fact, almost all patients were -- had complete follow-up for both all-cause mortality and for the occurrence of cardiovascular hospitalization.

Now, I want to review the primary results in ATHENA in two ways with a particular focus on the fact that this study had two objectives. First was an efficacy objective embodied in the primary end point of all-cause mortality and cardiovascular hospitalization. This efficacy objective was the primary determinant of the sample size in the original protocol.

And as I just mentioned, based on discussions between FDA and the sponsor, there was a key safety objective in this study embodied by the end point of all-cause mortality, and this was the primary determinant of the sample size of the study in the protocol amendment.

First, efficacy. Here are the results of the effects of dronedarone on the primary end point of all-cause mortality or cardiovascular hospitalization. You'll notice there are 917 primary end point events in the placebo group, 734 primary end point events in the dronedarone. There are over 1600 primary end point events in this trial. This difference between placebo and dronedarone was translated into a 24 percent reduction in risk with very narrow confidence intervals and a very small P-value.

If one looks at number needed to treat, treatment with dronedarone resulted in one fewer death or cardiovascular hospitalization for every 12 patients with atrial fibrillation treated with dronedarone for 21 months.

Here are the Kaplan Meier curves for all-cause mortality or cardiovascular hospitalization. There was a -- and you can see these curves separate early, maintain their separation throughout a period of follow-up --

24 percent reduction in risk.

Now, I want to turn from the primary efficacy objective to the primary safety objective. Here is all-cause mortality in the ATHENA trial. 139 deaths in the placebo group, 116 deaths in the dronedarone group. This difference reflected a 16 percent difference in risk. I want to focus, however, on the reason that all-cause mortality was the primary safety objective in this trial. Remember the whole purpose of looking at all-cause mortality, the whole purpose of getting 260 deaths, was to make sure that the upper bound of the 95 percent confidence interval was not greater than 1.5. And you can see the upper bound of the 95 confidence interval was 1.08, comfortably less than 1.5, and providing considerable reassurance that in the ATHENA population this drug is not associated with an increased risk of death.

Here's the Kaplan Meier curves for all-cause mortality, and they reflect the differences that you saw on the previous slide.

So we've got an efficacy objective that was achieved, we have a safety objective that was achieved. The question is, did these outcomes in ATHENA -- did they confirm the results of earlier studies? Did the efficacy objective results confirm the results of EURIDIS and ADONIS? And the answer is yes.

On the top of this slide you see the results on the primary end point in the ATHENA trial on all-cause mortality and cardiovascular hospitalization. On the bottom you see the analysis of this end point for

EURIDIS and ADONIS. I want to emphasize that this doesn't include stroke, as I mentioned earlier. If you want to see what the results are using the ATHENA-like end point, they are at the bottom of the slide. And you can see, if you compare the ATHENA-like end point for death and for cardiovascular hospitalization, there's a 24 percent reduction in risk in the ATHENA trial, a 26 percent reduction in EURIDIS and ADONIS -- so these results are strikingly concordant.

In contrast, the mortality results of ATHENA and ANDROMEDA are entirely discordant. If one looks at the 95 percent confidence intervals -- you have ANDROMEDA on the top, ATHENA on the bottom -- the lower bound of the confidence interval for the point estimate for mortality in ANDROMEDA is almost the same as the upper bound of the confidence interval for ATHENA. So the mortality results of these two trials hardly overlap at all.

So now I want to move the focus of the discussion from the results of -- the primary results of ANDROMEDA and ATHENA to the consistency of the results of ANDROMEDA and ATHENA.

First let me say, before I show you the data on cardiovascular hospitalizations and cardiovascular deaths, that you've received an FDA review which has raised a number of questions about the identification of deaths and cardiovascular hospitalizations by investigators, about the results of the classification of cardiovascular deaths by the steering committee. They have raised questions about operational modifications in the cutoff dates used to

terminate follow-up on individual patients.

We are prepared to discuss any and all of these in great detail. I just want to state now, to reassure the committee, that no matter how you analyze these data, whether you analyze it according to the way that the FDA might prefer or that the sponsor actually did in the briefing document, the results are the same. The results are not changed by doing it by an alternative method.

And in case you have no faith at all in the ability of physicians or investigators to distinguish causation -- and there's a part of me that would share that skepticism -- you might be interested in the results of the analysis of this trial on all-cause mortality and all-cause hospitalization. So if you took every classification in this trial and set it aside and said, if a patient died or was hospitalized, it counts, then there's a significant reduction in risk in the dronedarone group compared with the placebo group.

So with that in mind, I want to look at -- more closely at the composite end point, and I'm doing so for one primary reason. When you have a composite end point, you can't just show the results on the composite; you have to ask the question whether the components of the composite moved concordantly with the overall result on the composite and whether there's any particular component of the composite that drives the benefit. And that would influence your enthusiasm about any finding on the composite end point.

So there are two primary components here. One is cardiovascular

hospitalization and the other primary component is cardiovascular death. As I noted before, both were specified as secondary end points.

First let's look at cardiovascular hospitalization. What you see on this slide is the effect of dronedarone on hospitalization for cardiovascular reason on the top, hospitalization for non-cardiovascular reason on the bottom. And you can see that all of the effect on hospitalization in this trial was, on hospitalization for a cardiovascular reason, 26 percent reduction in the risk of death for a cardiovascular hospitalization, no effect -- no decrease and no increase -- in the risk of hospitalization for a non-cardiovascular reason.

Here are the Kaplan Meier curves, cardiovascular hospitalization on the left, non-cardiovascular hospitalization on the right. Again, an effect on cardiovascular hospitalization, no effect on non-cardiovascular.

Now, breaking down further the components of cardiovascular hospitalization, you can see 859 first cardiovascular hospitalizations in the placebo group, 675 first cardiovascular hospitalizations in the dronedarone group. A big chunk of these hospitalizations were for atrial fibrillation and other supraventricular disorders.

Now, let me emphasize it wasn't just for atrial fibrillation and supraventricular disorders. A lot of the patients who came in for atrial fibrillation or atrial flutter also had other reasons, other cardiovascular reasons, for hospitalizations. They had heart failure. They had myocardial

ischemia. But the investigator on the case report form ticked atrial fibrillation as the primary cause, which led to the analysis that you see on this slide.

Second is the fact that if you look at the tick boxes that the investigator checked as the primary reason for cardiovascularization [sic], for other major reasons for cardiovascular hospitalization, you can see there is a lower risk of hospitalizations related to worsening heart failure, lower risk related to myocardial infarction or unstable angina, and a lower risk related to cerebrovascular events.

I want to focus on the last two, primarily because they represent what -- these two are commonly grouped together as thromboembolic events in those who are at risk of coronary arterial thrombotic events. You can see the results of the ATHENA trial on the left, the results of EURIDIS and ADONIS on the right. Clearly, the confidence intervals on the right are larger than on the left because the number of events on the right are fewer than on the left, but the results are internally consistent for an effect on these thromboembolic phenomenon.

And, furthermore, if you took all of the atrial fibrillation hospitalizations and set them aside and you just asked -- just suppose they were totally ignored and one just asked whether there was an effect of dronedarone on the time to first hospitalization not due to atrial fibrillation and flutter -- this is a post-hoc analysis. I show it to you in

order to show the internal consistency of these results. Then you can see there remains a nominally significant reduction in risk in the dronedarone group.

So now I want to move from cardiovascular hospitalization to the other major component, the other major driver of the effect on the primary end point, which is cardiovascular death. There were 94 cardiovascular deaths in the placebo group, 64 such deaths in the dronedarone group. This represented a 30 percent reduction in the risk of death, with confidence intervals that not embrace 1. You can see the curves separate relatively early and continue to separate throughout the period of follow-up.

Here is the breakdown of the most common reasons for cardiovascular death in the ATHENA trial. Again, 94 placebo, 65 dronedarone. You can see the biggest components of this were, one, sudden cardiac death -- 35 events on placebo, 14 on dronedarone -- and thromboembolic events, stroke, myocardial infarction or unstable angina, pulmonary or peripheral embolism, more events in the placebo group than in the dronedarone group.

So if one looks at the relative risks for the components for the major drivers of efficacy of success on the efficacy end point, we have a 26 percent reduction in the risk of cardiovascular hospitalization, a 30 percent reduction in the risk of cardiovascular death, both with confidence intervals that do not include 1, and both major components of success on the efficacy end point.

I want to add one other thing before going to the final topic, which is that, as Dr. Naccarelli has already said to you, that there is a lot of overlap between elderly patients with atrial fibrillation and patients who otherwise get enrolled in major outcome trials for anti-thrombotic therapy, anti-platelet therapy, interventional procedures, and in these types of patients, there is a different kind of end point which is used in the trial, which is the end point of all-cause mortality and nonfatal stroke and acute coronary syndrome. This is referred to variably as a MACE end point or an APTC end point. And I -- given the importance of this end point in other trials, I wanted to show you what the effect of dronedarone was on this end point in this study.

Here is a -- here is the effect of dronedarone on all-cause mortality, stroke and acute coronary syndrome -- again, a APTC or MACE-like end point -- 262 events in the placebo group, 196 events in the dronedarone group. And this reflected a 25 percent reduction in the risk, which was nominally significant.

Let me also just emphasize that this is really interesting because this difference was seen in favor of dronedarone even though, in this study, more patients had discontinued the use of beta blockers in the dronedarone group than in the placebo group. Remember, a lot of these patients were taking beta blockers. This is dronedarone on top of beta blockers. Because of their synergistic effects on heart rate, there were a greater number of

patients who were pulled off of beta blockers in the dronedarone group compared with the placebo group.

If you believe beta blockers reduce cardiovascular risk, then you would think that the dronedarone group was being placed at somewhat of a disadvantage, and yet, in spite of the differential use of beta blockers post randomization, there was still a reduction in the risk of death and major thromboembolic events in the dronedarone group compared with the placebo group.

And if you focus on stroke or acute coronary syndrome -- and in this slide I tried to define these in every conceivable way, looking at stroke, stroke or TIA, stroke alone, hospitalization for stroke, fatal ischemic stroke. For acute coronary syndrome, I created the groups MI or unstable angina, unstable -- hospitalization for acute coronary syndrome, fatal acute coronary syndrome -- it doesn't matter how you cut this. There is about a 30 percent reduction in risk no matter how you do this analysis.

And, lastly, I want to focus on the reconciliation in the results of ATHENA and ANDROMEDA. You've already heard about all the results of these trials and the uncertainty accompanying the results of ANDROMEDA. But I want to do in this final segment is to assume, for purposes of discussion, that the mortality results of the ANDROMEDA trial are not due to the play of chance. That would be a cautious approach. The question is, how do we identify patients who will benefit from the drug and not be harmed? That's one of the

central questions posed to the advisory committee by FDA.

So at first one might think that it might be hard to distinguish between the ATHENA and ANDROMEDA populations, but the truth is these were very distinct trials, studied very distinct populations and got very distinctly different results.

So a lot of the differences here can be readily summarized -- and I think there's very little disagreement between the FDA and the sponsor on this. If you have non-permanent AF, no symptoms of heart failure, ejection fraction greater than 35 percent, class II heart failure, I think there's general comfort that dronedarone can be appropriately used in these patients.

Conversely, if you have class IV heart failure, you don't have an indication for the use of the drug, if you've been hospitalized recently, within, let's say, the last month for worsening heart failure, you shouldn't get this drug.

So the interesting transition group is the group with an ejection fraction less than 35 percent and the group with class III heart failure because this is the patient population that was represented in both trials. This is the patient population enrolled in ANDROMEDA and enrolled in ATHENA. So there's a small -- small segment, represented by these patients, enrolled in both studies.

So the question is, should dronedarone be prohibited in all of these patients or can dronedarone be used in a specific subset of these patients?

Now, to ask and answer that question, one has to examine what the benefit-to-risk relationship is in patients with left ventricular dysfunction, ejection fraction of less than 35 percent, or who have class III heart failure. So let me talk about benefit first.

But before doing that, let me just say that although it's nice to be able to say that one can distinguish between class II patients and class III patients, that one will let class II patients in and take class III patients out, I don't know anyone who actually feels that they can do that.

It isn't feasible to ask physicians to distinguish patients from class II and class III heart failure. And we see patients all the time who are at class II one day and class III another day. And if you distinguish between class II and class III, does that mean they would be a candidate one day and not a candidate another day? And different physicians classify class II and III differently. I think it would be very, very difficult.

And, similarly, I wouldn't want to distinguish a patient with an ejection fraction of 34 percent from the patient with an ejection fraction of 36 percent, particularly in most laboratories where echocardiography is not even quantifiably carried out.

Furthermore, it wouldn't be appropriate to exclude patients with an ejection fraction less than 35 percent or who have class III heart failure if, amongst these patients, there is an identifiable subset who have a favorable benefit-to-risk relation when dronedarone is used as indicated.

So with this in mind, I want to focus on this particular group of patients and ask about the benefit-to-risk relation.

First benefit. Here is the subgroup analyses of the primary end point in ATHENA. There are many, many of these subgroup analyses. They are all summarized in your briefing document, and they all show the same thing, which is there's an incredible consistency of the subgroup analysis; all the point estimates line up very, very nicely.

I want to call your attention primarily to the last two subgroup analyses, New York Heart Class and left ventricular ejection fraction, and you can see no heterogeneity. Class III patients don't respond any worse than class II patients. Patients with low ejection fractions don't respond any worse than patients with higher ejection fractions. In fact, one can argue that the point estimates are more favorable in these subgroups than in the corresponding groups.

If one looks specifically at the Kaplan Meier curve for the primary end point for ATHENA, class III patients on the left, ejection fractions less than 35 percent on the right, you can see point estimates for benefit in both types of patients and the magnitude of the point estimate is the same, if not better, than seen in the overall study. So there would be no basis for concluding that these patients don't benefit from treatment with the drug.

Now let's look at risk. Remember, the major way that we're looking at risk is all-cause mortality, so let's look at the subgroup analyses of all-

cause mortality. And I show you here subgroup analyses based on five pre-randomization variables. And I selected these five variables because they're the variables that would characterize patients who have class III heart failure and patients with a low ejection fraction.

And you can -- I highlighted in blue the results in the subgroup that represents the patients of interest. And you can see if you have a low ejection fraction, if you have class III heart failure, if you're getting a diuretic, if you're getting a beta blocker, if you're getting an ACE inhibitor, your point estimates for mortality are actually more favorable than if you don't have these characteristics.

And if you don't like looking at point estimates, if you like looking at upper bounds of confidence intervals -- and there are very good reasons to look at upper bound of confidence interval -- I want to just pull out the subgroups on ejection fraction and New York Heart Class, and I want to focus on the upper bound of the confidence interval in these complementary subgroups and point out that the upper bound for the confidence interval for mortality, all-cause mortality, is no worse in the patients with low ejection fraction than the patients with a preserved ejection fraction, 1.2 in both cases. And for New York Heart Class, the upper bound in class III is no worse than in patients with class I or II -- again, a 1.3, 1.4 upper bound in both cases.

So if you look at benefit assessed by the primary end point, it was

similar in the patients with low ejection fraction and in class III heart failure than in the other subgroups. If you look at risk assessed by all-cause mortality, it was not greater, and numerically, this risk was lower in these patients than in other subgroups.

So if you look at the ratio of benefit to risk, it was not less favorable in the patients with a low ejection fraction or those with class III heart failure than in the other subgroups.

So, based on this, I think one can reasonably conclude that dronedarone can be used effectively and safely in a specific subset of patients with a low ejection fraction or with class III heart failure as long as they were ATHENA-like.

So the -- based on all of this, I'd like to summarize the major findings of this presentation. First, the ATHENA trial demonstrated that dronedarone reduced the combined risk of all-cause mortality or cardiovascular hospitalizations in patients with a recent history or recent onset of atrial fibrillation. Both a reduction in cardiovascular mortality and in cardiovascular morbidity contributed significantly to the effect of the drug on the primary end point.

All examined subgroups, including patients with class III heart failure and with a left ventricular ejection fraction of less than 35 percent showed benefit.

Second, the effects of dronedarone in the ATHENA trial differed

dramatically from those in ANDROMEDA. The results of the two studies can't possibly be more different, both with respect to death and the effect on hospitalizations. You can see, looking particularly at hospitalizations, everything that went in the right direction with ATHENA went in the wrong direction with ANDROMEDA.

Third, differences between ANDROMEDA and ATHENA may have been due to imprecision of the estimates of risk due to frequent intramonitoring of a small number of events in the ANDROMEDA trial. And the ANDROMEDA trial had a very small number of events, short duration of follow-up, no monitoring -- didn't specify monitoring boundaries that accounted for multiplicity analyses, did frequent interim looks after one to two deaths, terminated the trial early. All of these are characteristics that are known to increase the imprecision of estimates and decrease the reliability of a finding.

Fourth, differences between ANDROMEDA and ATHENA may have been due to the fact that there was virtually no overlap in the types of patients enrolled in the two studies. And you can see here essentially the totally separate universes of patients represented in the two trials.

And even in the patients who are, quote, the small overlap population, those with a low ejection fraction and those with class III heart failure, they're different. The ATHENA patients were clinically stable and had non-permanent atrial fibrillation. The ANDROMEDA patients were recently unstable and didn't have a proposed indicated for treatment with dronedarone.

So, in summary, if one wanted to devise an evidence-based way of separating the patients who would benefit from dronedarone from those who might be harmed by the drug, it would appear that it could be summarized in this slide. For the vast majority of patients, there is no disagreement. The drug is beneficial in ATHENA-like patients and it may be harmful in ANDROMEDA-like patients.

In the overlap population, those with an ejection fraction of less than 35 percent and class III heart failure, if you're clinically stable and have an indication for the drug -- clinically stable meaning you haven't been hospitalized for heart failure and you haven't developed class IV symptoms in the last month, then you are an ATHENA-like patient and you benefitted from treatment with the drug and you were not harmed in the ATHENA trial.

Conversely, if you had these characteristics, you didn't benefit from dronedarone in the ANDROMEDA trial, and there was a meaningful concern about an increased risk of death.

I think these two trials, probably better than most applications that the committee gets to see, define the appropriate and inappropriate use of this drug for the proposed indication.

I now would like to go on to the next presentation, focusing on safety, by Paul Chew.

DR. CHEW: Good morning, Mr. Chairman, members of the committee, FDA, ladies and gentlemen. The safety profile of dronedarone has been

extensively studied in a broad range of patients with atrial fibrillation and flutter. The presentation will focus on the target population of patients with a recent history of atrial fibrillation or current non-permanent atrial fibrillation in whom dronedarone has demonstrated a favorable profile -- safety profile.

The safety data consists of two comparative trial data sets, comparing the proposed therapeutic dose of dronedarone, 400 milligrams BID, with both placebo and amiodarone. The placebo control data set pools data from five trials, focused on patients with a recent history or current non-permanent atrial fibrillation or flutter. The trials are ERATO, DAFNE, EURIDIS, ADONIS and ATHENA, which are described in the briefing package.

The mean follow-up in these studies was 12.7 months, representing more than 3600 patient years of total exposure. Nearly 2,000 patients were followed for 12 months, 1145 up to 18 months, and 425 for up to two years.

Additionally, the amiodarone control data set consists of a single active comparator study, DIONYSOS, a study specifically requested by European health authorities. The study was just recently submitted to FDA which has not reviewed the data. In this study, the median exposure was about seven months.

For this study, as well as the studies in the AF/AL pool, investigators were instructed to report any relevant clinical or laboratory events. These were defined by the clinical judgment of the investigators, and

these safety events were not predefined.

A review of adverse events by system organ class shows that adverse events were more frequent with dronedarone compared to placebo, 70.4 percent versus 67.5 percent.

The yellow highlighted lines show other imbalances seen with dronedarone in GI disorders, general disorders, mainly reports of fatigue and asthenia, investigations, mostly reports of increased measurements of creatinine and electrocardiograms, cardiac disorders, bradyarrhythmias and QT prolongation, and skin disorders, mostly non-serious rash.

In green is shown disorders associated typically with amiodarone. There was no imbalance versus placebo with dronedarone on any of these system organ classes, notably the nervous system, respiratory, eye disorders, hepatobiliary or endocrine.

The most common adverse events and the most common cause of discontinuation with dronedarone was related to GI disorders. The most common GI event was diarrhea. The majority of the GI events were tolerable, as evidenced by the discontinuation rates of 3.2 percent for dronedarone and 1.8 percent for placebo. These events were typically observed early, within the first week or two of starting treatment, and generally not considered serious or medically important by the investigator.

I'll now turn to renal events. While there were no increases in the rate of renal system organ class events reported by the investigator, there

were some specific renal findings. There were more reports of renal events for dronedarone compared with placebo, driven mainly as a result of increases in blood creatinine.

In order to capture any potential renal signals, we employed a specific database query method, the standard MedDRA query, or SMQ, which utilizes a standardized list of adverse event terms to cluster events of potential clinical concern -- in this case, acute renal failure. So you can see renal failure and acute renal failure are within this net because they may be reported that way individually.

Renal failure events were infrequent and most often not considered serious or medically important and did not require discontinuing therapy.

In ATHENA, serum creatinine was assessed systematically in the treatment period. In ATHENA, there was an early increase of about 10 micromole per liter on the left, or approximately a 0.1 milligram per deciliter, shown on the right, in serum creatinine seen by two weeks, day 14. Mean serum creatinine remained stable throughout the treatment period of up to two years.

This finding is consistent with the preclinical and clinical studies with dronedarone which showed inhibition of the LCT2 renal tubular transporter, a phenomenon which has also been observed with other agents, such as cimetidine and trimethoprim.

In these studies, there was no associated decrease in glomerular

filtration rate, indicating that the increase in serum creatinine was due to tubular secretion decrease -- and this is also described in the briefing book.

In DIONYSOS, the comparative study with amiodarone, systematic follow-up of serum creatinine was obtained in nearly all patients randomized. This was a double-blind study. Following end of treatment up to 12 months, there was a prompt return to baseline for dronedarone, shown on the right in blue.

Of particular importance in this population is the safety of a treatment in terms of its effects of electrophysiologic and clinical cardiac events, beginning with bradyarrhythmias. Consistent with the known calcium antagonists and antiadrenergic properties of dronedarone, there were more bradycardia events compared to placebo. QT prolongation was also more often seen with dronedarone.

Three studies included patients with normal sinus rhythm at baseline who underwent systematic EKG monitoring at every visit. On average, there was an increase of about 10 milliseconds in the corrected QT which was observed for dronedarone, consistent with its class III effect.

In the three placebo-controlled trials, bradycardia was often seen with -- more often with dronedarone, using the cut points above, less than 50 beats per minute and a decrease of greater than 15. And there were more reports of QT prolongation evidenced here by the QTs above 500 or changes more than 60 milliseconds from baseline.

In placebo-controlled trials, the incidence of ventricular tachyarrhythmias was low with no increase seen with dronedarone. There was one case of a nonfatal torsade reported with dronedarone in a woman with a baseline QT of greater than 500 milliseconds -- QT corrected. She discontinued dronedarone therapy and, after several months following discontinuation, this patient had ventricular tachyarrhythmia, as noted on the telephonic monitoring of her implanted cardiac defibrillator, indicating underlying disease.

Thyroid events were uncommon in the placebo-controlled trials and balanced between treatment groups. Remember that the rationale for modifying dronedarone to contain no iodine was specifically to avoid this problem of thyroid events. Hyperthyroidism, induced by amiodarone, is a very difficult condition to treat.

Another important difference in the chemical structure of dronedarone is its relatively low lipophilicity, a feature designed to reduce the risk of other events associated with amiodarone, such as neurologic events. Indeed, in placebo-controlled trials, the incidence of dronedarone neurologic events was low and comparable to placebo.

Another potential concern observed with amiodarone is interstitial lung disease. In the pooled studies, pulmonary events were very uncommon and well-balanced between treatment groups. In the ATHENA study, there was one report of a fatal diffuse infiltrating pneumonia with respiratory failure of

unknown etiology in a 72-year-old Asian woman who previously had been treated for two years with amiodarone before receiving nine months of dronedarone therapy after a one-month washout. Based upon what is known for amiodarone, interstitial lung disease may take time to occur.

Sanofi-aventis plans specific risk management activities to assess dronedarone's pulmonary safety, including epidemiologic database studies to maintain increased vigilance for any potential increase of these events.

We've also looked at hepatic events. In placebo-controlled trials, hepatic adverse events generally were balanced, with some increase in overall adverse events for transaminase increases with dronedarone, but no increase in serious events or those leading to discontinuation.

On this slide is shown patients who had an ALT greater than three times the upper limit of normal and a total bilirubin of greater than two times the upper limit of normal, because these patients may be at greater risk for hepatic injury.

The methodology employed to identify these cases included review of all clinical trial lab data for studies where LFTs were systematically collected throughout the studies, ERATO, EURIDIS, ADONIS, DAFNE and ANDROMEDA, combined with a manual review of all serious hepatic adverse events from all studies to identify cases that may have been identified upon ad hoc testing for adverse events.

There were cases reported on dronedarone, amiodarone and placebo

meeting these criteria with the respective incidence rates per patient year as shown above.

To provide some context for the dronedarone safety profile, DIONYSOS included directed evaluation of specific safety events of interest, based on the known safety profile for amiodarone.

This is shown -- the safety events of interest -- and in the dronedarone arm there was less thyroid, less hepatic, neurologic, skin and eye events. In this trial, there were no pulmonary events noted in either group. Gastrointestinal events, diarrhea, vomiting and nausea, were more frequent in the DIONYSOS trial with dronedarone, consistent with the previous experience in the other studies.

Beyond examining specific organ systems, we also evaluated potential drug-drug interactions by examining relevant adverse events. I'll review beta blockers, digitalis and oral anticoagulants.

The format for the next several slides is the same. On the left are shown are the specific events of interest with the number of patients. In the middle is the relative risk of these events with or without the specific drug or class -- in this case, beta blockers. And on the right are the P-values for a potential interaction, and a plot of relative risk and their confidence intervals.

In dronedarone-treated patients, there was an increase in bradycardiac events with concomitant beta blockers, but importantly, there was

no increase in heart failure or hypotension noted in terms of an interaction.

We also looked at digitalis because dronedarone inhibits the PGP transporter which is involved in the renal secretion of digitalis. And, therefore, in the placebo-controlled trials, there was a possibility of increased digoxin levels and intoxication reports.

As you can see here, there was more digitalis intoxication noted in patients receiving digitalis, at baseline in the upper middle of this slide, compared to patients who did not received digitalis at baseline but who may have subsequently started digitalis.

But, importantly, there was no significant interaction noted in GI events, bradyarrhythmias or ventricular arrhythmias between these groups.

Digoxin levels were systematically assessed in ATHENA. The mean change from baseline, 0.2 to 0.4, occurred early and plateaued with dronedarone.

In DIONYSOS, investigators were instructed to halve the dose of digoxin upon initiation of study treatment with no reports of toxicity in that trial.

In ATHENA, there was no increase in bleeding risk or INR levels. I'm showing here the INR levels, but there was also no interaction with dronedarone in terms of hemorrhage or anemia. INRs were very comparable with placebo throughout the study.

The key identified risks are use in atrial fibrillation/flutter

patients who have symptomatic heart failure at rest or with minimal exertion within the last month, or hospitalized for heart failure within the last month.

Contraindicated concurrent medications that could result in serious drug-drug interactions, specifically potent CYP3A4 inhibitors, other anti-arrhythmic agents, especially those that could prolong QT, and the management of the known increase in serum creatinine.

The following are potential risks that are being addressed via specific labeling recommendations and/or enhanced pharmaco-vigilance. Concurrent medications requiring caution: Digoxin -- I did not go over statins, but it's a cautionary note that, being a CYP3A4 inhibitor, that we will be taking precautions on the instructions and the use of statins -- as well as the amiodarone-like effects.

The first and fundamental step of the risk management will be to provide appropriate safety recommendations in the label.

We propose the following recommendations that will be further discussed with FDA: To avoid starting dronedarone in patients with the symptoms of heart failure with minimal exertion or at rest within the last month, or who were hospitalized for heart failure within the last month; to avoid the concomitant use of medications that could result in serious drug-drug interactions; to be aware of the effect of dronedarone on serum creatinine; for those needing digoxin, to decrease the digoxin dose by 50

percent at the initiation of dronedarone and to further monitor digoxin plasma levels; for those needing statins, use the statin per the respective label dosing recommendation when used with a CYP3A4 inhibitor; and to monitor for clinical signs of muscular toxicity.

And, finally, beyond labeling, we have designed a thorough risk management plan, designed to help assure the appropriate use according to the product label.

Based on the identified and the potential risks, the program includes a medication guide, a comprehensive communication plan for health care providers and targeted educational tools. Importantly, also an assessment program based on knowledge, attitude and behavior surveys, a post-marketing surveillance plan that includes enhanced pharmaco-vigilance activities to facilitate medical review and signal detection, epidemiologic case control studies to evaluate amiodarone-like effects and potential drug-drug interactions.

The education and communicate plan targets all the stakeholders involved in the management of patients with atrial fibrillation.

In conclusion, the safety has been well-characterized in the dossier in over 3200 patients with a mean follow-up of more than a year. GI symptoms, predominantly diarrhea, were mild to moderate. The increase in creatinine with a mean level of about .1 milligrams per deciliter, plateaued early after about 14 days and was reversible. Bradycardia was mild to moderate. Skin

rashes were mainly nonserious.

There are predictable interactions. We've discussed today beta blockers and digoxin. Although we have not discussed statins, we will be vigilant for those and will have specific instructions.

We believe that the identified and the potential risks characterized by the safety review to date are manageable ones with appropriate utilization of labeling and risk management tools.

And with that, I'd like to introduce Professor Camm.

DR. CAMM: Dr. Harrington, members of the committee, FDA representatives, ladies and gentlemen, I'm well aware of the shortage of time, so I will do my best to abbreviate my talk. You have my slides that I hope that you can follow.

Firstly, I'd like to introduce myself. My name is John Camm, and I am the head of cardiac and vascular sciences at St. George's University of London in the United Kingdom. I work at St. George's Hospital where I am a general cardiologist and a cardiac electrophysiologist. A large part of my work, of course, is looking after patients with atrial fibrillation.

I'm much involved in assisting the National Health Service to draw up patient care pathways for patients with atrial fibrillation, and I'm part of the NICE guideline on atrial fibrillation, and I'm chairman of the European Society of Cardiology forthcoming guidelines on atrial fibrillation.

In addition to that, I am the president of the Arrhythmia Alliance

and a founding member of the Atrial Fibrillation Association, which are, respectively, international and U.K. patient and care advocacy groups.

I've been asked by the sponsor this morning to summarize the benefit risk of dronedarone when used in the indication under discussion.

Firstly, I'd like to remind you that atrial fibrillation is very common. Those of you who are clinicians will know that your hospital beds and your outpatient clinics are more and more filled with patients coming with atrial fibrillation.

Theoretically, there are about 2-1/2 million Americans with this problem at the moment, and it's forecast that it may rise to as many as 15 million by the year 2050.

Importantly, both patients and doctors appreciate that this is not just a problem of palpitations. It is a condition associated with serious cardiovascular outcomes, an increased mortality, increases in hospitalizations, increased stroke rate and increased heart failure.

Very importantly, this condition is a major public health risk, and it's also important to public health finances because it consumes approximately 1 to 2 percent of health care budgets, mostly on hospitalization costs.

There is a serious unmet medical need, not only in thromboembolism, rhythm control and rate control, but very importantly with regard to the major cardiovascular outcomes associated with atrial fibrillation, none of which

have been successfully addressed by the conventional anti-arrhythmic drugs which we have available.

Against this unmet need, I think we should recall the major identified benefits associated with dronedarone. Dronedarone prolonged the time to first cardiovascular hospitalization or death, the primary end point of the ATHENA trial, and it reduced this outcome by 24 percent, an effect which was consistent across all major subgroups.

There was also a numerical reduction in all-cause mortality, but it was not statistically significant, but very important the upper bound of the confidence interval at 1.08 makes it very unlikely that this drug will be associated with increased mortality when used in the appropriate indication.

There are also exploratory analyses which showed marked reductions of all -- and cardiovascular hospitalization -- cardiovascular and sudden cardiac death.

Of course, this drug is also a conventional anti-arrhythmic agent. It's been shown to be effective both at rhythm control and rate control. In rhythm control terms, it delays the recurrence of atrial fibrillation decreases symptomatic episodes of atrial fibrillation, and reduces the number of AF episodes over time.

With regard to rate control, it decreases the ventricular rate response to atrial fibrillation both during atrial fibrillation recurrences and during permanent atrial fibrillation -- and that effect is seen on top of

standard rate control treatment.

When considering dronedarone as an anti-arrhythmic agent, I think you have to recall that physicians have a limited choice of other anti-arrhythmic agents. In most jurisdictions, this amounts to about five drugs: flecainide, propafenone, dofetilide, sotalol and amiodarone. I think all of the clinicians will know that these drugs are all associated with significant adverse events. For example, the class Ic drugs with the possibility of ventricular pro-arrhythmia, conversion of stable atrial fibrillation to uncontrolled atrial flutter, the aggravation of heart failure, for example.

Dofetilide and sotalol are often responsible for torsade de pointes. Sotalol may aggravate heart failure and exacerbate asthma or COPD. Amiodarone has a large catalog of multi-organ toxicities.

Most of these liabilities are seen much less frequently with dronedarone. But, of course, dronedarone itself has adverse safety signals. It does have GI side effects, nausea and diarrhea in particular. Generally, these are not dangerous. They occur relatively early, and they are manageable.

The increase in serum creatinine, which was puzzling and confusing at first, is now well-characterized. It's not due to renal toxicity, and it's managed relatively easily.

Drug-drug interactions have been extensively studied, and I believe that they can be managed.

The multi-organ toxicities seen with amiodarone-like toxicities are something that will require further investigations, and they will be further evaluated during a post-approvals phase.

There is, of course, unstable heart failure, recently unstable heart failure, which is a major problem, and these patients must clearly be avoided.

But having said that, I think that we should observe that this drug does address a major unmet medical need. Not only would it allow the treatment of atrial arrhythmia to be effectively and relatively safely undertaken without the liabilities which we are familiar with other anti-arrhythmic drugs, but more importantly, it will allow an improvement of cardiovascular outcome. So beyond merely reducing atrial fibrillation recurrences, we hope that it will impact on cardiovascular risks such as coronary events and strokes.

And this, of course, is the first anti-arrhythmic drug to reduce the combined risk of cardiovascular hospitalization or death.

What does this mean to the patient? I think the absence of pro-arrhythmic risk means that this drug may be initiated as an outpatient. The single-dose regimen and the lack of deleterious impact on oral anticoagulant management means that this drug has a potential for better compliance and adherence.

The decrease in AF and cardiovascular hospitalizations can be achieved, I believe, without an increased risk of mortality.

So I'd like to quickly address which is the right patient for dronedarone. I think that this is best viewed in terms of the two major studies that have been reviewed in detail this morning. The appropriate patient, I believe, is a patient with a recent history of atrial fibrillation or current atrial fibrillation which is non-permanent in nature, and in patients who have associated cardiovascular risks, and these were the patients that were recruited to the ATHENA trial, and these seem to have an excellent benefit risk.

The inappropriate patient is characterized by, one, has symptoms of heart failure at rest or with minimal exertion, or who has been hospitalized for heart failure within the last month. Such patients were recruited to ANDROMEDA, and there the benefit risk is poor.

So let me conclude, Dr. Harrington, by stating that the benefit risk for dronedarone in the treatment of appropriate patients is uniquely positive, and the appropriate patient is described in the indication, which reads, Multaq is indicated in patients with either recent history of or current non-permanent atrial fibrillation or flutter, and with associated risk factors because Multaq has been shown to decrease the combined risk of cardiovascular hospitalization or death.

Thank you. This concludes the presentation for the sponsor.

DR. HARRINGTON: Thank you, Professor Camm.

So the sponsor had stuck to their assessment that they would get

done by 10:00 a.m. That gives us about 15 minutes for questions from the panel before we take a brief break and then hear from the FDA. I will remind the panel that we will have a substantial amount of time after the FDA speaks to also ask additional questions of the sponsor, and we have this afternoon.

I want to be fair to everybody, so please -- I think you have an indicator on your microphone and Elaine will keep track of you, and I'm going to go one at a time.

So, Jim, why don't we start with you, and then Sanjay.

DR. NEATON: I have two questions and a request of the sponsor. So both Dr. Naccarelli and Camm I thought made a convincing argument about the importance of looking at morbidity and mortality -- you know, the effects of dronedarone on morbidity and mortality apart from AF. And I just wonder, then, if that's the case, if that's the thrust of your goal, why did you include AF hospitalization in your end point?

The second question -- and you can address both of them after you hear the second one, I guess -- I think the arguments laid out by Dr. Packer on a chance finding for the DIONYSOS trial are pretty convincing, and I think you cannot rule out chance. And reasons that perhaps we can discuss later for some of the subgroups, I think the argument that these are really different populations doesn't sit very well with me.

And if you think this is a chance finding, then I would like to see the sponsor look at the tables which are produced on page 99 of your report

where you've summarized the results over all your trials for your primary end point and for all-cause mortality, to include ANDROMEDA.

And I think the -- going back to the first part of my question in which you eliminate the AF hospitalizations, I think that summary or that trial overview should be done without that outcome in the primary composite.

DR. GURAL: In response to your question, maybe I will ask Dr. Packer to address the concerns raised about the inclusion of hospitalization for AF.

DR. PACKER: Yes. Jim, the real question is, if you're looking at major outcomes, how do you go about doing that? No one argues that mortality is important, so it's always included. And it's not only included because it's clinically important, but because of the issue of competing risks.

In -- there is a philosophical difference in how outcomes are looked at by individuals interested in coronary artery disease and in individuals interested in heart failure. Individuals interested in coronary disease and acute ischemic or thromboembolic events focus on hospitalizations of a certain type, usually for thromboembolic phenomena, whereas the heart failure specialist sometimes focuses on hospitalizations for heart failure or all cardiovascular hospitalizations.

Regardless of which approach you look, the threshold is still a hospitalization threshold. And the question is, what kind of cardiovascular hospitalization one wants to focus their attention.

Largely, that's determined by what you think your drug is capable of doing.

DR. NEATON: I agree. I mean, I'm just questioning the logic, based on what I heard in the introduction and in the final comments, of why you would include AF hospitalization in your primary end point.

DR. PACKER: The major reason for doing that is when people come in for a cardiovascular reason, that includes atrial fibrillation. It's not just for atrial fibrillation.

I tried to make that point. It's a very difficult assessment. If someone comes in to the hospital and has atrial fibrillation and pulmonary edema, severe heart failure, what was the -- did they go into the hospital because of the atrial fibrillation or the heart failure? The same -- they come in with atrial fibrillation and unstable angina; they come in with atrial fibrillation and a stroke.

I don't know how to make those decisions clinically. And, of course, our preference would be to say that regardless of how you categorize the hospitalization, it's still really important to the patient.

DR. NEATON: I agree the hospitalization is important to the patient. It's important to cost. But it doesn't get at directly as to whether a drug that reduces that, you know, incidence of atrial fibrillation has an impact on morbidity and mortality outside of that.

And you made some arguments based on blood pressure. The sponsor

made other arguments in his presentation based on other potential mechanisms of action. And it just doesn't seem to be logical, then, if you believe that, to define the trial outcome the way you did.

DR. PACKER: The only reassurance, I think, that one can give is that if you took out -- one could argue that maybe one ought to have prospectively taken out of the equation all hospitalizations where there was only atrial fibrillation, and particularly those in which there was a hospitalization only for atrial fibrillation for cardioversion, for example.

Let me just assure you that if you took all of those out, the results would not be changed either in terms of magnitude or statistical significance.

DR. NEATON: But you did try to take some of them out, and they actually did change quite a bit.

DR. PACKER: Not quite, because the analysis that you saw took out all hospitalizations for atrial fibrillation, including atrial fibrillation associated with heart failure, atrial fibrillation associated with unstable angina, myocardial infarction.

If you took out just the atrial fibrillation that led to cardioversion, there would be no material effect on the magnitude.

DR. HARRINGTON: Dr. Kaul?

DR. KAUL: Thank you, Bob. I have questions regarding efficacy for Dr. Naccarelli. I'll break it into three parts. Is 10 to 15 percent better

performance in maintaining normal sinus rhythm at short-term follow-up compared with placebo clinically important despite a statistically significant difference, especially given the attrition in treatment effect over time?

The second question I have is, is 50 percent loss of efficacy with dronedarone acceptable to obtain a nonsignificant 22 percent superior tolerability compared with amiodarone based on the DIONYSOS trial?

And the third part is, did dronedarone improve symptoms in ATHENA? Signs and symptoms of heart failure, edema, fatigue and dyspnea seem to go in the wrong direction despite reduced hospitalizations for congestive heart failure.

DR. NACCARELLI: Well, the first question was basically -- you're asking the question of the overall efficacy -- and if we could put the slide on, this was the primary end point of first recurrence of atrial fibrillation. And this was looked in multiple ways, symptomatic recurrence and all, and basically the data looks the same.

And this is a modest decrease -- and I think we would agree with that. But it's statistically and, I think, clinically meaningful. And I think it would be very similar -- and we don't have active control data against flecainide, propafenone, sotalol, dofetilide -- which are the other options -- but very similar to what we're used to seeing with all of other agents we use, short of amiodarone.

And one should also keep in mind that there were several hundred

patients enrolled in this trial who had prior exposure to amiodarone. So, you know, the -- you keep adding layers of therapy, you know for any new drugs. So this was in spite of patients being on amiodarone, you saw this effect.

So I do think this is clinically meaningful. I think it gives an option to treating our patients with another therapy if we exclude some of the issues, you know, related to ATHENA.

Now, the second issue -- I think you said that amiodarone was more effective in DIONYSOS in preventing recurrences, and so how does one weigh, I guess, the risk or benefit of amiodarone would be more likely to prevent a recurrence against dronedarone -- we have data to show that it would prevent hospitalization and the composite of mortality and cardiovascular hospitalization?

I think that the other thing that is not shown here is, of course, the long-term ravages of taking amiodarone. This was a short, six-month study. And anyone who has used amiodarone knows that although efficacy is higher than with the other drugs -- and arbitrarily the best we could say is it works two out of three times; everything else works one out of two times -- that, over time, the discontinuation rates for amiodarone are very high, as you know. And the vigilance that it takes, and the cost, the concerns of pulmonary toxicity, hepatic toxicity, neuro toxicity is high. And patients have to be discontinued. Hyperthyroidism, you know, is somewhat catastrophic in these patients.

So I think that, basically, a clinician would have to make that decision on a case-per-case basis on what's most important, you know, to chase.

I would make the argument that if we had this therapy as an option, that would work in half the patients, why not try that first, going for the secondary end point versus exposing the patient -- so as a patient advocate -- exposing the patient to a potentially more toxic drug that may have a better symptomatic recurrence short-term, but long-term may have some other problems. So I think there's a way of decreasing exposure.

The last question, I think we're going to have Milton -- because he's more familiar with the data.

DR. PACKER: Sanjay, before I address your question, Jim, I realize that you had asked two questions, and I didn't address -- just very briefly, I share your skepticism about ANDROMEDA, and that's why I described the factors that would lead to feeling uncomfortable that that's a definitive finding.

The problem is, how does one possibly proceed, given the fact that you've got this persuasive effect in ATHENA and this unpersuasive effect in ANDROMEDA? I can think of only two reasons. One is that you can go and do ANDROMEDA again. Or you can just assume that ANDROMEDA is real and try to describe, as accurately as you can, the differences in the population and make the assumption that there is benefit in one and detriment in the other, realizing that that assumption is not -- you know, it's trying to describe the

differences. Do you see what I'm saying?

DR. NEATON: My point simply is that I think there's a real possibility it's a chance finding, and I accept that -- and I think that was one of your arguments. And if that's the case, when you do the pooled analysis for the effect of the drug on all-cause mortality and first cardiovascular hospitalization or all-cause mortality, I want to see it included in that analysis.

DR. PACKER: Right. And we'll get that for you. Jim, let me just say from a clinical point of view, trying to distinguish between ANDROMEDA and ATHENA, the driving distinction here is how patients got into the trial. So the rational distinction is to be empiric as opposed to be inventive.

The biggest difference between the two studies is that clinically patients who were recently unstable were positively enrolled in ANDROMEDA. You had to be clinically unstable to get into ANDROMEDA. If you were recently clinically unstable, you were excluded from ATHENA. That's a very hard distinction between the two, one that is prospectively defined in the respective protocols.

Let me just add one thing. And it's not -- and it makes sense from a clinical point of view. There's one other class of drugs in the area of heart failure that, as clinicians, we say it's okay to give it in patients with class III and bad heart failure as long as they're clinically stable, and it's not okay to give it if they're recently clinically unstable -- and that's

beta blockers.

DR. NEATON: I guess -- I won't belabor this, but to push that argument, it certainly raises the question, what do you do when the stable patient becomes unstable six months later?

DR. PACKER: And I would like to show you the data that pertains to that, but now I'm feeling guilty about Sanjay.

Mr. Chairman, what would you like --

DR. HARRINGTON: Yes, so that is a question that I think we're going to have to come to in the course of the day. What I'd like to do, in the interest of time, is get to Sanjay's question. Let's hear from the FDA --

DR. PACKER: Perfect.

DR. HARRINGTON: -- and then we can -- we'll have about an hour for questions in total.

Bob, do you want to go ahead first?

DR. TEMPLE: I just wanted to ask probably, Milton, one question. I perceive some disagreement between what Dr. Camm said is the inappropriate population and what Milton said is the inappropriate population. Dr. Camm basically said leave out people with heart failure at rest or minimal exertion -- translates roughly to class III or IV to me. You emphasized that even class III might be okay if they weren't acutely unstable.

So I think you've said two slightly different things, and I just wondered what you think.

DR. PACKER: I think that the -- there is no difference, but I understand why there might be the perception of a difference. It depends on --

DR. TEMPLE: Probably that the words were different, huh?

DR. PACKER: Right. Well, all of these words have a history. The -- the fact is that -- here's the goal. The goal is to be driven by the precise language in the two protocols. So, again, the idea is to be driven the paper record and not look at it post-hoc.

So the paper record is, if you were class -- at rest or minimal exertion which, by the way, to a heart failure physician means class IV -- class III is not symptoms at minimal exertion. Class III is symptoms on less than ordinary exertion.

Look, I didn't invent this, so -- please. And I am certainly not going to defend the New York Heart Association in this.

DR. TEMPLE: No, but it's just that you emphasized that even people with pretty marked heart failure, if they weren't acutely unstable --

DR. PACKER: That's the point.

DR. TEMPLE: -- did okay.

DR. PACKER: That's the point. It's --

DR. TEMPLE: Whereas the acutely unstable ones in the ATHENA study were the ones who did badly.

DR. PACKER: And that's exactly the point. The analogy here, if you

read the protocol, is an analogy very similar to beta blockers. For beta blockers and heart failure -- we treat some awfully sick patients, but we make sure they're clinically stable before initiation of therapy.

We specifically say that if you have been clinically unstable -- you've got to be clinically -- you've got to be stabilized before starting treatment with a beta blocker.

Now, the analogy with beta blockade is not just an analogy of convenience. This is a drug that has antiadrenergic effects. And so it's sort of --

DR. TEMPLE: No. The point --

DR. PACKER: -- beta blocker-like.

DR. TEMPLE: The point is well-taken. I understand --

DR. PACKER: Yeah.

DR. TEMPLE: -- that you're saying the acute instability is the hallmark, not necessarily the sort of underlying severity of disease.

Anyway, we can talk about it later.

DR. PACKER: It is the instability -- recent instability which is the hallmark.

DR. HARRINGTON: Sanjay, is your question a quick one?

DR. KAUL: Well, I had this question about did dronedarone improve symptoms in ATHENA? I mean, signs and symptoms of heart failure went in the wrong direction. Dr. Naccarelli's slide 23 indicated that one of the

beneficial mechanisms might be related to improvement in symptoms. And the last amendment in the ATHENA protocol included collection of symptoms.

So do you have any data to show us whether it improves symptoms?

DR. HARRINGTON: So let's take that as the last question. If you could provide a brief answer, then we'll break for 15 minutes.

DR. PACKER: A brief answer?

DR. HARRINGTON: I know it's tough, Milton, but brief answer.

DR. PACKER: Sanjay, can I just make sure that we understand what you mean by symptoms. There are symptoms in ATHENA related to atrial fibrillation and flutter and there are symptoms related to heart failure.

DR. KAUL: Both.

DR. PACKER: Okay. With respect to symptoms -- it's not a short answer.

DR. HARRINGTON: Why don't we do this. Why don't you -- I suspect you have a slide on this. Why don't you have your slide teed up. We'll go ahead and take a 15-minute break, and then when we come back at 10:30, you can start with that, and then we'll turn to the FDA.

(A recess was taken from 10:16 a.m. until 10:31 a.m.)

DR. HARRINGTON: We're going to begin -- we were left hanging with a couple of questions, and the sponsor has responses to three, and we've agreed that they will show two pieces of data now and answer Dr. Kaul's question. Then there's a third question that some of this might be worked out in the

course of the FDA discussion. We're going to wait until the FDA presents before we get into that issue.

So the two pieces of data.

DR. GURAL: First, as it pertains to death across all studies, I'll ask Dr. Packer to address that concern from James. Okay. Thank you.

DR. HARRINGTON: So this is Jim's question on death -- the combined trials in death.

DR. GURAL: Yes. Exactly.

DR. PACKER: Could I have the slide up, please.

Jim, this is what you were asking for. This is a meta analysis of death across all placebo control trials. It includes ANDROMEDA. And you can see, putting -- and the assumption here, like in any meta analysis, is we're going to assume here that there's no meaningful heterogeneity of the response because, if there were meaningful heterogeneity, the point estimate would be an oversimplistic way of looking at the data.

We have not looked at heterogeneity in this analysis, so just to let you know, what you're seeing is a point estimate which assumes that the results with ANDROMEDA may, in fact, be the play of chance and, therefore, it can be reasonably summated with the results of other studies. Is that fair?

DR. NEATON: Yes, I think that's fair, but I think it's probably also fair -- and see if you agree -- that it's quite unlikely that if you were asked the question about heterogeneity in these six studies, the result would

be certainly not statistically significant, and so that you're kind of left kind of with the overall --

DR. PACKER: Well, to add further entertainment value, heterogeneity is a low power test.

DR. NEATON: Right. And so -- but basically -- I just wanted to kind of see the point estimate there and the upper bound, the 1.18, which is still within your bounds for safety, but certainly shows less of a hint toward any potential benefit.

DR. PACKER: And that's the whole point. What we're seeing on all-cause mortality is neither a favorable nor an unfavorable effect on all-cause mortality.

DR. KAUL: I just want to follow up on this.

DR. HARRINGTON: Go ahead.

DR. KAUL: Can I have the slides back?

DR. HARRINGTON: Sure.

DR. KAUL: Actually, I reproduced the results using a fixed effects model and justified on the basis of an insignificant heterogeneity P-value, P-value of .24, and your caveat is well-taken.

But there is substantial clinical heterogeneity between the am versus the other five trials. And one could conceivably justify doing a random effects model, which I've done, and the risk ratio is 1.11 point estimate, going from .71 to the upper bound of 1.72.

DR. PACKER: On the random effects model.

DR. KAUL: Random effects model.

DR. PACKER: Okay. The -- I mean, let me just -- Sanjay, I need to emphasize, we're not -- we would not want to say that -- first of all, if you think you have that much clinical heterogeneity, a random effects model does not fix the problem. If you think you have that much clinical heterogeneity, my personal opinion is you shouldn't be doing a meta analysis that pools the results in the first place.

So I don't think that a random effects model -- all a random effects model does in this situation is it widens the confidence interval to a degree which I think both statistically and clinically is totally inappropriate.

So we wanted to address the issues, Jim -- I mean, I'm just assuming that in this analysis ANDROMEDA is a fluke.

DR. HARRINGTON: So let's get on to the other question which has to do with the symptoms and the measurement thereof.

DR. GURAL: Yes. Dr. Gaudin will answer these questions on AF recurrence.

DR. GAUDIN: Good morning. Christophe Gaudin. I'm head of cardiovascular clinical development at Sanofi-aventis. During the trial we documented and analyzed the recurrences of atrial fibrillation or atrial flutter, the cardioversion that occurred during the trial as well as the heart rate that visits -- plan visit of a trial.

For recurrence, we look at patients who were in sinus rate at baseline and the Kaplan Meier analysis of this recurrence show a hazard ratio of 0.75 P-value less than 0.001 with 950 events in the placebo group and 779 events in the dronedarone group.

Next slide, please.

Time to first electrical cardioversion was also analyzed and showed a hazard ratio of 0.68, a P-value less than 0.001, 481 events in the placebo group, 339 events in the dronedarone group for this end point.

Next slide, please.

Looking now at heart rates, we differentiated patients depending on -- at the time of collection of this information, whether they were in atrial fibrillation, in atrial flutter or in sinus rate, and observe in all situation a difference between dronedarone and placebo group, a difference which was about eight beats per minute for patients when they were in atrial fibrillation or atrial flutter, a difference of 3.5 beats per minute when they were in sinus rate.

DR. GURAL: Mr. Chairman.

DR. KAUL: That really doesn't answer my question about symptoms.

DR. GURAL: That is the available data that we have on the symptom --

DR. KAUL: Didn't you have a survey that you were collecting to look at symptoms? Didn't you use a --

DR. HARRINGTON: Sanjay, give him a little more help. What symptoms are you specifically interested in? Shortness of breath?

DR. KAUL: Exactly.

DR. GURAL: The dyspneas.

DR. HARRINGTON: Shortness of breath, palpitations --

DR. KAUL: Palpitations and discomfort, any chest discomfort.

DR. GURAL: Part of that was going to be after we had the discussion with the FDA.

DR. HARRINGTON: Okay. Let's do that, then. That's fair enough. But let's not take it off the table.

DR. GURAL: No, no. It comes back.

DR. HARRINGTON: Okay. Great. So why don't we turn the discussion for the next 45 minutes to the FDA, and Dr. Karkowsky who will lead us through the FDA analyses, and then we'll have about 45 minutes or so, 50 minutes before lunch.

DR. KARKOWSKY: Good morning, Chairman, committee members, sponsor, colleagues and those in the audience. I'm going to present some of the FDA thought process in the use of dronedarone in atrial fibrillation.

Next slide, please.

The reviewers for this application are as noted in this slide. There are other individuals who are responsible for various parts of the application that are not listed here, but they will have their input in the

future.

Before I start talking about a lot of information, there are things to consider in various preclinical or nonclinical parts of the application. With respect to the biopharmaceutic aspects of dronedarone, dronedarone demonstrates nonlinear kinetics, so a small change in dose adds to a more than proportionate increase in the serum concentrations.

Dronedarone is poorly bioavailable, 4 percent in a fasted situation and 15 percent fed. It is a CYP3A4 substrate.

In the presence of chronic ketoconazole dosing, there are increases of nine-fold in the Cmax and 15-fold of the AUC of this drug. Dronedarone also interacts with PGP and increases digoxin levels -- digoxin exposure by 2.5-fold.

There is a lot unknown about where this drug goes for only about 10 percent of the plasma radioactivity after an orally administered dose -- tracer dose can be accounted for by the drug and major metabolite. At least 30 metabolites, nearly all unidentified, were isolated after tracer studies. 20 of these metabolites represent at least 1 percent of the administered dose.

With respect to toxicology points to consider, dronedarone is potentially a mutagen. It was positive in the same assay. It was negative in three other mutagenic assays.

The executive CAC, or carcinogenic advisory committee, considered the results of the animal carcinogenicity studies to suggest drug-related

tumors in the animal models. Dronedarone is a teratogen in at least one animal species.

With respect to the pharmacology of dronedarone, dronedarone is potentially a negative inotrope. It blocks sodium channel. It blocks beta 1 adrenergic sites. And it also is a generation of adenylyl cyclase. And, as such, it might have a greater effect in a more severe heart failure population.

Dronedarone would likely prolong cardiac repolerization. It blocks potassium channels, e.g.

The structure of dronedarone and amiodarone is shown below. There are several differences. The main differences are, on amiodarone, there's two iodines. Those are absent on dronedarone. On dronedarone, there's a methane sulfonate. Those are absent on amiodarone.

On amiodarone, there's a two-chain carbon link here. There's a three-chain carbon link here. And the side chains on the nitrogen group are a butyl group here and a methyl group -- and an ethyl group here.

So dronedarone, even though it looks a lot like amiodarone, it may not be an analog of amiodarone. Although the differences in the design of this molecule were designed to mitigate the toxicity of amiodarone, but the multi-channel effects of dronedarone and amiodarone may be different based on the concentrations generated and the sensitivity of the individual channels to those concentrations.

And, in addition, the activity and concentration of active metabolites may be entirely different and add different effects to the treatment of dronedarone or amiodarone.

Efficacy studies. There were two types of efficacy studies performed, the DAFNE study which was a phase 2 dose ranging study, the EURIDIS study which was a delay of recurrence in atrial fib, and the ADONIS study, which was also a delay in recurrence. And the EURIDIS and ADONIS studies were performed under the same protocol. There was a rate control study, the ERATO study, which was a Holter-based rate control study.

Now, there were two morbidity and mortality studies, and I'm going to spend most of my time talking about these. The ANDROMEDA study was in heart failure patients. They did not have to be in atrial fibrillation or flutter. It was a safety study. This study is a rather standard study, when an anti-arrhythmic wishes to come to market, to determine if, in a vulnerable cardiovascular population, there are adverse mortality outcomes.

ATHENA study is a different study. It was done in a population with a history of afib/flutter. The study was performed to define a population for which dronedarone may be safely used.

With respect to the delay of recurrence and the rate control studies, these were reviewed by the sponsor, and I'm only going to say one point: The DAFNE study was the only study that explored a dose range and concluded that the lowest dose, the 400-milligram dose BID, which was studied,

was to be brought into the outcome development programs.

Lower doses were not studied. The 400-milligram study actually had the best effect, although not statistically significant, compared to the other doses.

Morbidity and mortality studies. The ANDROMEDA study. The primary end point to the ANDROMEDA study was the time to death or hospitalization for worsening heart failure. The inclusion criteria include patients who were symptomatic within the past month. They could have been hospitalized and, if they were hospitalized, they could have been ready for discharge. They could have been referred to a specialty heart clinic with just the symptoms in the past.

Patients were to be of New York Heart Association II to IV. They could be ready for discharge, had they been hospitalized. They had to have a wall motion of less than 1.2 based on 2-D echo and have at least one exacerbation of symptoms over the last month. They did not have to have atrial fibrillation or, if they had atrial fibrillation, they could have chronic atrial fibrillation.

The exclusion criteria included patients with acute pulmonary edema, recent need for either pressors or a respirator or a recent MI.

The hospitalizations and deaths were adjudicated by an external committee. The study was discontinued early due to an excess of deaths among dronedarone patients.

This slide shows the events that were observed in the ANDROMEDA study. There was an increase in the number of deaths -- there were 12 in the placebo group and 25 in the dronedarone group -- but there was also an increase in the number of patients who died or had worsening heart failure, the number of people who had worsening heart failure and were hospitalized, and the total number of cardiovascular hospitalizations.

With respect to the causes of death as adjudicated in the ANDROMEDA study, 9 of the 12 deaths in the placebo patient population were adjudicated cardiovascular. There was one that was non-adjudicated. 24 in the dronedarone population were adjudicated as cardiovascular. If you do the calculation, the point estimate for that hazard ratio is about 2.7. If you add the one patient in the placebo group that was not adjudicated, it's 2.4.

With respect to the causes of death, the predominant cause of death was worsening CHF. There were two patients in the placebo group and ten patients in the dronedarone group that died from worsening CHF.

There was also a numerically greater increase in the number of arrhythmic deaths in the dronedarone study compared to the -- in the dronedarone group compared to the placebo group.

With respect to a breakdown as to the causes of death in the population, there were -- most of the deaths occurred in the New York Heart Association III class. There were 17, or 9.6 percent, in the dronedarone group versus 3.8 percent in the placebo group. But although there were

relatively few in the New York Heart Association II group -- there were 5 out of 118, or 4.2 percent and 5.6 percent in the dronedarone group -- that comes out to a hazard ratio of 1.3, albeit very small numbers.

With respect to wall motion index, I broke these up based on categorical breakups of the wall motion index at baseline so that I didn't have overruns. I broke up them up to about a quarter of each -- into quartiles. And most of the effect was seen -- negative effect -- in the low and next to lowest groups with wall motion indexes of less than .9, although there is a fairly high increase in the mortality rate among those with wall motions of 1.1 to 1.2 compared to placebo, which had a 4.1 mortality rate.

The sponsor's initial hypothesis suggested the mortality was a consequence of early discontinuation of ACE inhibition or ARB as a result of dronedarone's ability to inhibit creatinine secretion. The discontinuation of ARB directly led to subsequent mortal or morbid events.

Note. This hypothesis requires that an asymptomatic creatinine increase provoked the discontinuation of ACE inhibition or ARB use.

In this slide I look at the number of patients who were in each category of ACE and ARB use during the clinical study. Of the 317 and 310 patients in placebo and dronedarone respectively, 50 and 36 patients did not have ACE and ARB use at baseline. So the inhibition of creatinine -- alteration of creatinine clearance could not have possibly affected the outcome. There was a 16 percent mortality rate -- 6 events -- in the

dronedarone group, and only 2 percent in the placebo group.

With respect to those that were on ACE inhibitors at baseline and remained on the ACE inhibitor throughout the study, there were 255 patients, and the number of mortal events was the same.

With respect to those who were on ACE inhibitors at baseline and discontinued, there were 12 such placebo patients, only one which died, and there were 9 in the dronedarone group, of which 47 [sic] died.

So the question is, did those who discontinued ACE and ARB discontinue for an asymptomatic creatinine increase or were there some other reason for the discontinuation of the ACE/ARB medication?

The next slide shows the causes of those who discontinued during that clinical trial. For those who discontinued ACE and ARB, none of them were stopped from these drugs based on asymptomatic creatinine increases. Most of them were stopped at a time that they had either heart failure or they had some evidence of worsening renal function.

Consequently, the increase in mortality of those with dronedarone in the ANDROMEDA study could not be attributed to an inappropriate discontinuation of ACE or ARB.

Now, the outcome of the ANDROMEDA study resulted in a non-approvable recommendation by the agency. The division indicated that approval could be reconsidered if efficacy and safety could be demonstrated in a different and defined population.

In order to accomplish this, the sponsor performed the ATHENA study. The inclusion criteria for the ATHENA study were predominantly elderly -- that is, greater than 75 years old -- subjects with a history of at least one normal sinus rhythm and one episode of afib or flutter within the last six months. If they were not at normal sinus rhythm at baseline, there was supposed to be an attempt to convert them after anticoagulation.

The original protocol originally allowed for patients to be over 70 years with those ECG documentations or less than 70 years but have additional risk factors, and these risk factors included diabetes, hypertension or a LAD of greater than 50 millimeters on 2-D echo.

The heart failure exclusion criteria were unstable hemodynamics, e.g. pulmonary edema, New York Heart Association IV, and the need for pressors.

With respect to the road map of the study, there were three major amendments. The first amendment included -- altered the enrollment of patients to older subjects, but also included an interim analysis after half the events that were anticipated were to have occurred. At this time, there were 11 mortal events that were recorded.

The second amendment dated in August 2006 increased the sample size to 4300 from 3700. At that stage, there were 45 mortal events already.

An interim analysis was done shortly after that particular point in time. There were 3,673 patients who were enrolled at that time. There were

46 mortal events with a very small difference between the treatment groups, and 693 total end points captured. There were 342 in the group A and 251 in group B. At that stage, the P-value for the primary end point was 0.001, borderline for when the interim analysis was to be stopped, but they continued the study.

Amendment 3 transferred categorization of mortal events to the steering committee, and a symptom assessment was also added at this time. At this stage, there were 83 mortal events.

The statistical analytic plan was submitted after the interim look and after all patients had completed the study.

The secondary end points in the -- in the statistical analytic plan were rearranged at this time, with cardiovascular hospitalization looking -- being placed at a higher -- hierarchy over that of cardiovascular mortality. I should note that the changes did not alter the conclusions, either by us or the sponsor by much, but I would point out that sending in a statistical analytic plan after the study is over is something we try to dissuade people from doing.

The primary end points of the study were timed to first cardiovascular hospitalization or death, and the secondary end point as a hierarchy were all-cause death, cardiovascular hospitalizations and cardiovascular death in that order. The time to follow-up was one year after the last subject enrolled. The date of that enrollment was December 30th,

2006. Therefore, the follow-up period that we entertained was through December 30th, 2007.

With respect to the disposition of subjects in the ATHENA study, there were 4,637 subjects enrolled, and most of them completed. There were two lost to follow-up in the placebo group.

Now, patients who were discontinued from drug were to be followed till the end of the study to capture additional hospitalizations and mortal events. So those that completed study on the placebo group and on the dronedarone group were about 1600 patients, and the reasons for discontinuation were substantially different in the two groups.

In the placebo group, the major reason for discontinuation was "other," and "other" included recurrence of events, it included need for prohibited medication, as well as for some administrative reasons. And in the dronedarone group, the major reason for discontinuation was for adverse events.

This is the sponsor's analysis of the time to first cardiovascular hospitalization or death. It was extremely significant. The P-value, according to the sponsor, was 10 to the minus 7th, and that number was reproduced by our statisticians.

The first in the hierarchy of secondary end points was all-cause mortality, and there was no statistical difference comparing placebo to dronedarone in this metric.

There were 135 placebo deaths. There were 115 dronedarone deaths, and the log rank P-value for this was 0.24. Since all-cause mortality was not significant, additional analyses are, therefore, exploratory in nature.

With respect to the first cardiovascular hospitalization in the ATHENA study, per sponsor, there were 859 hospitalizations in the placebo group and 675 in the dronedarone group. There's a difference of about 8 percent between the two hospitalizations.

Almost the entire difference can be accounted for atrial fibrillation hospitalizations. There is a 7 percent difference in the atrial fibrillation hospitalization favoring dronedarone.

Some of the other causes of hospitalization favored dronedarone; some favored placebo. So if you pick and choose after that, you sort of have to prespecify which ones you're going to pick. None of the other hospitalizations exclude 1 as a confidence interval.

So with respect to the first cardiovascular hospitalizations, the major difference in first hospitalization favored dronedarone. Nearly all of the effect was due to atrial fibrillation hospitalizations. The case report form, however, did not capture whether the subject was hemodynamically unstable, has an exacerbation of heart failure, or was admitted for anticoagulation. it is unclear why these patients were hospitalized for atrial fibrillation.

The next slide gives you what information was given in the case

report forms. It is a very skeletal case report form. It asks for whether this was initial or a prolonged hospitalization. It asks for the dates of hospitalization and the days in the ICU. It then asks was the person hospitalized for cardiovascular reasons? And if it was, it refers you to the next slide, which is a checkoff box, or a numerical insert box to define what the causes of hospitalization are.

There is no additional data, except that there is an asking whether you have CHF or not, and it doesn't say with this is an exacerbation of ongoing CHF. It's not descriptive of what really -- why the patients were hospitalized for afib.

With respect to the last of the -- last of the secondary end points, the categorization of mortal events, the data was collected by the investigator through case report forms. The information, again, was minimal. The events originally were characterized by the investigator, but then the steering committee recategorized -- and I'm using the word "categorize" as opposed to adjudicated because these events were not -- neither the events for hospitalized or for mortal events were really adjudicated. And they were categorized either as cardiac arrhythmic, cardiac non-arrhythmic, vascular non-cardiac, or non-vascular.

The committee consisted of five independent cardiologists and three of the sponsor's members. Only the cardiologists were involved in the categorization. The categorizations occurred after the interim look. The

steering committee, however, was to be blinded as to the results of that interim look and were only told whether the study was to be continued or to be discontinued.

The cardiovascular mortality rates up to December 30th, 2007, were as follows. There were 91 placebo patients who died from cardiovascular reason and there were dronedarone patients, 65, who died for cardiovascular reason. The nominal log rank value is 0.037.

So the next question is, do cause-specific measurements clarify or merely allow for a second look at the data where you've already decided that you didn't have a mortality outcome?

And what I did is I looked at the causes -- we looked at the causes of what was considered cardiovascular and what was considered non-cardiovascular events as categorized by the steering committee -- and some of these are difficult to interpret with respect to this particular study.

For example, hemorrhage, whether it was a GI hemorrhage -- a hemorrhage caused by a metastatic process was considered a cardiovascular event. Unknown causes were considered cardiovascular events. Whereas there were many that are considered non-cardiovascular, including asthenia, respiratory failure, edema, pneumonia, renal failure, failure to thrive and death which were not considered cardiovascular events.

So the case reports forms only captured a small amount of data. The initial assessment by the on-site investigator had ECG and renal data that

could have masked treatment, for example, QT prolongation, creatinine increases and GI symptoms.

There was some question I had about the consistency of categorizing end points, and only a few shifts in the categorization -- if you take the end point that the FDA took, that would be two events; if you took the time that the sponsor chose to the -- to count events, it would be five events -- would remove any nominal effect.

The errors in classification add a different form of uncertainty. All-cause mortality includes events not likely to be altered by the use of an anti-arrhythmic drug.

I'd like to give you one example of things that I thought were very interesting with respect to the way they were categorized. This was a patient treated with dronedarone. The event was considered a brain contusion and not considered a cardiovascular event. This is a patient who was anticoagulated, fell, became unconscious, had a large right subdural hematoma and subsequently died. This was attributed to a non-cardiovascular event.

This is a placebo patient. This event was treated as a cardiovascular event. This patient fell, had a large intra-cerebral bleed, and eventually the patient died.

It's very difficult for me to see why the two cases were treated differently. Both of them should have been treated as non-cardiovascular.

What I'm trying to point out is not that the sponsor was unblinded,

but that there were some errors that are -- that creep into the process of an adjudication. If this had been the primary end point, that might have been acceptable. But this was a subordinate analysis secondary to a missed mortality claim.

Summary regarding cardiovascular mortality. Cardiovascular mortality was only an exploratory analysis. There are potential errors in the characterization of events. The results are inconsistent with the results of the ANDROMEDA study, which demonstrated an increase in cardiovascular -- both deaths and also hospitalizations and other events.

The gradient and the poor outcome relative to heart failure status makes it difficult to interpret.

In summary, the ATHENA study was successful in demonstrating a decrease in the time to first cardiovascular hospitalization or death. Overall mortality, the primary/secondary end point was not different, comparing placebo to dronedarone. Cardiovascular hospitalizations, as an exploratory analysis, suggests that the benefit was due to atrial fibrillation hospitalizations. CV deaths, as an exploratory ana, was suggestive of a benefit in the ATHENA population, but it was an exploratory analysis.

Safety. What I've got on the next slide are the safety from the ADONIS, EURIDIS, ERATO and DAFNE studies. These were the initial time to recurrence and rate control studies that were performed by the sponsor. Placebo patients were exposed half the time of a -- the 400-milligram

dronedarone group, there was about a 2-to-1 ratio in the exposure. The number of deaths in the placebo group I have as three, the number in the dronedarone group as nine. The deaths per patient year is slightly higher in the dronedarone group, but with a small number of events, it's an unstable estimate.

Putting together all the deaths in the studies that we've got, there were three deaths with a hazard ratio of 0.009 compared to nine deaths in dronedarone in the earlier studies. In the ANDROMEDA studies, there were 12 versus 25 overall, an increase of 13 events in the dronedarone group. As those adjudicated as cardiovascular, there were nine, or possibly ten, if you take the non-adjudicated death, versus 24.

In the ATHENA study, the overall difference, there was a 20 percent positive, which is just about equal in opposite to the 13-event that went in the other direction in ANDROMEDA. In those that were categorized as cardiovascular, there was a 26-event difference compared to the 15 in the other direction in the ANDROMEDA study.

With respect to heart failure deaths -- I thought this was interesting because of the potential for this drug to be a negative inotrope. The vast majority of the people who died in ANDROMEDA died from heart failure deaths. It was ten versus two.

With respect to those in ATHENA, even though with a numerically favorable mortality, there were more heart failure deaths in the dronedarone

group than in the placebo group.

With respect to other adverse events in the ATHENA group [sic], there were several things that stuck out to me. The first is that there were events that are related -- well, there are gastrointestinal events which seem to be the primary reason that people discontinued from the study. There was a marked increase in the number of events of diarrhea, vomiting and nausea.

Also noted, there were increases in those -- the creatinine increases that seemed to be worse in the dronedarone group.

But also of interest to me were the number of patients -- and they're highlighted and underlined -- they're highlighted in red -- of evidence of worsening heart failure. These are symptoms that often occur with heart failure, peripheral edema, fatigue, asthenia and dyspnea. All went with about 25 to 30 events favoring placebo.

So what I'd like to do is compare the two populations to the way I see them. In the ANDROMEDA study -- let me first say that it would have been unlikely that the population in the ATHENA study would overlap with the population in the ANDROMEDA study because I think it would have been unethical, after you've stopped the study, for adverse events to include the same population. So, in essence, the two populations have to be distinct and separate.

The population in the ANDROMEDA study were either recently hospitalized or seen in a clinic for heart failure, having at least one

symptom within the previous month, and receiving in hospital if they were -- the minimum of IV diuretics. Their age was 70. They were mostly male. And they had a median wall motion of 0.9. Ejection fraction is not stated, but if you estimate what the ejection fraction is, based on the wall motion, it's somewhere around 30.

The distribution of New York Heart Association at baseline was almost -- median of about a New York Heart Association class III.

In contradistinction, the ATHENA population was an elderly population with a history of afib and flutter and normal sinus rhythm. They were mostly elderly and predominantly male. Wall motion was not counted, but the median ejection fraction in this population was 57 percent.

If you look at the distribution of heart failure, 70 percent of the people who enrolled in the ATHENA study had no heart failure, and of those, there were very small numbers who had anything worse than New York Heart Association class II.

So how sick was the ANDROMEDA population? How does one answer that question? And the only way I could think of doing it was looking at the mortality rate in the ANDROMEDA population compared to a population that was hospitalized for decompensated heart failure. This data was taken from the pooled VMAC study which was the study of nesiritide, and this included both the nitroglycerin and the nesiritide-treated patients.

You can see that that population is sufficiently sicker. At time

points -- we have 30 days, 60 days and 6 months -- the mortality rates were about 6 percent, 16 percent and 22 percent for the heart failure populations that were hospitalized for decompensated heart failure. In the ANDROMEDA population, the placebo group had a heart failure population -- heart failure mortality substantially less.

So the only thing I conclude is these were substantially less unstable than those that normally come into heart failure trials.

So where do we stand now? We have two data points. We have the ANDROMEDA data point, which is represented on the right, and the ATHENA data point. On the X axis I've plotted arbitrary heart failure severity. The confidence intervals for the ANDROMEDA don't extend through 1 with a point estimate of about 2.1. The range of severity in the less sick direction, which was the class II patients, have a point estimate of 1.3 relative to the mortality in the placebo group; however, these are very small numbers, and that's the difficulty in looking at the tails of any population. You get to very small numbers and get unstable estimates.

The mortality rate for the ATHENA study, however, was below 1 point estimate with confidence intervals that marginally lap above the confidence interval of 1.

Again, the median heart failure status of these patients was fairly mild, and one then has to make a decision: Where does that point inflect? If I did not have the ANDROMEDA study, the confidence intervals for the

populations that seem to be more severe -- class II, class III -- would yield comfort. But I have to believe that, if you accept the ANDROMEDA study, then there's got to be some point where the severity of heart failure is going to move subjects into the adverse risk part of this graph.

So there are two studies with remarkably different outcomes. Both studies contribute data points to the risk based on heart failure status. If not for the results of the ANDROMEDA study, subgroup analysis -- subgroup analysis of the ATHENA study would have offered comfort. In the presence of the ANDROMEDA study, results -- there has to be an inflection point to negative mortal outcomes based on the degree of heart failure.

Small numbers in the tails of the population or in subgroups of populations make the conclusions less reliable, both for risk and for comfort. And, as pointed out by other people in this room already, people don't stay static in their heart failure status; they progress over time. So what would be the recommendations for those people who progress in their heart failures -- the severity over the course of treatment?

So my conclusions are the results of ADONIS, EURIDIS and ATHENA suggest a benefit in delay of recurrence of afib. ANDROMEDA study suggests subjects with heart failure have an adverse outcome. ATHENA study suggests no overall adverse mortality outcome in patients without severe heart failure and a decrease in afib hospitalization, but I don't know where the cross-over point is and where the neutral point is for saying this patient should not be

treated with dronedarone because of their heart failure. Thank you.

DR. HARRINGTON: So let's try -- we have about an hour for questions, and let's try to do it in two phases. First, let's try to confine your questions to the FDA, and then we'll bring the sponsor back up for additional questions to them.

So, Dr. Wolfe?

DR. WOLFE: In light of your presentation and the written material that we were handed out a couple of weeks ago, can you just comment overall on the degree to which the evaluation of the study is impaired by, A, the lack of adjudication as was the case with ANDROMEDA, and, B, the sketchy -- which I think is a generous phrase of yours -- case report forms which fail to, at least what I've seen, give any kind of clue as to the variety of different reasons that could have been the cause for the atrial fibrillation. How does this impair your ability, our ability to really make any kind of conclusions from that study?

DR. KARKOWSKY: Well, I think the conclusions are that the primary/secondary end point didn't succeed. Had this policy been the primary end point and if it was sufficiently comforting down several P-values less than that, it probably would not have made any difference. But this was a marginal effect for cardiovascular mortality after a failed hierarchical end point.

In large trials very often the smaller the case report form is, the

more it's easier to perform that study. But I think this case report form could have captured a lot more data with minimal effort and been much more instructive as to how we interpret the data.

DR. HARRINGTON: Other questions?

Go ahead, Jim. And then Bob.

DR. NEATON: You alluded to the subgroup analyses in ATHENA, and I just wondered, how do you reconcile the fact that, when you look at the subgroup analyses by New York Heart class and ejection fraction -- and you also included a subgroup analysis of a sort in your report where you looked at people enrolled before and after the amendment, and the more severe higher -- patients with a higher death rate after the amendment seemed to do better.

How do you reconcile those results with ANDROMEDA?

DR. KARKOWSKY: I think the populations are entirely different. I think the ANDROMEDA population is a sicker population. I think what you have in ATHENA is predominantly a non-heart failure population. It's 70 percent no heart failure with only a smattering of people with New York Heart Association's II, III and IV.

And if you look at the class III patients, they do reasonably well in ATHENA. But if you look at the class II, the point estimate goes in the wrong direction.

DR. NEATON: But don't you think there's some kind of continuum of risk here? Why should there be this trend, if anything, that in ATHENA, the

sicker patients are doing a little bit better?

DR. KARKOWSKY: I have no idea.

DR. NEATON: It doesn't add up to me. It goes back, in my mind -- it suggests to me that this is -- the ANDROMEDA findings were just a chance observation.

DR. KARKOWSKY: Well, I would argue that it wasn't just mortality that went in the wrong direction in ANDROMEDA. It was heart failure hospitalizations. It was all hospitalizations for cardiovascular reason.

So in the absence of data to say that something is a chance finding, it's interesting to speculate, but I have no way of discounting the ANDROMEDA data.

DR. HARRINGTON: I mean, another way, Jim, perhaps, to look at it -- and I thought that Dr. Packer made this point this morning -- is that when the observation was made in the first study, every attempt was made to exclude those types of patients from the next study. So it's hard to say, you know where that -- where's the gap in the continuum? You know, and I think the point is being made that what we have is an evidence gap. You can't just discard it as being chance. I think you'd have to say that there's a level of uncertainty here that's not fully answered.

DR. NEATON: But he also said, I think -- and I think the report shows -- that people in ATHENA progress into a state of heart failure like ANDROMEDA. And some of -- they did not do bad either.

DR. KARKOWSKY: Well, if they had afib at the time, it may or may not have been the same type of heart failure. And if you look at the heart failure -- those who progressed to class III or worse, they were slightly more in the placebo patients, but the requirement for more aggressive therapy was somewhat greater in the dronedarone patients.

So hard to say what to do with those patients if the reason they progressed was due to their atrial fibrillation at the time.

DR. HARRINGTON: So I've got several people waiting. Let's go to Bob Temple, Jonathan Fox, Dr. Calhoun.

DR. TEMPLE: Avi, in responding to Dr. Wolfe's question, you focused mostly on the lack of detail about mortality. I think he was asking about both, however, both the mortality finding and the hospitalization finding, which also wasn't terribly detailed, although Milton has reported impressions of why people were hospitalized. To you have a view of the hospitalization finding? And I have one other question, too.

DR. KARKOWSKY: Well, the hospitalization findings are based on -- I mean, there was such an overwhelming effect on hospitalizations, and if you look at the primary reason that was ticked off, it was afib. It was hard to say that that would change with anything else.

The question is whether any of these subordinate hospitalizations -- that is, whether the heart failure hospitalization was really an afib hospitalization that they checked off the heart failure because that was the

worst of the symptoms at the time.

So what it does to me is it says, you give the minimalistic interpretation of what was prevented, which to me was afib, because there's such a broad signal there.

DR. TEMPLE: Okay. The second question. You're trying to figure out what degree of heart failure leads to trouble and, you know, we've heard Jim is not so sure there's anything there, but leaving that aside, Milton's proposal was that it isn't so much the severity of heart failure but the acuteness of the heart failure, and he analogized that to people who do very badly with a beta blocker when they're acutely in heart failure but, in the long run, we know beta blocker saves their lives even though it exacerbates heart failure.

Do you have any -- what's your reaction to that distinction?

DR. KARKOWSKY: I think one can look at -- can I go back to my slides? I think it's the third from the last slide. Can you go to the end? It's the slide with the two data points. Next slide. That one.

There's two ways to look at this. Consider this a Venn diagram. You have a population and -- you have two different populations. One could write, Don't treat the population that you saw was bad. One could also say, Only treat the population that you know was good. That's the difference between the two ways of looking at it.

The way Dr. Packer presented it, I believe, was more, Don't treat

the population you know that was bad and assume that everybody else is good. I don't know if that's the correct response because we don't have data -- very much data, and they are unstable estimates because they all go -- all the confidence intervals that he showed go above 1.

DR. TEMPLE: Avi, I'm asking a slightly different question, and obviously they'll get a chance to -- you're rating it by severity.

DR. KARKOWSKY: Right.

DR. TEMPLE: Okay. The alternative hypothesis that I heard -- maybe you didn't hear it the same way -- was it isn't so much ultimate severity whether you're class I, II, III, IV, whatever those things mean, but it's what happened to you in the last couple of days. Were you acutely hospitalized and made very ill? And that that seemed to be the risk in ATHENA. And I just wondered what you thought of that distinction.

DR. KARKOWSKY: When I used arbitrary units, that was the arbitrary units based on what got you into the two studies. I can't differentiate in the two studies whether it was the instability, the degree of heart failure or both. I don't have any data for either group in between that's of sufficient magnitude to make you comfortable because there are small numbers of people who had class III in ATHENA and the point estimates go above 1, which means that it could have an adverse event effect.

Whether it was the instability or whether it was the degree of heart failure, I can't tell from the data I've got.

DR. HARRINGTON: Dr. Fox?

DR. FOX: Thank you. I have two questions. The first relates to the composite primary end point and what I perceive to be the agency's interpretation that the primary end point analysis was driven mainly by the hospitalizations. I think you've, you know, demonstrated that quite clearly. But there seemed to be a discounting of the minor component because, as a stand-alone analysis, it didn't reach compelling significance.

I guess it has implications for other trials and, thus, for other sponsors that -- I mean, the whole reason why we use composite end points is because, as stand-alone analyses, they are underpowered; otherwise, they would be made stand-alone end points.

So I just wonder, unless there is quantitatively assessed heterogeneity in the outcome of the components or if one of the clinically important components, as in this case, may, for other reasons you've talked about, have been close to neutral or otherwise unimpressively different, is there a reason to discount the -- a minor component if, by stand-alone analysis, it doesn't have its own P-value?

DR. KARKOWSKY: If I may answer, I think part of the problem here is you've got a diverse -- you've got a second study which says the opposite. And, again, if I didn't have ANDROMEDA, I would have come to a different conclusion and a different recommendation.

With ANDROMEDA present, if you can't discount it or make it go away

by some other method, you're stuck with one population where you know it's a hazard for and one population where you suspect it might be useful for.

DR. FOX: That's a fair point. So my second question relates to your comments around the statistical analysis plan. Typically these documents are not filed with the agency until well into a major long-term outcomes trial like this one. And even though you -- I guess you made more of a parenthetical comment that the agency discourages sponsors from submitting their SAP following study closure. However, my own impression is that it's okay to do that as long as you do it before the database is locked and unblinded.

DR. KARKOWSKY: The problem you have here is two-fold. First of all, there was an interim analysis, so you had some idea of what you were seeing. In this case, it didn't alter the effect very much, but it raises questions: What did you see in the interim analysis that made you change your focus on a secondary -- on your end point?

And, number two, there's no reason you can't submit an initial plan and then, when you write up your statistical analytic plan, those things that have come up in between clearly describe and say how you've done them so that we can go back and look at them and say, this is reasonable; this doesn't alter the outcome of the study.

There is an enormous amount of discomfort because I've seen statistical analytic plans for other drugs where they threw out half the

population, and just by chance the population that it didn't work in, by the time they came to the statistical -- it did not happen here. I want to make that very clear. It was a parenthetical comment with a disclaimer that it was not a major issue here.

DR. FOX: Let me just try and make sure I understand. I thought that even though it was after an interim look, that the unblended results of that analysis were revealed only to an independent DSMB, not to the sponsor.

DR. KARKOWSKY: That's --

DR. HARRINGTON: That is indeed correct.

DR. KARKOWSKY: And that's what was said in the --

DR. FOX: So almost all these trials have at least one interim --

DR. KARKOWSKY: But once you unblind a trial -- and I've never seen a trial that's not unblinded, and I don't -- it's just a bad policy. There's no reason that a statistical analytic plan can't be put in place before you finish the study.

DR. HARRINGTON: Okay. Dr. Temple is chomping to answer here, so let him weigh in.

DR. TEMPLE: Well, I didn't want to answer that one, but we do have --

DR. HARRINGTON: Well, then forget it.

DR. TEMPLE: We do have a continuing problem with late modifications, and we are urging everybody to do it earlier, even though

everyone says, oh, well, don't worry; it was totally blinded. But we really would like to see that done earlier.

I wanted to comment on the components of the combined end point --

DR. HARRINGTON: Can I do one thing, Bob, before you do that?

DR. TEMPLE: Or I could just do it later.

DR. HARRINGTON: Because I think the sponsor wants to make a question about who actually was privy to interim data.

DR. GURAL: Absolutely.

DR. HARRINGTON: So that would be helpful, and just make that quick, though.

DR. GURAL: Okay. The access to the unblinding of the data was only for the data monitoring committee. It was not to the sponsor. The steering committee only receiving a single notification that said, Continue the study without modification. That's what they received. So they did not have access to the --

DR. HARRINGTON: Who actually did the analysis? Who was the group that did the analysis? Were they within the sponsor or were they an independent group?

DR. GURAL: No, it was an independent group outside of the sponsor's control.

DR. HARRINGTON: Mike, go ahead. And then Milt.

DR. LINCOFF: But you had the mortality data to change the sample

size, so --

DR. HARRINGTON: Aggregated.

DR. GURAL: Aggregated.

DR. LINCOFF: Aggregated, but still you had -- so what other aggregated data was available to the steering committee as well?

DR. GURAL: The steering committee -- the data monitoring committee had access through the external statistician for that information. The company did not have the information. It was the data committee who made the recommendation to the steering committee to increase the number of patients to be enrolled into the trial to meet the end point of the determination of the right number of patients needed to meet the number of 260 events.

So that was the recommendation. It wasn't the company who knew this information; it was the data monitoring committee who knew the information.

DR. HARRINGTON: Do you want to clarify, Dr. Packer?

DR. PACKER: Just a clarification for the record. The statistical plan was in the original protocol. The only reason that there was a, quote, late submission was at the request of the FDA who said, you know, you have three secondary end points here. If you want a claim for any of the secondary end points, you have to create a hierarchy, so please submit a modified statistical plan that specifies the hierarchy. And that was it. That was the only change that was made in the final statistical plan. Everything else was specified in the original protocol.

So to get to -- it's very important for the committee not to have the impression that, one, the sponsor knew anything that was going on during the course of the study, and two, there is any meaningful change in the statistical plan filed at the end of the study, other than to respond to an FDA request.

DR. GURAL: And just to make one last confirmation, the study -- the statistical analysis plan was submitted in advance of database lock and unblinding of the trial.

DR. HARRINGTON: Okay. Jim, quick question.

DR. NEATON: So you changed the plan for stopping the study to the target number of events, 260, from the number of primary end points, from 900. Were the -- did the DSMB have any monitoring guidelines at all around the primary end point that they used? Because obviously they must have seen gigantic differences, probably even at the first interim analysis. So were there any guidelines -- what guidelines did the DSMB use for the primary end point analysis?

DR. PACKER: The primary data safety monitoring board's safety mission was mortality. Tom Fleming, who was on the data safety monitoring board for ATHENA, wrote a rather complex series of rules that would allow the data safety monitoring board to assess benefit to risk at certain points in time.

Those rules are not easy to summarize quickly, but essentially say

that their primary goal is to assess mortality; any assessment of risk has to include an assessment of benefit, i.e. the threshold for stopping the trial because of risk would be lower if there were no benefit. Does that help?

DR. NEATON: Basically it was a judgment on their part concerning the primary end point with a guide toward 260 deaths. And so they looked at the data and decided the study should go to the end?

DR. PACKER: Exactly.

DR. HARRINGTON: So let me just go through the list so people know where they are. Bob, you're next. Dr. Calhoun, Emil, Dr. Swenson and Dr. Krantz.

DR. TEMPLE: Okay. This is so interesting. Things keep coming up. We strongly encourage companies to not even have a sample size, but to size their study by the number of end points, so we like that -- blinded, of course. And we also often urge companies not to stop for anything but mortality.

Anyway, I just wanted to comment on the components of a -- of a combined end point. That's a major problem for us, how to present those data without exaggerating or distorting the thing. And we've given some advice in our labeling rule and the guidance that accompanies it. And what it says is that when you have a combined end point, you should always show the components of that end point. And we don't want you to put P-values next to it unless it's a planned secondary end point or anything, but we do want you to show it.

So that's our general bias.

In a couple of cases, however, where it was perfectly clear that nothing was going on with some components of the end point, we have made the labeling say it only worked on stroke, you know, the life study showed an effect on a nominal combined end point. But it was perfectly clear that death and heart attacks weren't affected at all, so it says that it changes stroke.

So you have to look at it intelligently -- and Avi has given some reason why you might not want to make too much of the lean on mortality, given the other study. But, anyway, it's a big problem. We agonize about it all the time.

DR. HARRINGTON: So, Bob, let me explore that a bit because I think it gets at one of the issues of Jonathan's question. In the composite in many of the trials that we see, there is a composite because any one of the events is infrequent, and you need all of them to have reasonable sample size to achieve an -- to achieve an overall positive outcome. That's not the case here.

IN this case, you have one which was assumed to be extraordinarily well-powered, and the other one, as Milton I thought nicely pointed out, what the goal was.

Do you interpret those two situations differently?

DR. TEMPLE: Well, I think death is usually included in trials because it seems irresponsible to leave it out, not because you expect the

events to be -- the result to be driven by that.

In this case, there was -- it was overwhelmingly likely that cardiovascular hospitalizations were going to be the thing that drove it. And you could have made that the primary end point and just looked at death, but it's very common to include death, stroke, MI in combined end points. I think it's at least partly because it seems irresponsible not to include death in the end point. It's still --

DR. HARRINGTON: So that's a critical question for us today, though, because one of the questions we're going to explore is that if we believe the drug should be approved, how should the label read? And right now the label indication reads that the composite -- but, in fact, this is a little bit of a funny composite. It was overwhelmingly powered for one, and the other was put in there in part because of the earlier study and part, as you say perhaps to be responsible.

DR. TEMPLE: Right. But we have a variety of ways of dealing with that. Sometimes it says this was the composite, but all the action was here. You know, there's a lot of ways to deal with that. That's --

DR. HARRINGTON: That's what I was hoping you'd say so --

DR. TEMPLE: The discussion will be helpful.

DR. HARRINGTON: Hold on a second. Is that the same topic? Okay.

DR. KAUL: I want to follow up on Dr. Temple's discussion. I think a formal analysis of heterogeneity across the different components of the

composite end point would be helpful. If I recall, in the life study, there was a statistically significant heterogeneity, and that's why the label was confined to stroke benefit. Whereas in the present study, which was a lack of protein inhibitor study, there was not much of an impact on mortality, but because there was no formal significant heterogeneity, the label was for all the three combined end points, so I think that point might be worth following up later.

DR. TEMPLE: But in life it wasn't -- I mean, there may have been an analysis of heterogeneity, but we just looked at the number of deaths, and it was equal. So I don't care whether it was heterogenous or not. They weren't going to get that claim.

DR. HARRINGTON: Same issue, Jim?

DR. NEATON: Yes, same issue. I just want to go back -- I want to remind the sponsor because, on this issue, I asked for two tables. I just saw the second table on mortality. I'd like to see the first table, which I think addresses this point, pooled across the four studies or five studies, or maybe six -- I forget now -- the outcome that excludes atrial fibrillation because I think it's a very important question that's being raised: Is the outcome being driven primarily by atrial fibrillation or not?

And I think if you -- your best estimate, if you think ANDROMEDA is kind of a chance finding, is the pooled results across all those studies. And so that's page 99, the first table, taking out the atrial fib

hospitalizations.

DR. HARRINGTON: So Dr. Karkowsky presented you some data there. He pointed out that there's an 8 percent absolute difference between the treatments, of which 7 percent is accounted for, if I remember right, by the afib hospitalizations. Do you want more than that?

DR. NEATON: Yeah. That's the one trial. That's ATHENA. If you look across the trials, my guess is that hazard ratio is going to be somewhere between .9 and .95, but let's do the result.

DR. HARRINGTON: They're going to get that after lunch, so let me get back in the order here. Dr. Calhoun?

DR. CALHOUN: Thank you. It seems to me that ANDROMEDA has generated a great deal more heat and smoke than light -- and, Dr. Karkowsky, you've indicated that a large piece of your uncertainty actually is a result of the ANDROMEDA trial. So this is a trial in which the diagnosis was different -- it was heart failure, essentially, rather than arrhythmias. The severity was different -- it was more severe rather than less severe. The acuteness was worse; that is, that patients enrolled in ANDROMEDA were subacutely or acutely ill. And the analysis was different in which it may have actually encouraged false positive stopping of the study early on.

So I have a question for the agency and a question for the sponsor. The question is for the agency: Is the ANDROMEDA study something that was suggested or mandated by the agency?

DR. KARKOWSKY: It's -- a vulnerable population study is often asked for and required for anti-arrhythmic drugs. I point to the Diamond study for dofetilide and for sotalol there was the Julian study -- and there are other studies where it is part and parcel of demonstrating safety in a vulnerable population.

DR. CALHOUN: It just seems to be the wrong population in that there was no rhythm disturbance in these patients.

DR. KARKOWSKY: Well, you could have prevented ventricular arrhythmias in that population. So it's --

DR. HARRINGTON: So, Bob, do you want to comment --

DR. KARKOWSKY: So it's probably ethical.

DR. TEMPLE: Well, you're discussing a tricky question: Who is it reasonable to do the population -- this was our response to CAST and various other data suggesting that anti-arrhythmics are not as wonderful as people might have thought they were, and abandoning the surrogate end point and all that stuff.

We have asked that any drug that's got an arrhythmia claim provide reasonable assurance that they're not rubbing people out. Okay?

So for sotalol we happen to have a post-infarction study that Desmond Julian did with an 18 percent -- not quite significant -- benefit. So that was reassuring.

For dofetilide we had the two Diamond studies, one in heart failure,

one in coronary artery disease, and they were at least neutral. So that was pretty reassuring.

And the ANDROMEDA study was this version. You could probably debate how likely it was that this would be good for you. But people with heart failure die of arrhythmias, and dronedarone is an anti-arrhythmic so that seemed reasonable. And it was intended to provide assurance that if you merely showed that if you reduced the rate of recurrent atrial fibrillation, which is what those earlier studies had shown, that you weren't harming people. That's why they did it. But then it turned out they were harming people, so they had to do ATHENA.

We're asking that for any anti-arrhythmic drug.

DR. HARRINGTON: Are you satisfied, Dr. Calhoun?

DR. CALHOUN: Well, not entirely because, again, it just seems like it's the improper population. This is not the first drug you'd reach for when someone is admitted to the hospital with congestive failure in my ICU. And so it may just be the wrong population.

So the response I'd like from the sponsor is, is this -- generally, sponsors have some idea of how a study will -- what the study outcome is likely to be before they do the study, and I was uncompelled by the biologic rationale that you provided on your CC-38 slide that there was a compelling rationale for taking the data from the combined EURIDIS, ADONIS study, and studying, then, the effect on major events in high-risk patients in ANDROMEDA

-- and obviously I must be missing something, so I'd like to hear why you drew that together.

DR. GURAL: If we -- and Dr. Packer. The EURIDIS and ADONIS trial, the one that you saw -- not on slide CC-38, but the way that was originally proposed by Milton and by Jerry, were indications of what was used to design the ATHENA trial.

So -- but perhaps I'm misunderstanding your question completely. Go ahead.

DR. PACKER: I understand your question. Can we have slide CC-38.

There is one -- the arrow between EURIDIS, ADONIS and DIONYSOS and ANDROMEDA is not a biological arrow; it's not a therapeutic arrow; it's a chronological arrow. And I think you're hitting the nail on the head. There is nothing seen in EURIDIS, ADONIS and DIONYSOS or any of the earlier trials that leads to a hypothesis that was tested in ANDROMEDA.

DR. CALHOUN: Okay. That was the sense of my question. Thank you.

DR. HARRINGTON: Okay. Next is Emil.

DR. PAGANINI: Perhaps a foolish question, but nonetheless, a multi-syndrome, multi-national study probably speaks to a variation or variability in practice. And hospitalization for various issues are variable across countries and across practice.

Was there any -- this is to FDA. Was there any -- or to the sponsor -- any subgroup analysis as to site differentiation for hospitalization, and

was there any difference there?

DR. KARKOWSKY: Our statistician looked at the U.S. sites as a total site, and the hazard ratio was not that different from the studies as a whole. I think it was a little bit less, but it was .8 -- but clearly in the right direction.

DR. HARRINGTON: Can you remind us roughly the percentage of U.S. sites versus other?

DR. KARKOWSKY: I don't have the number offhand.

DR. HARRINGTON: Can the sponsor provide that?

DR. GURAL: In the ATHENA trial, about 1,400 patients were enrolled from North American sites.

DR. HARRINGTON: Emil, did you have another question?

DR. PAGANINI: No.

DR. HARRINGTON: Dr. Swenson?

DR. SWENSON: Yes. My question regards the fraction of patients in the ANDROMEDA study that were the hospitalized subset as opposed to the clinically unstable. Is that data known?

DR. PACKER: All. They were all. All were hospitalized. All had a history of class IV symptoms within the prior month. They were qualifying criteria to get into the study. So the answer to the question is 100 percent.

DR. SWENSON: Okay. That just wasn't clear in the key inclusion criteria. It looked as if there might be other ways that these patients could

be brought into the study, absent immediate or recent hospitalization.

So then if they're all a hundred percent hospitalized, to what extent is just hospitalization itself within a very recent period of time with the multiple things that happen uniquely in hospitals directed at heart failure, with heavy IV diuretic use and possibly much more immobility and other factors like that, relevant to the issue of a greater signal for mortality in that study as opposed to a much more benign look at it from the ATHENA population?

DR. KARKOWSKY: I have no way of answering that question. With respect to the inclusion criterion for the study, there is an inclusion criterion that said they could have been referred to a heart failure clinic with symptoms in the previous month. Don't know how many and didn't see a database description that said these are the ones that were all hospitalized.

But if they were hospitalized -- in fact, I have one of my slides, and I don't have it with me; it's one of my supplemental slides -- I cut and paste the inclusion criterion from the sponsor.

Let me see...

(Pause in the proceedings.)

DR. KARKOWSKY: It says, Consecutive patients hospitalized with CHF. In this context, hospitalized means admitted to the hospital or referred to a specialized heart clinic, including the day hospital in the department. So that's where that information came from. This is the inclusion criteria from

the study report.

DR. HARRINGTON: Milton, do you want to provide some context? The question was -- I think you're saying that a very complicated hospitalization for heart failure, what's the meaningfulness of an early rehospitalization? Is that essentially your question?

DR. SWENSON: It gets to that. And then, is there precedent in any other disease states where it's been divided along these lines?

DR. HARRINGTON: Okay. We'll let Dr. Packer --

DR. PACKER: When patients come in with decompensated heart failure in a hospital, there are two major risks that happen to them. One is the risk of their underlying condition, which is clinically unstable. That's why they're coming into the hospital. And the second is the risk of what physicians do to them, which of course we like to think that everything we do to them is favorable, but we actually, in a sizable number of interventions, we don't know.

So they get, in many cases, intensive IV diuretics. Maybe that's good; maybe it's not good. They get other interventions. I cannot dissect across all of the things that patients -- that happens to patients with heart failure as to what increases the risk that you saw in the ANDROMEDA trial. I do want to emphasize, however, that whatever it is is exactly the same kind of phenomenon that we see with beta blockers.

You asked whether we see a differential between patients with recent

clinical instability and patients who are clinically stable in any other therapeutic -- with any other therapeutic agent, and the answer is we see exactly the same thing with beta blockers. If we start beta blockage in a clinically unstable patient, they get into trouble.

If we start beta blockage in a patient with the same severity of disease but doesn't -- who does not have a recent period of clinical instability, they don't get into trouble. And that's amply reflected in the guidelines for beta blockage.

So the hospitalized patient, acutely hospitalized patient, doesn't get beta blockers. The stable patient with the same severity has an indication for beta blockade -- and the reason why that's particularly interesting is that the way that beta blockers work is they work as antiadrenergic drugs, and this drug is an antiadrenergic drug.

DR. HARRINGTON: Are you satisfied, Dr. Swenson?

DR. SWENSON: (Nodding head.)

DR. HARRINGTON: Okay. Dr. Krantz?

DR. KRANTZ: I just wanted to add to that. I think, you know, when you look at patients hospitalized with heart failure, and it's the same criteria -- they haven't had pulmonary edema for 12 hours; that's when we initiate beta blockers. But, in contrast to dronedarone, se see significant mortality benefits with inpatient admissions. We did an RCT, and there's lots of observational data to support that.

So I guess I'm a little unclear in terms of what the difference here is. Are you telling me that everyone got this drug started as an inpatient in ANDROMEDA?

DR. PACKER: They were randomized.

DR. KRANTZ: No, but the question isn't randomization, but actual receipt of the medication in the hospital or not, because clearly for beta blockade, which this drug has that property, that reduces mortality by about 40 percent at six months, whereas this seems to increase mortality. So could --

DR. PACKER: Your reference to beta blockers reducing mortality if they're started in the hospital at six months -- I just want to make sure we're talking about the same data. Which data is that?

DR. KRANTZ: I think you published a retrospective look at Copernicus. There's a study from -- maybe I'm thinking of the wrong trial, but OPTIMIZE has that data.

DR. PACKER: Oh, OPTIMIZE.

DR. KRANTZ: And you've seen --

DR. PACKER: Yeah. Remember, OPTIMIZE is a -- is largely an observational study. It doesn't have the protection of randomization. Copernicus actually didn't -- had a very small segment of the patients who pertained to that. As far as I know, that segment was never analyzed separately for the mortality effects of carvedilol.

DR. HARRINGTON: I think that's correct.

Dr. Krantz, you were on the list. Did you have another question or was that the question you wanted to get at?

DR. KRANTZ: I still didn't hear whether the patients were started with the drug in the hospital or not.

DR. HARRINGTON: They were.

DR. KRANTZ: Okay. Thank you.

DR. KARKOWSKY: If I may, this is the requirement from the protocol. I put it up on the slide.

DR. HARRINGTON: Same question? Because I'll put you on the list. Let me make sure that people know -- we've got 15 minutes before lunch. Dr. Nelson, Dr. McGuire, Lincoff, Kaul and Black.

And if we could first try to finish up with FDA. And then we can come back to the sponsor. Again, we'll have time this afternoon.

DR. NELSON: My question may overlap a little bit, but I could try Dr. Karkowsky first. One of the things that wasn't presented here and wasn't clear to me is the issue of dose response to the medications. And I know that in the DAFNE or the ADONIS studies where they tried to do some dose finding, many patients couldn't tolerate higher doses of drugs. And I just wonder if you had any insight into that and what specifically the treatment adverse effects were that had them stop therapy.

I know that there was no death in that study, and they stopped the

treatment, you know before any significant outcomes.

I mean, this has real implications for post marketing of the drug because, obviously, in a controlled setting, the potential drug interactions could be assessed very carefully, you know the physiological parameters and, you know the intake of the drug with food and all could be monitored much more carefully. So -- I mean, I'll ask you, but perhaps the sponsor --

DR. KARKOWSKY: I have minimal data, and the data seems to -- I think it was GI symptoms, but the sponsor would know better than I do.

DR. NELSON: Could we switch to -- I don't know however you switch that so that -- okay.

As part of the clinical development program, you are correct, we evaluated the dose evaluation for the phase 2, 3 program based on the results of the DAFNE study, and in that study we evaluated doses of 400, 600 and 800 milligrams.

And, indeed, the recommendation to start at the 400-milligram dose came from a previously conducted study which Dr. Radzik will be able to describe to you, along with the adverse events that we saw in the 6 and the 800-milligram. So, David, if we could start with the study --

DR. RADZIK: David Radzik, clinical development, Sanofi-aventis. The choice of the 400-milligram BID regimen was based first on phase 1 data, where we determined the minimum dose with a something or a detectible effect, on ECG, QCTCF prolongation, which was regarded as a surrogate for rhythm

control.

Please focus on the first dot on the left. This is the baseline. And then we have the effect of the administration of dronedarone at the dose of 200 milligrams BID, the bottom curve, 400 milligrams BID, the middle curve, and 800 milligrams BID.

As you can see, there was no effect versus baseline with the 200-milligram BID. The first dose to give an effect was 400-milligram BID, and that is the dose which was selected for the DAFNE dose ranging trial.

Slide on, please.

DAFNE was a dose ranging trial on 270 patients, randomized to 400-milligram BID, 600-milligram BID and 800-milligram BID. There was a first period of one week where patients were looked at. They were all in atrial fibrillation at randomization. And we looked at spontaneous conversion. Only 3 percent of these patients converted spontaneously in the placebo group. These were all patients with persistent AF. There was a moderate increase, but with a dose response for conversion in the dronedarone groups.

After this first phase, there was an electrical cardioversion, and then patients were followed for the end point of AF recurrence, and as you can see, in the 400-milligram BID in the middle of the slide, there was a relative risk reduction of 55 percent in the incidence of AF recurrence.

There was no dose response for this end point in this study while, if you look at the bottom row, you see that, concerning side effects,

tolerability was very good in this study; the only significant side effect was diarrhea, and we can see that, whereas in the 400-milligram BID, the proportion of patients with diarrhea was similar to placebo, there was a dose-related increase with the higher doses.

For this reason, we selected the 400-milligram BID dose for further development because it was effective for AF recurrence and it was well tolerated. The EURIDIS and ADONIS trial later confirmed that this dose was effective for rhythm control and well tolerated.

DR. HARRINGTON: Go ahead, Dr. Nelson.

DR. NELSON: You know, I mean, I see that, and I understand diarrhea is a problem, but obviously there's got to be other adverse effects. And I imagine that, although you might suggest that the QT prolongation may not be dose-related -- I'm not sure if that's what you said -- but obviously there's going to be -- I think it's obvious that the more drug you put into your body, the longer your QT is going to get. I mean, this is a, you know, mechanistic, I think, certainty.

So since there are a lot of drug interactions that could potentially raise your drug level and since many of these patients potentially can have -- I guess what I'm really asking is, are there data from the studies that actually look at drug levels in people and the adverse effects that they suffered compared to what the drug levels should have been, given the 400-milligram dose? Does that make sense?

DR. HARRINGTON: So you're trying to tease out the relationships between actual concentration and adverse clinical outcome.

DR. NELSON: Right. I mean, I'm sure they had to measure drug concentrations at some point. And if you give a hundred people 400 milligrams, you're going to get a range of serum concentrations. Some will be lower than, you know, the mean and some will be higher than the mean. Some will be much higher than the mean, right, the outliers, for whatever reason, whether they have a metabolic issue, hepatic metabolism, 3A4, polymorphism, a drug interaction. We know that there's a two- or three-fold bioavailability issue based on the food that you've eaten.

So there's a lot of factors that go into the serum drug level, and I was wondering if there's a relationship between the serum drug -- I say dose response. I guess I really kind of mean serum concentration response.

DR. HARRINGTON: Please -- unless the FDA has done that analysis. No. Okay.

DR. KARKOWSKY: The only data I have is in the review, which is the sponsor's concentration data.

DR. GURAL: Indeed the question that you're asking has been studies. We've done some population pharmacokinetics trials as part of -- analysis as part of the EURIDIS, ADONIS and the other studies.

I'm going to ask Dr. Newton to address that specific aspect of it, and then we can explore, if you need additional information.

Dr. Newton.

DR. NEWTON: So the data you're asking for is dronedarone as the victim. And when we look at dronedarone as the victim, there's intrinsic factors, like you're talking about with age, weight and gender, and extrinsic factors, which are coadministered drugs which would affect cytochrome P453A4.

We've looked at that both in clinical pharmacology studies as well as population pharmacokinetic studies.

Slide on, please.

This slide sums all those factors. And when you look at gender, male versus female, age, focusing on mainly under 65 versus over 75, and weight, you can see the variation is really in the 20 to 40 percent increase in exposures. When you combine all those, take low body weight elderly females, it's only a 60 percent increase in exposure.

And then if you add the effect of a moderate inhibitor -- remember, strong inhibitors are contraindicated -- moderate inhibitors of verapamil, diltiazem, things like that -- there's only approximately another 50 percent increase, which would result in approximately a 2.4-fold increase.

And all these factors were studied as part of ATHENA because we didn't contraindicate moderate inhibitors and we didn't restrict these intrinsic factors.

DR. HARRINGTON: Dr. Newton, I think part -- so you're showing the population-based pharmacokinetics, but what about -- which I think Dr.

Nelson's question gets at -- did you actually have drug levels of the individual patients in the large clinical outcome study and do any relationship between those individual patients and their drug level and their occurrence of side effects -- is that your -- okay.

DR. GURAL: There's a combination of things. We have a combination. We have -- not only do we have some blood level determinations, but we can also show you, as part of the safety evaluation, we looked specifically at the potential for drug-drug interactions during the ATHENA trial and during the development program to answer the specific question that you're asking.

First I'll ask Dr. Newton to describe some of the pharmacokinetics, and then Dr. Chew potentially to describe some of the adverse events.

DR. NEWTON: So as part of the EURIDIS, ADONIS and ANDROMEDA study, we did do the population pharmacokinetics, and we did identify those factors which would increase exposure, and those are age, weight, gender. And Dr. Chew has the data on showing what impact those have on the outcomes in ATHENA.

DR. GURAL: Which is looking at the safety outcome. Dr. Chew.

DR. CHEW: Slide on, please.

What you see here is the demographic that Dr. Newton showed had the highest likelihood of having an increased exposure, elderly women, less than 60 kilograms, with or without CYP3A4 inhibitors. And what you have at the top is the composite of those risk factors, and then the pair-wise down below.

And on the right side you can see the relative risk of an

interaction. We expect that dronedarone would have more interactions, but there does not seem to be an interaction across the CYP3A4 in this demographic -- with no interaction.

DR. HARRINGTON: Are you satisfied, Dr. Nelson?

DR. NELSON: I mean, I guess I am satisfied, if everybody else is. It's not really answering my question. Should I try it one more time maybe?

DR. HARRINGTON: Please.

DR. NELSON: So if you were -- just using the QT duration slide now -- let's just make the assumption that the longer your QT, the more likely you are to have torsade or some other bad outcome. And let's just also make the assumption that the higher your drug level, the more likely your QT is to be longer and, therefore, the more likely you are to have an adverse outcome.

Is there a dose response -- a number, a serum level of X equals, you know, a certain risk of having a QT of Y and a bad outcome of Z, or some sort of direct relationship -- and the reason I ask is because, again, in the post-marketing world, they're not going to follow the protocols the way you want them to, and people are going to have these very high serum concentrations, for whatever reason. And this is one of the safety issues that you really have to consider.

DR. GURAL: Although -- I understand better now your question. We didn't measure specifically plasma levels at -- don't leave, Dr. Chew -- at the time of an adverse event, but we knew those factors that could contribute

to an increase in exposure.

So if we looked at the elderly patient or the underweight patient or one who is taking a potent inhibitor, we could then assume that those patients are the ones that are having the increase in exposure, 1.2-fold up to 1.6-fold. And we looked at that subset of patients to see whether or not they had specific changes in their safety profile, in particular the QT.

So I'll ask Dr. Chew to review the data that we have on that.

Dr. Chew?

DR. CHEW: May I have the slide on, please.

This is looking specifically at the QT interval in this demographic of elderly women less than 60 [sic], greater than 75 years of age. And, again, looking at QT, with a P-value of .55 as shown above.

DR. GURAL: And this is with an exposure factor of about 1.2.

DR. CHEW: Next slide, please.

And this is the -- looking at the other intervals, the 12-lead EKGs, just to show that there is -- as you would with most class III agents have a prolongation in the QT.

DR. SWENSON: Quick question along those lines, then. What do we know about the deposition and the fate of this drug in people with class IV and these decompensated -- I could predict that maybe 400 milligrams BID is possibly just too high in those people. You've given us the weight and the gender and the use of cytochrome inhibitors.

DR. GURAL: The patient -- the intended patient population does not include class IV, congestive heart failure. I'm not sure whether we have specific data in the ANDROMEDA trial. I will ask Dr. Newton if he can come and address that question.

DR. HARRINGTON: You're asking, Dr. Swenson, if they have enough data to understand what the drug concentrations might be in the setting of advanced decompensated heart failure?

DR. SWENSON: And could that underlie the negative signal?

DR. NEWTON: We don't have a lot of data in class IV, but we definitely have data in I, II and III -- slide on, please.

So this shows the post-hoc pop PK parameters on Cmax and AUC across the different classes of heart failure. The ends are on the first column, and there's no effect of heart failure up to class III. And class IV, as I said, we have very little data on.

DR. HARRINGTON: That's helpful. We have Dr. McGuire, Lincoff, Kaul and Black.

DR. McGUIRE: I want to come back to this, trying to decipher the context of the reduced afib hospitalizations. One potential scenario is afib was admitted to initiate an alternative anti-arrhythmic for people who failed rhythm control in a clinical environment where rate control is the state of the art.

And what I'm wondering is if there's some bias of investigators here

in a so-called rhythm control study to have a higher propensity to admit patients for cardioversion and taking people off study drug to initiate inpatient those anti-arrhythmics requiring inpatient initiation.

So getting along the lines of removing afib hospitalization from the overall analysis -- I would also be interested to see an on-protocol analysis of the same end point; that is, patients throughout the study who were treated -- particularly in ATHENA, but ideally for all studies combined -- patients who stayed on study drug.

Did you have an opportunity to have a look at protocol treatment outcomes?

DR. KARKOWSKY: We have not looked at that data.

DR. HARRINGTON: Darren, are you trying to get at the same question I think Sanjay is trying to get at, which is what's the end point being driven by?

DR. McGUIRE: Right.

DR. HARRINGTON: Is it hospitalization for cardioversion? Is it hospitalization for institution for another medicine? Or is it that people feel bad --

DR. McGUIRE: Right.

DR. HARRINGTON: -- and come to the hospital?

DR. McGUIRE: Exactly. I'm trying to get at, were patients admitted based on clinical grounds because they were having morbid experiences or were

they admitted to clean up an EKG?

DR. GURAL: Do you want the sponsor?

DR. HARRINGTON: Unless the FDA has more to add on this. I mean, you had indicated, I think, that, by the case report form, it was difficult for you to tease that out.

DR. KARKOWSKY: There was nothing on the case report form --

DR. HARRINGTON: Okay. So perhaps the sponsor can help with that.

DR. McGUIRE: And part of the impetus for that query -- and I don't remember the numbers offhand, but it seems to me that 50 percent of the mortal events occurred off study drug. I may be recalling that incorrectly, but it seems like a large proportion of the primary outcome events occurred after study drug discontinuation.

DR. GURAL: During the break we said we were going to come back and address that specific question. So I will ask Dr. Packer, because we have a number of information to share with you in that regard.

DR. HARRINGTON: So why don't we then make this the last response -- I realize I've left Lincoff, Kaul and Black hanging, but we'll have time right after the public hearing, if that's acceptable -- and we'll break for an hour for lunch. So why don't you, Milt, make this the last series of discussions.

DR. PACKER: Sure. Darren, let me just make sure -- I think there are two separate questions. One is, were the patients -- what proportion of the hospitalizations for atrial fibrillation resulted in electrical

cardioversion? Would that be helpful?

DR. McGUIRE: No. We have those data in the briefing document. I'm more interested in -- and it's somewhat reassuring that, if I recall, about 40 percent of the so-called afib hospitalizations had underlying heart failure as the impetus for hospitalization.

But if you take those with heart failure and those with hemodynamic instability, which we would all agree is a clinical indication for admission for afib, then what are you left with? Are you left with people who have recurrent or persistent afib perceived by the investigator to be failing in anti-arrhythmic therapy and, therefore, admitted not just for cardioversion, but more likely -- or similarly likely -- for initiation of an off-study drug -- of an alternative anti-arrhythmic requiring hospitalization for initiation?

Does that...

DR. PACKER: Just to make sure, because if we can't get it now, maybe we can get it after the break -- but I just want to make sure that we understand what we're looking for.

Amongst the patients hospitalized for atrial fibrillation, setting aside -- you know the proportion that were electrically converted, so we're not talking about those individuals. We're not talking about the people who came in with worsening heart failure, because that's in the briefing document. What you're talking about is a subset of patients who were hospitalized for atrial fibrillation, didn't have heart failure, who weren't cardioverted, and

the question is why?

DR. McGUIRE: Right. And very specifically, I'm curious about how many patients were initiated on an alternative anti-arrhythmic for reasons that aren't heart failure or hemodynamic instability; therefore, solely for the purpose of restoring sinus rhythm, which is kind of out of context for current clinical practice.

And I think the best way to get at that is to look only at the analysis in patients who were persistently treated with study drug throughout the study interval.

DR. GURAL: We will look to see what available data we have during the break to make sure --

DR. HARRINGTON: Go ahead, Sanjay.

DR. GURAL: -- that we answer your question.

DR. KAUL: Just so that you -- I give you the opportunity to collect this data. I think the bottom line is what we're trying to get here is to address the robustness of this end point. And one way you can respond to this is to share with us how many of these hospitalizations led to mortal or irreversible morbidity. Or were they just simply due to convenience because of the variability in the practice pattern?

So I think that's the question. Robustness of this end point. Any impact on symptoms that could impact quality of life and health status.

DR. HARRINGTON: Okay. So you have your charge for lunch.

DR. GURAL: You want after lunch, then.

DR. HARRINGTON: After lunch.

DR. GURAL: Okay.

DR. HARRINGTON: So we'll break now till 1:15. For the panel, there is lunch available in the Montclair room, room 1105. And just as a reminder to the panel members that we should not be discussing the meeting at lunch time. We should do that in the public forum.

See you at 1:15.

(Whereupon, at 12:16 p.m., a lunch recess was taken.)

AFTERNOON SESSION

(1:15 p.m.)

DR. HARRINGTON: Why don't we go ahead -- people go ahead and take their seats. We'd like to begin the afternoon session.

The plan for the afternoon is that we're going to open up with the open public hearing. We have a series of people who would like to make some remarks.

Following that, I'd like to turn back to the questioning that we had this morning, and we'll take it up with Dr. Lincoff, Kaul, Black, and then whoever else would like...

From the panel's perspective, this is really the chance to continue to ask questions of both the FDA and the sponsor. At about 2:30, a quarter of 3:00, I would like us to turn our attention specifically to the questions that FDA has provided us. If it's sooner than that, terrific. But I'm going to try to move the conversation along so that we're actually going through the questions 2:30, quarter of 3:00. Many of them we've started to discuss, but this is going to give us an opportunity to more fully flesh those out.

So I'm going to read a statement, which we're asked to read at the beginning of the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee

meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The issues and comments -- the insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect.

Therefore, we would ask that you speak only when recognized either

by me, as the Chair, or by Elaine, and thank you for your cooperation.

If we could have the first speaker introduce yourself.

DR. LEVY: Good afternoon. I'm Dr. Susan Levy. I'm a long-term care medical director. I'm an internist and geriatrician. I work at a long-term care nursing home in the Baltimore area, Levindale. I'm actually here representing my colleagues who are long-term care medical directors as a member of the American Medical Directors' Association which is located in Columbia, Maryland. To my knowledge, I don't have any personal relationship with the drug company here today. I am not aware -- was not made aware of whether the organization has received any monies, but no one is paying for me to be here today or to have driven here today or for anything related to my appearance here today.

What I'm here basically to do is to appeal to you all as colleagues about our concerns for atrial fibrillation. Many of this I think you already know. Obviously, atrial fibrillation is a major problem among the frail elderly, particularly the population that we care for, the most frail of the frail, in our long-term care settings.

There have been no real major changes in treatment for atrial fibrillation that have been available to us probably over about the last 20 years. However, we know that hospital admissions related to atrial fibrillation, both paroxysmal atrial fibrillation and uncontrolled atrial fibrillation has increased significantly over the same time period, partly

relating also to the aging of the population that we're seeing and serving.

It's our number one arrhythmia that we deal with. I see patients every day who are being managed for either -- in atrial fibrillation or have a history of paroxysmal atrial fibrillation. The incidence clearly is continuing to increase. It's more prevalent that we're seeing in the patients that we serve. It's associated with an increased mortality. I think that's something that all of you know. And certainly well related to some of the strokes that we see in many of our patients -- 15 percent of strokes are probably related to atrial fibrillation.

We often see that on the long-term care side because there many patients who then lose function and end up in long-term care institutions as a result of strokes from which they have not recovered, and their ongoing need for management of their associated cardiovascular problems.

Actually, we do know from studies that atrial fibrillation adversely affects the quality of life. That's one of the things certainly as a geriatrician, also serving patients in the community, why new medications to help manage this problem are so important to us.

We do know that currently literature suggested that we focus primarily on rate control in those patients with established atrial fibrillation, but this still leaves us with a number of patients who have intermittent paroxysmal atrial fibrillation.

We also know that the management of patients long-term with

anticoagulation with the therapies that we currently have available to us are often very problematic. They are difficult. They have significant side effects. So better management of atrial fibrillation, potentially not requiring us to have to use these medications for as long a period of time -- also very important for patient safety and for the well-being of the population that we serve.

Again, we know what -- the medications and the regimens that are currently approved and available for atrial fibrillation. We have not had any real major improvements in the regimens that we've been able to use more recently. We do have information that probably rate control is an acceptable alternative in many -- in many seniors to help manage atrial fibrillation. We certainly want to support the ongoing research and development and ongoing approval of medications that may help manage this very difficult problem for many of our seniors, both in a long-term care setting and the community.

Thank you.

DR. HARRINGTON: Thank you, Dr. Levy.

Our second speaker, if you could come to the microphone, introduce yourself and --

MR. BARANSKI: Yes, Mr. Chairman. My name is Jim Baranski. I'm with the National Stroke Association. I personally have had no financial transactions with the sponsor, nor has our organization. The sponsor did not pay for me to be here today, and I did fly commercial. And I am the CEO and

executive director of the National Stroke Association.

And what I'd like to do is really provide not so much for those of you who are in patient practice, but for everyone else, the points of view that we hear from the physicians that we work with -- and, again, recognize we're the cerebrovascular side of this -- but to share with you the physician side, what we hear, as well as the patient side.

And, you know, I think the physician side can be pretty much summed up into four words: big problem, few options. And we hear that time and time again.

You're all familiar with the current treatments for afib. Not all of you may recognize the size of this problem. We heard earlier about the 2-1/2 million patients with AF, but in addition to that, there will be 780,000 strokes in the upcoming year. Of those 780,000, we know that roughly 15 percent are resultant of AF, a known risk factor for stroke.

In addition to that, we have 6 million -- it's estimated -- 6 million stroke survivors in this country who are desperately, desperately trying to seek any alternative to prevent a recurrent stroke. So I certainly can understand why physicians say big problem and few options.

From the patient perspective -- and, again, I'll try to go quickly out of respect for the number of items that you have in the parking lot from this morning -- the patient perspective -- you know, a typical conversation that I might hear from a patient -- and, again, this is primarily a stroke

survivor -- would be -- and I don't mean to simplify this conversation, but it oftentimes goes something like this.

So let me understand. The doc tells me that they can treat my bum ticker, which just isn't ticking quite right, and because of that, it creates a clot, and there's this other tool or therapeutic that can be used to treat that clot, and the two together don't work so well, but yet I don't want to have another stroke; I certainly don't want to have another clot; what are my options? And if I go with what's going to kind of control my ticker, there are some long-term issues with that.

And I usually then hear something like, gee, we can improve my sex life. There's a tool for that. But what about my problem? What about this problem?

So I think that, as we reflect on how we try to interact with patients and try to educate patients, it always comes down to what's coming around the corner, what options are there coming around the corner.

And to the extent that -- well, actually, you know what? I need to say one other thing. As I listened to this morning's discussion -- and particularly when I think about the current economic climate and the headlines that we hear, you know, and see every day -- this term that's really new to me in the last year or so, toxic assets, keeps popping up into my head.

And from the patient's perspective, it's almost as though that's their headline, toxic assets. There has to be another option. Find me

another solution.

That's it. Thank you.

DR. HARRINGTON: Thank you, Mr. Baranski.

And our final speaker is Melanie True Hills from the StopAfib.org group and the American Foundation for Women's Health. Ms. Hills?

MS. HILLS: Thank you. Good afternoon. I'm Melanie True Hills, CEO of the American Foundation for Women's Health and StopAfib.org which is an atrial fibrillation patient advocacy site, resource.

Sanofi-aventis is one of a number of sponsors of StopAfib.org, but they have not paid for me to be here today. I'd like to thank the committee for the opportunity to speak on behalf of the afib community. It's not my voice; it's the voice of thousands and perhaps millions of people with atrial fibrillation.

I am an atrial fibrillation survivor. In 2003, my heart skipped some beats and started racing. I got dizzy. My right leg went cold. My right eye went fuzzy. I had blood clots and a near stroke from atrial fibrillation.

Episodes started coming frequently. Once you've had blood clots, afib becomes frightening. Would I be off by myself and have a stroke? My family wouldn't let me go anywhere by myself. Afib is physically exhausting, and it's emotionally draining, not just for you, but for your family too. And the financial toll. Huge medical bills. Trouble getting insurance once you

have afib. Lost time from work and, for some, even losing their jobs and their careers. Afib can be financially devastating. But we don't talk about it because we're too embarrassed.

Well, since I was never stable on Coumadin for genetic reasons, I was a stroke walking around waiting to happen. So I had a surgical procedure in 2005 that cured my afib and gave me back my life and my freedom, and I have been free of afib for three-and-a-half years, and I'm thankful for it every day.

Well, after being cured, I couldn't stand on the sidelines and watch as others suffered, so I created a website, StopAfib.org, for anyone with afib to provide information and answers. We're the number one U.S. arrhythmia site.

Every week I talk with hundreds of afibbers, and many of them say, my doctor insists that I go on amiodarone, but I'm scared of the side effects.

Well, I realized that someone needed to speak on behalf of the afib community, so that's why I'm here today.

I reached out to them for their experiences with amiodarone, good and bad, and no -- with no indication as to why I was asking. And responses flooded in. Some said they had just started on amiodarone and it was working fine. Others had been on it for several years, and it worked great for them. For others, it didn't work, or had stopped working. And for some it made the afib worse.

Some had side effects that were bothersome, such as nausea, vomiting, dizziness, aversion to food, aches and pains, rash, sun sensitivity, decreased energy and flu-like symptoms. Some consider these worth living with. Others decided to stop amiodarone and their symptoms reversed.

One said, I only realized how badly it made me feel after I stopped the amiodarone. Most, however, had serious side effects, such as thyroid damage, liver problems, kidney problems, and potential failure, lung and breathing problems and respiratory distress, vision problems such as halos and corneal delamination, skin discoloration, severe hair loss to the point that they needed to wear a wig, and cognitive problems and speech loss that caused several to lose their jobs.

Most had multiple problems, and many were so miserable from amiodarone that they just couldn't function.

Doctors believe that amiodarone paralyzed one patient's diaphragm. IN another, amiodarone fried her nervous system, and even today she still shakes endlessly and can't sleep. An artist can no longer paint due to her blurred vision and trembling hands. And one retired doctor had flu-like symptoms and died from amiodarone-induced pulmonary toxicity.

But most surprising to me were the responses that came in saying, we're anxiously awaiting dronedarone. What's taking the FDA so long? I heard that over and over. One retired doctor even said, my wife and I may go to Europe so she can get it because she's having so much trouble with amiodarone.

Another said, dronedarone is my last hope before considering surgical procedures.

I hadn't even told them why I was asking, as I didn't want any bias, but believe me, the atrial fibrillation community is far from unbiased over this.

After so many such comments, I asked for more input to share with you today, and I was stung by the responses. Here is what one woman asked me to share with you. She said, I developed afib in 2002. I already had hypertrophic cardiomyopathy, severe to moderate mitral regurgitation, and my left atrium was enlarged. I couldn't tolerate afib. I was put on amiodarone and given an ICD pacemaker. I took amiodarone for almost three years, and the results were miraculous. But then I developed amiodarone-induced thyroiditis. Surgery to remove the thyroid was deemed too risky, with my heart condition, so I spent a year off of amiodarone, though my endocrinologist wanted to radiate and destroy it. I got my thyroid back to normal, but I suffered from afib as the amiodarone wore off.

Two years ago, she continued, I had heart surgery with a MACE procedure and was afib-free for a year. But then it came back. I was faced with destroying my thyroid and going back on amiodarone, the only drug I can tolerate. I consider myself lucky that it only attacked my thyroid and not my lungs or liver. But I would risk losing my life to be afib-free.

She also said, I am counting the days until I can take dronedarone,

and will travel abroad to get it if I have to. I am an invalid in afib. The only drug that guarantees sinus rhythm will kill me, but some day I will have no choice unless dronedarone is made available. I live every day with a crippling fear of afib. So I pray and plead please allow this drug into the U.S.

So today the afib community is asking you, won't you please give us options. Won't you please give us solutions. Won't you please give us our lives back. Thank you.

DR. HARRINGTON: Thank you, Ms. Hill.

So that was the final of the open public hearing speaking, and now the open public hearing portion of the meeting has concluded, and we will no longer take comments from the audience.

The committee will now turn its attention to address the task at hand, careful consideration of the data before the committee, as well as the recent public comments.

So -- yes?

DR. GURAL: Do you want us to respond to the questions of --

DR. HARRINGTON: Yes, why don't we do that. Why don't we start with the questions that were hanging from this morning. You have some additional data for us. And then I'll go to Drs. Lincoff, Kaul and Black, in that order.

DR. GURAL: Well, if we could -- could we have that slide off.

We take very seriously the comments that you've made this morning

and have prepared responses and reactions to those questions. And I'm going to ask Dr. Packer to come and address those. We are prepared to answer any questions that you may have. We may not have all of the data right at our disposal, but we can generate the information as needed.

Dr. Packer?

DR. PACKER: I'm going to go through these in some arbitrary sequence. If I don't address the questions, please remind me that the question that you asked was not answered.

Let me begin by emphasizing that when -- almost all the analyses you've seen are timed to first event analyses. That means that if the first event that a patient experienced was atrial fibrillation, that the analyses that you've seen for the primary end point would not include events like myocardial infarction or stroke that occur after the onset of atrial fibrillation.

There is an unfortunate masking phenomenon that occurs when you use a composite end point for a primary -- for a primary analysis, a time to event analysis. And a number of committee members wanted us to essentially remove the masking effect because none of the analyses, or very few of the analyses that you saw this morning, did so. Since atrial fibrillation was a prespecified part of cardiovascular hospitalization, you saw a lot of atrial fibrillation, and it tended in this study, that if a patient had two cardiovascular hospitalizations, one for afib and one for myocardial

infarction, the afib hospitalization occurred before the myocardial infarction hospitalization. So you want to keep that in mind.

Sanjay asked about whether -- if having atrial fibrillation portended bad things happening to the patient. You wouldn't be surprised to know that the answer is yes, atrial fibrillation is a powerful prognostic factor in these patients regardless of treatment.

Can we have slide XX-6 up.

Sanjay, you specifically asked about death. And this is the analysis of time to death from the -- up to the end of the study in patients -- from the point of time when patients were hospitalized for atrial fibrillation. Let me emphasize that you need to understand that this analysis is confounded because it is an analysis -- not only is it post-hoc, but it's based on a post-randomization variable, and there are all sorts of reasons to view analyses based -- without the protection of randomization very carefully.

So I put this up for information purposes, and not for the purpose of showing any conclusions. But since you asked, this is what happened with respect to mortality in the patients after their first hospitalization for atrial fibrillation in terms of death. And you can see that there were 22 deaths in the placebo group after a hospitalization for atrial fibrillation and 8 deaths in the dronedarone group after hospitalization for atrial fibrillation.

You can look at the relative risk at the bottom, but frankly, I

wouldn't pay much attention to it because of the confounding issue.

Jim, you look like you have a question.

DR. NEATON: Yeah, I kind of support that question, but I don't think this addresses it. What I think -- to me, the more relevant statistic here -- this is not surprising --

DR. PACKER: This is not intended to be --

DR. NEATON: No, no. I --

DR. PACKER: This is descriptive.

DR. NEATON: Yeah. I realize that. And so it's not surprising, this 22 and 8, because there's just a lot more afib in the placebo group. And so the question is, what is the increased risk of death for a person who develops afib versus a patient that doesn't?

DR. PACKER: And -- irrespective of treatment. From at least epidemiologic data, you have seen that the increased risk of death of two-fold. And that analysis was done in this study -- does anyone know the magnitude of the increase? We can get that for you, but I wouldn't be surprised if it were similar to the population-based epidemiological studies.

So irrespective of treatment, at least in the literature, it's a two-fold increase in risk, Jim.

Second point. Jim, you specifically asked about the drivers of non-AF hospitalization in the ATHENA trial -- and can we bring up slide XX-2.

You can always tell when sponsors make up slides during a break

because they have XX in front of them. And this comes -- Jim, this comes -- this is an adaptation of a table in the briefing document. This is a table on page 89, table 43. I refer you to the table because it has all the results. This is the main reason for first non-AF cardiovascular hospitalization in the ATHENA trial -- this is the breakdown of the components. You have previously seen the Kaplan Meier curves, so these are the individual components.

I reproduce on this slide every single cause of cardiovascular hospitalization that had more than 50 events. And you can see, regardless of whether we're talking about worsening heart failure, myocardial infarction, whether we're talking about any of the above, the numbers are lower in the dronedarone group compared with the placebo group. And if you take -- and, in fact, if you look at the relative risks, they are strikingly similar to the overall effect on non-AF hospitalization.

So this -- the reason why this is a particularly interesting analysis is this removes the masking effect. So Sanjay wanted to know if -- you know, I'm really concerned about atrial fibrillation. It seems like all of this is driven -- or a lot of this is driven by atrial fibrillation. It only appears that way because when you get atrial fibrillation, you don't see the hospitalizations afterwards.

So now I'm taking out the atrial fibrillations so you can see the hospitalizations afterwards and you can see the robustness of the data.

DR. HARRINGTON: So this was not censured if you had another AF

event. This is all of the non-AF hospitalization. Okay.

DR. PACKER: Right. So --

DR. NEATON: If I could ask a question just along those same lines. So each one of these lines is timed to first event?

DR. PACKER: Yes.

DR. NEATON: So a person could contribute to more than one line there?

DR. PACKER: Yes.

DR. NEATON: Okay.

DR. PACKER: Wait a minute. Let me see. No. No. Okay. In order to --

DR. NEATON: So that's the analysis you probably want to do, because --

DR. PACKER: Yeah.

DR. NEATON: -- otherwise there's got to be some censuring going on here if the multiple events --

DR. PACKER: Yeah. Jim -- let me put it this way. This table fixes the problem of censuring due to atrial fib. It doesn't fix the problem of mutually interactive censuring. However, you have already seen analyses in my presentation which were focused on individual cases for which any preceding event and the potential for censuring was removed.

And you saw that the results of that analysis is very consistent

with this analysis.

Darren asked a question about deaths occurring on and off study drug during the course of this study. Darren, let me just make sure that I understand. I think your concern is that if a patient came off of -- had atrial fibrillation or something and wasn't doing well, came off of placebo, that they might be put on an anti-arrhythmic drug that was toxic, and that would adversely affect the placebo arm, and that -- the differential use of toxic anti-arrhythmics might contribute to the mortality effect. Is that about right?

DR. McGUIRE: No. It's actually simpler than that. Is -- the question is -- I'm just trying to figure out, for these afib hospitalizations, what -- the reason they were hospitalized.

You know, as a clinician, I know -- I decide to admit a patient with afib most commonly for heart failure or hemodynamic instability, much less commonly for rate control, and even less commonly for cardioversion.

So I'm trying to figure out, were people being admitted just because they were in afib again or were they being admitted because they were suffering morbidity?

DR. PACKER: And the answer is the latter. I thought you were asking a different question, so I apologize. We actually have a number of analyses in progress to address that, but let me just make one point which I think would be most comforting, and that is that, of all of the patients who

had atrial fibrillation in the trial who underwent cardioversion, only 30 percent were hospitalized. 70 percent of the patients who developed atrial fibrillation were not hospitalized, and they're not included in any analysis that you've seen today because the analyses you've seen today are based on hospitalizations. So that's one piece of information.

DR. HARRINGTON: So are you implying, Milt, that the 30 percent got hospitalized for their cardioversion -- implied is that they had some symptoms, and that the other 70 percent were able to be handled without hospitalization? Or you just don't have that data?

DR. PACKER: I don't think we have that data. I would say that a substantial -- the vast majority of hospitalizations for afib were not cardioverted. That you've seen in the briefing document.

The vast majority of cardioversions were not hospitalized. So it's sort of like a Venn diagram with a little bit of overlap, but one doesn't explain the other. Darren, does that help?

DR. McGUIRE: Not really, and my guess is we may not be able to get to this answer based on the scant data that were collected. But I guess my concern here is when the principal driver of this clinical outcome is admission for afib, there are really a number of reasons to admit afib, one of which would be the bias of the investigator in a rhythm control trial that, if you show up at my research clinic in afib again, I may admit you just because you're in afib, feeling perfectly fine, but your EKG is in atrial fibrillation

and not sinus rhythm, so I may admit you either to stop study drug and initiate an anti-arrhythmic or to cardiovert.

The latter has been addressed, the cardioversion, but I'm still not completely satisfied that these patients aren't being admitted simply because they're in afib for rhythm control.

DR. PACKER: I don't know why a physician would admit a patient to a hospital for atrial fibrillation just because they had -- I mean, you would want to do something. Remember, most of the atrial fibrillations in this study, when they recurred, weren't hospitalized. They were cardioverted outside. So -- but I don't have the data that can address that.

But I do want to make the point that it only appears that afib drives the hospitalization end point in a time to a first event analysis because of the masking effect. If you take out the masking effect -- and I just showed you that data -- it's clear that there is a reduction in cardiovascular hospitalizations for non-afib reasons across a whole host of clinically relevant end points.

DR. HARRINGTON: So let me stop you there, Milton.

Dr. Karkowsky, I'd like you to maybe weigh in on this because you specifically pointed us to the 8 percent difference, 7 percent of which was the afib. And obviously you looked at the -- you know, what Milton is doing is looking at all the components of the composite, so to speak. Do you agree with his interpretation?

DR. KARKOWSKY: We have not done that analysis yet. What we did look at was the time to the initial event. It's hard to figure out how one would tease out, from the data that I saw on the case report form -- how one would go about getting that information.

The sponsor has much more facility with its own data sets than I do. But I don't have any information other than --

DR. HARRINGTON: Than the principal time to event analysis?

DR. KARKOWSKY: Right.

DR. HARRINGTON: Okay. Let's -- do you have another comment?

DR. PACKER: Yeah. I just wanted -- because the committee also had a couple of other questions, and I want to -- and, again, if I don't answer them, please let me know.

Sanjay, you had questions about a quality of life -- an arrhythmia quality of life assessment scale in the ATHENA trial. Let me just describe -- this was implemented as a protocol amendment during the course of the study. There was no baseline evaluation in the vast majority of the patients.

Patients were given this questionnaire at the time of scheduled study visits. And that's very important because if you take someone who has atrial fibrillation and they have episodes of recurrence between scheduled visits, they're going to be highly symptomatic between scheduled visits, but by the time they come to a scheduled study visit, they may or may not have the atrial fibrillation and they may or may not have associated symptoms.

So the difficulty in this interpretation is that the questionnaire was given at study visits, not at the time of recurrence of atrial fibrillation. So one could be terribly symptomatic between study visits, but not because of the interventions for the atrial fibrillation -- you wouldn't see that effect at scheduled visits. Is that helpful?

DR. KAUL: Are you implying that the data are uninterpretable? I haven't even seen the data.

DR. PACKER: The quality of life assessment data?

DR. KAUL: Yeah.

DR. PACKER: Yes, I'm implying they're uninterpretable.

DR. KAUL: So why was the questionnaire given to the patients?

DR. PACKER: Well, they are interpretable, but in the -- well, no, they're not uninterpretable. They are interpretable for the context of what the patients were experiencing in their study visits. And you may or may not put a lot of weight on that.

DR. HARRINGTON: So do you have the actual data that you can show us, and then we can interpret it and give our view of it?

DR. PACKER: No problem. Hold on. We'll try to get the back-up slide.

DR. HARRINGTON: Okay

DR. PACKER: Sanjay, the -- but just remember, what you're looking at are questionnaires given at scheduled study visits.

DR. KAUL: I understand.

DR. HARRINGTON: Dr. Temple wants to weigh in here with something.

DR. TEMPLE: Actually, I had a question. If -- it's important to distinguish between the primary end point, which is time to first event -- and only counts first events; it doesn't count later events -- and the overall analyses.

For example, I think Avi showed the component of time to first event that were things other than AF, and they were more or less even. It was only in the later data that you get that thing that Dr. Packer showed where it's like -- where there's a borderline effect.

So I want to be sure of one thing. If the patients went off the drug, their events were no longer counted; whether they were deaths or other things, they weren't counted after they were off the drug, right?

DR. PACKER: No, no, no. This is a true intention to treat analysis, Bob.

DR. TEMPLE: So if they were hospitalized for an event after being off the drug, they were counted?

DR. PACKER: They were counted.

DR. TEMPLE: Okay.

DR. PACKER: No, no. This is intention to treat from the time of randomization to the end of study regardless of patients were maintained on randomized treatment.

DR. TEMPLE: Okay. And that is all of the events through the end of the study, whenever it is.

DR. PACKER: All the events for all the analyses that you've seen --

DR. TEMPLE: I see, okay.

DR. PACKER: -- without exception.

DR. TEMPLE: There was some issue about whether deaths that occurred after the drug was stopped should be counted.

DR. PACKER: I would be more than happy to address that.

DR. TEMPLE: And I thought the conclusion was they shouldn't be.

DR. PACKER: Okay. Can I have the backup slides on --

DR. TEMPLE: Is that a point Avi made?

DR. PACKER: -- that? This is a new question, Bob.

DR. HARRINGTON: Okay. It's Dr. Temple, so we'll go along with it.

DR. PACKER: Okay. This is not the right slide. Can I have the slides on the difference between the FDA cutoff and the sponsor cutoff?

DR. GURAL: We can explain them.

DR. PACKER: Let's see. I think we're going to get them in about ten seconds.

While we're finding them, let me --

DR. GURAL: Let's explain the difference in the cutoff dates.

DR. PACKER: We will get that. Let me just emphasize that -- yes, this is great. The -- there are -- the original protocol said that the

patients would be followed for one year after the last patient was randomized. And that would imply a common -- that's summarized under what is called common study end date. That common study end date was December 30th, 2007.

The sponsor, because of difficulties getting some patients back to the clinic in the time frame specified in the protocol, extended the follow-up for patients until they could all return to the study visit. That's listed under the column "extended analysis." And that is what the sponsor did as their primary analysis, and that is what I showed throughout the presentation.

DR. HARRINGTON: So was there a set date that differed from the December date and --

DR. PACKER: It was not -- Bob, it wasn't a common study end date. It was extended on an individual basis based on scheduling issues on an individual patient.

DR. GURAL: But all deaths were up to 14 days only.

DR. PACKER: Right. So -- but the deaths were only up to 14 days after the common study end date.

DR. HARRINGTON: And, Dr. Karkowsky, when you did your analysis, you used the common study end date?

DR. KARKOWSKY: That's correct.

DR. HARRINGTON: And what -- could you explain to us, Dr. Karkowsky, when you do the analyses in the two different ways, what do you find?

DR. PACKER: I actually have those slides up, if you want.

DR. KARKOWSKY: Thank you. What we observed was that, for the primary event rate, the all-cause mortality -- sorry, cardiovascular hospitalization and all-cause mortality, we didn't even bother redoing it because the P-value was down to 10 to the minus 8.

When you do all-cause mortality, the P-value changes from .17 to .25, both nonsignificant. When you do the cardiovascular mortality rate, the P-value changes from -- I think it was .25 to about --

DR. PACKER: .25 to .37.

DR. KARKOWSKY: -- .37. So it modified it a little bit. It was not a direct impact on a conclusion.

DR. PACKER: Just to reassure you, let me have the backups so that you can see that what Dr. Karkowsky -- no. The one that you had before. You can show that one, but show the previous one.

DR. HARRINGTON: Bob, is this the essence of your question?

DR. TEMPLE: Well, partly. I'm probably showing, you know, my --

DR. PACKER: Okay. Can we see that?

DR. TEMPLE: I'm probably also showing my -- I don't know -- retrograde attitudes. But I'm always curious about the on-therapy data too. I mean, I know absolutely out ITT and why that's virtuous and how it protects you, but it also obliterates things.

Did you do an analysis -- an on-therapy analysis too? You probably did. No? You didn't even do one?

DR. PACKER: That's -- there's a religious principle involved.

DR. TEMPLE: I know. I know. I don't share it entirely.

DR. PACKER: I -- you know, it -- like our -- we need papal disposition [sic] to be able to do that, and it wasn't --

DR. TEMPLE: Oh, no. You can do it. You know, you just can't count it. That's all.

(Laughter.)

DR. TEMPLE: All right. Another time. Forget it.

DR. PACKER: Are you telling me I'm allowed to look, but not act on my -- never mind.

DR. TEMPLE: Something like that. It's the way you didn't put P-values down for your secondary end points that you weren't allowed to look at anymore --

DR. PACKER: Oh, I --

DR. TEMPLE: -- because you failed on the overall mortality.

DR. PACKER: Oh, no. We can talk about that.

DR. HARRINGTON: Let's -- so do you have the data --

DR. PACKER: Yes.

DR. HARRINGTON: -- slide for us?

DR. PACKER: Yes. This is -- behind you.

DR. HARRINGTON: Okay.

DR. PACKER: Okay. The -- you can see the delta between the two

analyses. It's a very small fraction of the total events. That's summarized in the difference in the -- on the right-hand side of the slide. And -- next slide -- no, not that one. The one that has the hazard ratios. You had it up just a second ago. Yes. May I have that?

This is the difference in, if there is a difference in, what the analyses would look like if you had a common study end date or if you used the extended follow-up and, frankly speaking, I don't see any material difference between the conclusions here.

DR. HARRINGTON: Okay. Thank you. Do you have the quality of life data or the symptom data?

DR. PACKER: Do we have that? I think I saw it just about -- it was up here about 30 seconds ago.

Okay. Bob, just to let you know, there's just -- we have a couple more things, and I think we're done.

DR. HARRINGTON: Terrific.

DR. PACKER: Okay. Can we see that slide?

Sanjay, these are the data that you're referring to. This is the checklist scores -- this is sort of an atrial fibrillation checklist score that was done per study visit. You can see no treatment effect at the study visits. And that's what you were referring to.

And, again, I'll emphasize that these assessments weren't made at the time of recurrence.

DR. HARRINGTON: These assessments ask the patient to recall their worst day or their -- I'm not familiar with this quality of life score.

DR. PACKER: Neither am I. As I understand it, they asked patients to historically remember things up to a month prior to the time of assessment. I don't know of any quality of life assessment that asks people to remember their worst day.

DR. HARRINGTON: So this is a -- this is not based on diaries; this is all based on recall.

DR. PACKER: That's correct. And -- and it was only on the last visit, Bob. It was done at 12 months and 18 months -- is that right? -- after randomization. So if I gave you the wrong impression that this was done at every study visit, it was not. It was done all the way at the end of the study and asked people about how they felt in the prior month, and of course is confounded further by the fact that you had to be alive to --

DR. HARRINGTON: To feel good.

DR. PACKER: -- at the end of the study to have this assessment.

DR. HARRINGTON: Sanjay?

DR. KAUL: Well, I can't comment on the validity of this tool, but if I take it at face value, I think it would be a reasonable interpretation that placebo is as effective with dronedarone or, conversely, dronedarone is as ineffective as placebo.

DR. PACKER: Are you qualify that in any other way?

DR. HARRINGTON: We're going to come back to this during the discussion because one of the questions has to do with the meaningfulness of what we're observing here.

You said there were two other points that --

DR. PACKER: Right.

DR. HARRINGTON: -- the sponsor wanted to cover.

DR. PACKER: Sanjay also asked about symptoms of heart failure. This was the first question that you asked. The reason we postponed addressing it was because we wanted Dr. Karkowsky to show the data first so that we could address it. If we addressed it before he showed it, people might get confused.

Can I have the slide up, please.

This comes directly from his review -- and he summarized these data for the committee just an hour ago during his presentation. And he highlights -- he raises the question, is there a heart failure signal here in the data? And he -- in order to support the possibility of one, he pulls together three pieces of evidence. One is the imbalance in deaths in ANDROMEDA. Let me emphasize that, in ANDROMEDA, there was an excess of death across almost all categories. And so this is representative of what was seen in ANDROMEDA in general.

Second is ATHENA -- the deaths in ATHENA, a split of eight on placebo and ten on dronedarone.

And then selected adverse events in the ATHENA trial -- and what you see here is peripheral edema, dyspnea, fatigue and asthenia.

Let me just emphasize that these are pretty nonspecific symptoms. They aren't specific to heart failure. They can be caused by a wide variety of conditions. I don't know if too many heart failure investigators that focus on fatigue and asthenia as being meaningful ways of looking at this, but I do want to emphasize something which is perhaps far more important.

These are spontaneously recorded adverse events, and there's something interesting about how investigators report adverse events. Next slide.

This is a slide on hospitalizations for heart failure during the course of ATHENA. Now, hospitalizations for heart failure we know -- or at least as best as we can assess -- are for heart failure. This is bad heart failure. You go into the hospital. It is for the disease that one is worrying about, a signal about.

You can see 132 events in the placebo group, 112 such events in the dronedarone group.

Next slide, please.

DR. HARRINGTON: Before you go too far --

DR. PACKER: Sure.

DR. HARRINGTON: -- how can you say that you know that this is bad heart failure when we were already told that you didn't adjudicate anything

and all you have is the tick box? So all you know is that they ticked a box that said this was heart failure.

DR. PACKER: They ticked a box that said this was heart failure.

DR. HARRINGTON: And I'm okay with that, but let's not say that we know that this is bad heart failure. You didn't adjudicate these to get source documents -- at least that's what Dr. Karkowsky tells us --

DR. PACKER: And -- it was not adjudicated, but I'm not certain an adjudication procedure with tell you it was bad heart failure. It would just tell you it was for heart failure, which means that an adjudication procedure would give you the same information as the investigator.

DR. HARRINGTON: My heart failure and your heart failure may not be the same, which is one of the reasons that one adjudicates, to lend a measure of consistency across the data set. This is Joe in Durham, Milt in Texas and Sergio in Russia are all checking the box that they determine to be heart failure.

DR. PACKER: Right.

DR. HARRINGTON: Okay.

DR. PACKER: And that's -- Bob, that's a hundred percent correct, but remember, all adjudication does is doesn't provide accuracy. It just --

DR. HARRINGTON: Oh, it provides consistency.

DR. PACKER: -- provides consistency. It's precision.

Okay. So now you've got -- just for the record, this is

hospitalizations for heart failure, according to the investigator, split 132 placebo, 112 dronedarone; reaching class IV heart failure during follow-up, 54 on placebo, 42 on dronedarone. The most important point is that -- next slide -- is that, for reasons that are operationally, perhaps, obvious, when someone is hospitalized for heart failure, the investigator doesn't -- almost stops reporting the AEs to the sponsor. The AEs are reported largely during outpatient visits. A lot of the AEs are not reported during hospitalization.

So just to show you that although -- let's see -- a hundred, for example, on placebo -- a hundred hospitalizations were -- for heart failure were not accompanied by report of heart failure as an adverse event, only because this is up to the investigator. Whether an investigator reports an adverse event or not is entirely at their discretion, whereas here they actually had to tick a box as the cause for the hospitalization.

Next slide.

Now, let's just put this all together. If one takes all of the AEs for heart failure, all of the hospitalizations for heart failure and all of the times that heart failure was ticked during a hospitalization for atrial fibrillation or anything else, there are 556 such events in the placebo group, 518 such events in the dronedarone group.

If you look at first serious heart failure event and -- the difference between the top and the bottom is that heart failure was called a serious adverse event, according to the regulatory definition -- there's 381

such events in the placebo group, 275 such events in the dronedarone group.

And just out of curiosity, to complete the answer -- next slide -- here are the Kaplan Meier curves for first heart failure event. In all -- in all placebo-controlled trials in patients with atrial fibrillation and -- next slide -- time to first event for all serious heart failure events in all placebo-controlled AF trials.

DR. HARRINGTON: So this does not include the ANDROMEDA data.

DR. PACKER: It does not, but the number of heart failure events in ANDROMEDA was --

DR. HARRINGTON: Small.

DR. PACKER: -- small and would not materially alter these analyses.

And let me -- one more slide. Can I have slide XX-1, please. Okay. Can I have that up, please.

There was some discussion -- and Bob Temple, I think, initiated some of this before the lunch break -- as to whether one can reliably distinguish clinically stable from recently unstable patients with heart failure. And I just want to remind the committee and create a framework for this because this is actually familiar territory to cardiologists.

You can see that, for amiodarone, all the trials have been done in clinically stable patients. The conclusion is that this drug is neutral for mortality in these patients. Recently unstable patients have not been studied.

For beta blockers, the effect in clinically stable patients is favorable. The effect in clinically unstable patients is thought to be adverse.

For dronedarone, the effect on all-cause mortality in clinically stable patients with heart failure is neutral. The effect in patients who have been recently unstable, according to the results of ANDROMEDA, are adverse.

And just at the bottom, please understand that amiodarone is actually approved for use in patients with heart failure without any mention about clinical stability. And beta blockers are approved in patients with heart failure or left ventricular systolic dysfunction with a mention of a contraindication for recent clinical instability.

So this basically brackets the possibility and I hope creates a framework for further discussion.

DR. HARRINGTON: Great. All of this data was very, very helpful.

Sanjay, do you have a question?

DR. KAUL: Well, just a comment. I mean, with all due respect, all the data that I have seen -- I mean, basically what I'm led to believe was that there was no systematic attempt made to capture the symptoms associated with heart failure or general symptoms associated with atrial fibrillation which, given the results of the ANDROMEDA trial, frankly, is a missed opportunity.

DR. PACKER: Perhaps a missed opportunity, but again, the ATHENA trial was all about morbidity and mortality.

DR. HARRINGTON: There's another list of -- unless it's directly related, I'm going to go down the other list of questioners.

DR. NEATON: I had a question they were going to get from me, but they didn't --

DR. HARRINGTON: So hold that question, just out of fairness to everyone who's been waiting.

Mike, you've been waiting since before lunch.

DR. LINCOFF: I originally, and still do, have a question regarding mortality, but I also have a question that sort of follows from what was discussed here, so if I could do that as well.

You mentioned -- and I think it may be the first time -- the different types of afib, that many had afib, some were cardioverted, some weren't, some were hospitalized. And we may have heard that, but I don't recall. Do you have that data particularly comparative? I realize you may not have it right now, but I'm kind of curious about what the rates of recurrences were in the different treatment groups and the different types of afib.

I realize that's not as hard of a clinical end point as hospitalization, but it's certainly still relevant in a drug that's supposed to prevent afib.

DR. PACKER: Do you mean in ANDROMEDA?

DR. LINCOFF: No, no. In ATHENA.

DR. HARRINGTON: In ATHENA.

DR. PACKER: Oh, that's easy. I'm sorry. Mike, I just want to make sure that I understand. The breakdown that you saw was a breakdown for ANDROMEDA. The only patients enrolled in ATHENA were the bottom row.

DR. LINCOFF: Bottom row.

DR. PACKER: The only patients enrolled in ATHENA were the bottom row of ANDROMEDA.

DR. LINCOFF: No, no. I understand they all came in with afib, but do you have recurrence rates? Because you had mentioned that only a certain -- you know, that only a proportion of the atrial fibrillation events then led to cardioversion and only a proportion of those led to hospitalization. So were you talking about ANDROMEDA or ATHENA for that?

DR. PACKER: That's the ATHENA trial.

DR. LINCOFF: Is that data available divided by group? How many afib total events there were, for example. I mean, what was the magnitude of suppression of afib by the study agent? What was the management of suppression of afib that required cardio -- I mean, aside from the hospitalization, which you've already presented?

DR. GURAL: Indeed that data is available. Dr. Gaudin --

DR. HARRINGTON: Mike, this is the total burden of afib that you're

trying to get at.

DR. LINCOFF: Recognizing that it isn't all symptomatic, but on the other hand, I think we all agree that atrial fibrillation events are -- ideally could be prevented if you do so without toxicity.

DR. GAUDIN: Just to make sure I will answer right to your question, you wonder whether -- what was the rate of recurrence, for example, of atrial fibrillation and atrial flutter in these patients? Is my understanding correct?

DR. LINCOFF: I'm sorry. If I understand you --

DR. GAUDIN: Sorry. I just wonder if -- in order to answer to your question -- whether you are referring to the rate of recurrence of atrial fibrillation/arterial flutter in these patients; is that correct?

DR. LINCOFF: Yes. Independent of whether or not they required hospitalization --

DR. GAUDIN: Yes.

DR. LINCOFF: -- or cardioversion.

DR. GAUDIN: Slide on, please.

So I think this is the information you were asking for, the rate of recurrence of patients. This is in patients who had sinus rate at baseline in order to analyze recurrence, and the recurrence were less in the dronedarone group than in the placebo group, with a hazard ratio of 0.75.

DR. HARRINGTON: Anything else, Mike?

DR. LINCOFF: Yeah, then I had a three-part question that all related regarding mortality. So if I could bring the discussion back to the mortality in ANDROMEDA -- and also in ATHENA. We've heard a lot of discussion about whether or not the findings in ANDROMEDA were related -- were potentially statistically spurious related to the DSMB review, and also about the population in ANDROMEDA and whether it was really relevant.

So my questions are both for the FDA and for the sponsor in terms of the design and who sort of led to the design.

I recognize that testing a vulnerable population with an anti-arrhythmic was, of course, important, but was that vulnerable population ideally the one that we intended the drug to be used for? So who chose to include a predominantly non-afib population in ANDROMEDA? Was that sort of pushed by the FDA or was that something that was originally part of a hypothesis that has since been disproven by the sponsor and investigators?

Related to that was, who designed the DSMB charter in terms of this sort of review of mortality every two patients? Was this a later decision by the DSMB? Because we always have to deal with the idea that, when you have interim reviews of mortality, you take a risk that you may have a spurious finding, you set a boundary, a stopping boundary that you believe will protect safety, and then you have to live with it.

So if this is what was prospectively defined, particularly if it was prospectively defined by the sponsor, then I think the burden of proof -- or

the assertion has to be that this is real.

And then, finally, the third piece of that is, given that one of the major drivers for ATHENA was, of course, to either refute or confirm or whatever this mortality problem in ANDROMEDA, why wasn't there adjudication of mortal events in ATHENA?

DR. GURAL: Okay. Perhaps for the design of the study, we'll ask Dr. Packer, as well as the discussion on the DSMB. Please.

DR. PACKER: I know I'm going to forget one of the three questions, but we'll try. I think Dr. Karkowsky tried to be as accurate about the history, about how ANDROMEDA was created. It all stems from the fact that there's a -- always a universal concern that anti-arrhythmic drugs in general can increase mortality in somebody. And although one might think that the best way to do that would be to target individuals who have an indication for the drug, sometimes individuals who have an indication for the drug don't have a particularly high mortality rate.

And so, consequently, it has been historically accurate -- and Avi, if I'm wrong, help me out here -- it's been historically accurate that the FDA has asked sponsors to move from their indicated patient population to the a population that is considered to be most revealing of a risk, if a risk existed.

And that was suggested by the FDA to the sponsor, and that was the basis for ANDROMEDA.

Is that helpful?

The second question -- I know I'm going to -- constitution of the DSMB. The data safety monitoring board -- I don't know if they had a charter or not. To a large degree they decided that they would be allowed to look at deaths as they came in, as they wanted. The only rule that they made up in advance was the rule that, at any point in time, they might be able to stop the study if there was a nominal P less than .05. So --

DR. HARRINGTON: But that wasn't necessarily a nominal P based upon formal interim analyses.

DR. PACKER: Right. It is a nominal P --

DR. HARRINGTON: Right.

DR. PACKER: -- but it is not a real P.

DR. HARRINGTON: Right. That was my question.

DR. PACKER: Right. I want to -- that's why I hasten to use the word "nominal." I mean, the error rate here isn't 5 percent. As you saw from the simulation, the error rate is 18 percent. But that's what they did. Bob?

DR. HARRINGTON: The last question -- go ahead, Bob.

DR. TEMPLE: On a safety matter, nobody would let you use O'Brien-Fleming boundaries for a safety thing. You've got to do something like this; otherwise, people would decry the ethics of it.

DR. HARRINGTON: I'm not disputing the safety issue --

DR. TEMPLE: But it does mean there could be an error rate -- I

mean, the point Jim is making. That's true.

DR. HARRINGTON: Correct.

DR. TEMPLE: That's true.

DR. HARRINGTON: Dr. Karkowsky?

DR. KARKOWSKY: I don't know what the DSMB saw, but there was a consistency across not just death, but cardiovascular hospitalizations, and I think that one has to take into account the fact that they felt responsible for the patient population. I don't know how many would have said, let it go, based on an extra 20 or 25 hospitalizations and an extra 15 or so deaths.

DR. HARRINGTON: Particularly when you're moving outside an area of indication.

DR. LINCOFF: And I'm certainly not challenging the ethics of this. I'm saying that this is a sort of standard practice for DSMB, and in the end you have to accept it, even though it introduces uncertainty anytime a trial is terminated --

DR. TEMPLE: For a bad outcome, right. I mean, we don't want people stopping for a good outcome.

DR. PACKER: I mean, it wouldn't be unusual for there not to be a nominal P less than .05 rule. Sometimes you have asymmetric curvelinear functions so that the reason for stopping for harm would be less stringent than the reason for stopping for benefit.

But those O'Brien-Fleming boundaries for harm still make some

accommodation for multiplicity of comparisons in that they are curvelinear in the negative direction, but not as markedly so as in the positive direction.

DR. TEMPLE: But, Milton, I mean, no one would put .00001 for harm, you know. Just -- nobody would tolerate that.

DR. PACKER: It is clear from the feelings expressed by the data safety monitoring board that a big driver to their recommendation to stop the trial was the fact that the patients who were being exposed here didn't have an indication for the drug.

And it puts the data safety monitoring board in the most awful position possible when they see a nominal P less than .05 in a patient population that isn't proposed for the indication for the drug being developed. It's a --

DR. HARRINGTON: Go ahead, Bob.

DR. PACKER: -- weird situation.

DR. TEMPLE: I'm curious about that. There must have been some view that these people could benefit, or no one would have tolerated that study. I can -- we were talking about this among ourselves -- of course not with the committee -- at lunch, and there are reasons to think that people with severe heart failure might die arrhythmic deaths and things like that, but you guys most know -- there must have been a reason to expose that population. You can't just do a human safety trial, you know, as if it's a dog study. So there must have been a reason.

DR. PACKER: The rationale is that amiodarone has anti-arrhythmic properties on the ventricle as well as the atria. Drugs that have anti-arrhythmic properties in the ventricle might have an anti-sudden death in patients who are at risk of sudden death. And as a result, all of the objectives of the trial were two-sided.

So I just want to make that clear in case anyone is -- would like to think that, you know, there was something amiss here.

DR. HARRINGTON: If it had gone the other way, Bob, a hypothesis would have been generated as to the benefit.

DR. TEMPLE: Worse than a hypothesis; a claim.

DR. HARRINGTON: And the final question that Mike brought up --

DR. PACKER: Right.

DR. HARRINGTON: -- which I think is certainly on my list of questions -- was the adjudication issue.

DR. PACKER: Right.

DR. HARRINGTON: Why would you not have adjudicated these mortality -- you did in the ANDROMEDA study.

DR. PACKER: Right. Okay. Let me first mention one thing. The driver to the mortality discussion in ATHENA was a safety point where adjudication didn't matter because it was all-cause mortality and everyone was hoping that the upper bound of the confidence interval would be less than 1.5, and the trial was specifically powered to have 260 deaths to be able to

achieve that. Insofar as that was the primary driver, adjudication wouldn't have mattered.

However, there was another end point called cardiovascular mortality, and the question is whether cardiovascular mortality is something that investigators can distinguish or whether the -- or whether it's something that you need an adjudication process.

Let me just emphasize -- just clarify one thing that Dr. Karkowsky said. He said that there was -- there was an adjudication process. It was transferred to the steering committee -- did I say that --

DR. HARRINGTON: He actually referred to it as a categorization process, in contrast to an adjudication process.

DR. PACKER: Right. And it would be fair to characterize it that way. It was not adjudication in the way that anyone on this committee would define. It wasn't like you got all of the study report and the patient-level data. It was more of the fact that this is what the steering committee wanted to do -- can I have the first slide up, please. And, Bob, I'll be brief. But you don't believe me.

DR. HARRINGTON: I don't.

DR. PACKER: This is the -- now, let me just say, the original protocol says it was going to be investigator-determined. The statistical plan said it was going to be investigator-determined. Aside -- it was never going to be anything but investigator-determined.

The steering committee, independent of any regulatory mission here, wanted to classify the deaths in a way so that the results of ATHENA could be compared with the results of earlier trials carried out by the members of the committee.

And the specific amendment that created this said that this additional classification was to be used descriptively and wasn't to be -- to create the formal assessment of drug efficacy or safety -- one moment. I know where you're going. Next slide.

These are the descriptions. I am absolutely not going to read it, but it's four categories. Next slide.

These are the differences between the steering committee investigator classifications. There's a high degree of concordance, but perhaps most importantly -- next slide.

Regardless of which one you want to look at, the results aren't meaningfully different. It's a 30 percent reduction in the investigator assessment and a 29 percent reduction in the steering committee classification.

Now you're going to ask --

DR. LINCOFF: I'm going to say that's meaningless because the investigators only had the information that the -- I mean, the steering committee only had the information the investigators had.

Now, if you only wanted to do this as a secondary post-hoc analysis,

that's fine. But you have this as a secondary -- a principal secondary end point. You want to at least make some sort of assessment of cardiovascular death, and you can't do that with the information you collected.

DR. PACKER: Unless you are entirely reliant on the investigator judgment. Remember one thing. Adjudication increases precision, not accuracy. Any set of adjudication principles -- unfortunately I've spent more time on adjudication committees than I would like to admit to anyone. You go in with an arbitrary set of rules. Those rules don't represent accuracy. They only represent consistency.

DR. HARRINGTON: Go ahead, Bob.

DR. TEMPLE: These classifications are always very difficult, and they've been difficult for decades. The only additional data that people sometimes get is the record of the hospitalization, so you have the intern notes and all that kind of stuff. But, otherwise, what are you going to get?

They could have asked the investigator to write a narrative of why the hospitalization occurred. All of those things would have informed it more. But this is a continuing problem, which is why a lot of people like total mortality, if they think most of the deaths are going to be of the kind they're interested in.

DR. HARRINGTON: I thought that Dr. Karkowsky, his example was a very good one, which is that similar situations classified by investigators in different ways -- and that's what Milt's point is. It brings consistency when

one adjudicates as opposed to this way.

DR. TEMPLE: I have a whole very long ancient paper showing numerous examples on classification. It's murder. I think, by the way, the only possible remedy is to test-drive these things by finding, you know, some admissions and having a classification and testing it out beforehand. If you don't do that, it's very hard to do it after the fact.

DR. LINCOFF: But it's also in the context of the agent you're testing, and that's why I think it's more important that there be -- because it would be adjudication by people who have that in mind.

For an anti-thrombotic, if somebody bleeds, if you're testing an anti-thrombotic, that's a cardiovascular death because they took that anti-thrombotic because of their cardiovascular disease.

For this, an anti-thrombotic -- a bleeding death, I mean, unless it's directly related to the fact they came in with afib and -- you know, I mean, so there is a lot of subjectivity.

Now, you're right, the best thing is a body count. But on the same token we've also heard that, well, there's a lot of other things that interfere with that, and you may lose the effect of the drug.

So we can't have it both ways. If we want to just talk about total body count, fine. But if we're going to have any presentation and statistics and P-values about cardiovascular death, then I still maintain that it would have been much more accurate and precise, given the context of the agent being

tested, that -- if it had been adjudicated.

DR. TEMPLE: No, I agree. But it really is helpful to test-drive it beforehand so you run into these -- so you try to figure out what your rules are.

DR. PACKER: Just one point of clarification. Mike, I don't disagree with you. So, yes. But let me just -- one point. If you look at the two examples that Dr. Karkowsky put up, I actually tried to imagine myself on an adjudication committee and looked at them, and I actually would have classified them the way the investigator did, and here's the reason why.

One came in with a subdural hematoma. One came in with a subarachnoid bleed. Okay. Those are pathophysiologically not the same condition. And depending on how one prespecified the rules, the subdural would not be cardiovascular and the subarachnoid bleed could be.

And I -- you know, you make up the rules.

DR. HARRINGTON: So let's move along with the questions. I have Dr. Black, Dr. Neaton -- Dr. Kaul had gotten in there --

DR. KAUL: No, no. I have a couple of questions.

DR. HARRINGTON: So let me get a couple of people in who haven't spoken yet. So let me go to Henry, Bob, you and Dr. Neaton.

DR. BLACK: Thanks, Bob. I just want to express some anxiety and unease about the data, especially what Dr. Karkowsky showed us -- that maybe the investigators could have told what arm they refer to. They were

misclassifying things. Do you think all the errors, potential errors you said, were profound enough and important enough to have changed the results?

DR. KARKOWSKY: We did -- Valeria or Dr. Freidlin did a sensitivity analysis, and all you needed to do is if you picked the one-year cutoff, change two people's outcomes. If you picked, as the sponsor chose, the 14-day-plus cutoff, you needed five events.

So the question is, how robust is the convincing data from that vantage point?

DR. BLACK: The one thing I can take a little --

DR. TEMPLE: That's for death, he's talking about. That's --

DR. BLACK: Yeah.

DR. TEMPLE: -- survival, cardiovascular or other --

DR. BLACK: Yeah. The one -- I think this misclassification which we talked about -- and a lot of things seemed to happen that just, as I say, make me uneasy -- I think I can take some comfort from Dr. Packer's slide CC-75, which is mortality. That I think we can count and can be pretty sure that people really were dead. And it seems to be pretty much what we got.

DR. HARRINGTON: Mr. Dubbs?

MR. DUBBS: I just want to preface, before I ask my question, with a comment that I'm not a scientist, not a physician. I'm a lay representative. And I apologize if my question is not articulate in terms of the science.

But I'm not clear -- once someone is on the study drug, the slides

all talk about time to first recurrence, and then the other slides talk about one year after commencement of the trial. Does that mean that the patient is on this drug for a lifetime? And what is the statistic that you have about patients after this first year if they're continuing on the drug, and patients who stop the drug after one year.

DR. HARRINGTON: So no need to apologize. That's actually a very observant question. And one of the limitations that we always have in these trials which, by necessity, are a bit artificial because -- as your point is -- that patients will be asked potentially to take this forever, and yet we only have a year's worth of experience.

So maybe the sponsor could comment. Do you have some data on the effect in people with the drug beyond a year?

DR. GURAL: In fact, what we have -- clearly your question is that we do administer the drug to the patient until they have their first occurrence, but they can continue on beyond the first occurrence. And the common study end date means -- that's when all patients, the last data is available and the patients discontinue the treatment with the drug.

So they're not on it the lifetime of the -- they're only on it the lifetime of the study which, in this case, the average duration of treatment was 21 months, and we did have patients who went up to 30 months of treatment.

I'm going to ask Dr. Gaudin to address the experience we have in patients over one year and beyond the first experience of a recurrence -- or a

hospitalization, I'm sorry.

DR. GAUDIN: We did not perform specifically an analysis of patients who had one year -- or more or less one year of treatment, but we performed a Nelson analysis that show any hospitalization during the course of treatment of a patient. I hope -- can have the slide on. I just comment on the slide before it's coming.

So when we performed this Nelson analysis, we observed that the rate of hospitalization was continuously, over time, decreasing in the dronedarone group versus the placebo group. And I hope we can have the slide on in a few seconds.

DR. HARRINGTON: In following up on Mr. Dubbs' question, is there any long-term safety data available? Is the drug approved anywhere in the world?

DR. GURAL: The drug is not currently approved anyplace in the world. The first approval will be here in the United States, hopefully, after you vote positively. And that -- the long-term exposure for the drug is presented by Dr. Chew, was identified as over 425 patients treated for more than two years of exposure.

DR. HARRINGTON: Did you have another question, Mr. Dubbs? Go ahead.

DR. GAUDIN: Slide on, please -- maybe.

DR. HARRINGTON: Here we go. Let's let them do this, and then we'll

come back to you.

DR. GAUDIN: Okay. This is the analysis I was mentioning. So in this analysis, all of the events of hospitalization over the duration of follow-up are taken into account. And that shows that the benefit of treatment is going on over time of treatment, and we have experience up to 30 months of treatment, a mean duration of follow-up of 21 months in this study.

DR. HARRINGTON: Go ahead with your second question.

MR. DUBBS: I don't know if this is the right time to raise it, about the indication that's being sought by the sponsor.

DR. HARRINGTON: Go ahead.

MR. DUBBS: Is it okay? All right. First of all, how do you get these names for these drugs? It's interesting. But --

DR. HARRINGTON: We'd be here all day if they tried to answer that.

(Laughter.)

MR. DUBBS: It seems to me that in the indication at the very end you say "and with associated risk factors." Much of the discussion today has been focused on the risk factors -- the two major trials that we've discussed. And I wonder why the sponsor put that at the end. It seems to me that it would be more appropriate, in seeking an indication, that -- where you first mention the drug is indicated in patients, that you ought to say, at that point, who have certain risk factors, or don't have certain risk factors, and then go on to the rest of it.

I just wondered why you put that at that end. It seems to me that it downplays it rather than emphasizes it. And that somebody who is quickly reading it may not get to the end.

DR. GURAL: Do you want the sponsor to respond?

DR. HARRINGTON: Sure.

DR. GURAL: Okay. Clearly, when we were designing the ATHENA trial -- and if the amendments that were made identified that one of the risk factors associated with the use of the drug -- and I will ask -- in atrial fibrillation -- I'm going to ask Dr. Naccarelli to come to the podium to describe those various risk factors.

In atrial fibrillation you have -- age is one of them. You have left ventricular dysfunction. You have a number of known risk factors that contribute beyond just age of the patient.

DR. NACCARELLI: The ATHENA trial, which was the pivotal trial presented today, if you remember the enrollment -- and maybe someone could pull that slide that was shown by Milton -- that in order to get a high risk population whether would have events, you wanted to make sure that they had risk factors associated with bad outcomes.

Now, if you remember -- if you look at these patients, these are elderly patients with comorbid events. They have hypertension. They often have diabetes. They have congestive heart failure. They have coronary disease.

Can I have the slide on, please.

so you can see that -- if you look on the bottom where it says "with one or more of the following" -- these are risk factors for stroke that was mentioned by some people. These obviously are diseases that are existing in -- at the same time with atrial fibrillation, so hypertension, diabetes, a patient who has already had a stroke, a large left atrium, top chamber of the heart, an ejection fraction that's been depressed. Some people would -- in most of the stroke risk factors would include congestive heart failure. The latter two, left atrial diameter, ejection fraction kind of fall into that.

So this was an attempt to enrich the population, but also, to be fair, these are what patients have. So if you look at the entry criteria, if you look at the randomization of the patients, you will see that 80-odd percent of the patients had hypertension, X percent had diabetes, X percent had these -- because this is, in fact, where this disease lives. It lives -- it's a chronic recurring disease, and it -- and it lives with these other diseases, you know, in commonality.

In fact, hypertension, by the Framingham study, was the number one cause of atrial fibrillation. And, of course, age is another comorbid event, so that by the time you're 80, about 8 percent of patients will have atrial fibrillation.

So if we just look at -- these are the qualifying characteristics -- if I could have the BA-13 slide.

So you could see here that, if you look at hypertension, over three-fourths of the patients in this trial also had hypertension. 20 percent also had diabetes. 13 percent also had had a prior stroke. 20 percent had a dilated left atrium, a markedly dilated left atrium. And a small number had a depressed ejection fraction.

DR. HARRINGTON: Bob --

DR. TEMPLE: Isn't what Mr. Douglas [sic] asked was why you didn't mention the risk factors first and the atrial fibrillation second? Isn't that what you were asking?

MR. DUBBS: Yes.

DR. TEMPLE: That's all. I mean, the short answer is they might use it for people with risk factors who didn't have atrial fibrillation, which isn't what we want either, but I don't think he was asking why you put a high-risk population in.

DR. HARRINGTON: He was trying to draw your attention to the risk factors. I agree.

DR. FOX: Mr. Chairman, can I just comment --

DR. HARRINGTON: Yeah, go ahead.

DR. FOX: -- from sort of the sponsor's perspective. I think it's worthwhile noting that I think what Mr. Dubbs is referring to is perhaps the stylistic construction of the proposed indication, and maybe its semantic feel. But it's worthwhile noting that proposed indications undergo extensive

discussion with the agency before they make it into the label, and I think it's highly unusual that it would ever wind up in the label verbatim as proposed.

DR. HARRINGTON: While we're on the topic of what the --

DR. TEMPLE: But, again, just to say -- I mean, we would ordinarily say -- we would ordinarily put first what the primary thing you're treating is, and then put the qualifications. Maybe we should rethink that, but that's certainly what we would ordinarily do.

DR. HARRINGTON: Along these lines of the patient population that's being treated, all day we've heard referred afib/aflutter, and this morning somebody specifically brought up -- I think it was Jerry -- that aflutter, in fact, we know is the minority of these supraventricular arrhythmias.

One of the questions we're going to grapple with this afternoon is whether or not the drug should specifically say afib/aflutter and not isolated aflutter. Do we have any data as to the effect of the drug in the isolated group of aflutter patients?

DR. GURAL: Yes, we do. In anticipation of the question, Dr. Gaudin.

DR. GAUDIN: Slide on, please.

We performed an analysis according to the rate of patients at baseline and show similar results, whatever it was with patient in sinus rate, atrial fibrillation and also atrial flutter.

DR. HARRINGTON: Thank you. I think the next is Jim Neaton, followed by Emil, followed by Dr. Calhoun.

DR. NEATON: My question went back to this morning. I thought you were going to generate table 49 on page 99 across the five studies. The results for ATHENA were interesting, but most of those were in your report anyway.

DR. PACKER: It's a work in progress.

DR. NEATON: So is it fair to say that -- I mean, it looks to me the best that I can do with the available data here that -- so what you reported for ATHENA for -- if you look at non-AF hospitalization -- is a 15 percent reduction, and that's quite a bit smaller than if you look at AF, which is a 38 percent reduction in ATHENA.

And so that -- if you were to combine the other trials for the non-AF, I'm presuming that .85 is probably going to be something closer to .95.

DR. PACKER: No, it probably will go the opposite way.

DR. NEATON: How can it, if you add ANDROMEDA? Even adding ANDROMEDA puts it over .9.

DR. PACKER: Oh, okay. Right. I thought you meant all the AF trials.

DR. NEATON: No. I'm trying to get an idea -- I mean, again, going back to what I said this morning, you said -- I'll quote -- there is an unmet medical need for drugs that improve morbidity and mortality beyond reducing

recurrences of AF.

And I think -- and I think that the kind of presentation and the data kind of so far still leave me wondering about whether this is a chance observation or not in ANDROMEDA. And so one bound on what you're doing for these outcomes looks at all of them, I think.

DR. PACKER: And, again, in order to be able to do that, the team is working on that and hopefully will have it in a short period of time.

Just two pieces of information that are relevant, and that is that just -- one has to wonder whether, when you look at all cardiovascular hospitalizations, what's the driver of that? And -- because the problem is that there are a lot of cardiovascular hospitalizations which are less important than other cardiovascular hospitalizations.

So what we tried to do, in the course of today's presentation, is to do two things. One was to show you the effects on the cardiovascular hospitalizations which have been the focus of end points in other trials with other drugs. So specifically myocardial infarction and unstable angina, transient ischemic attack and stroke, worsening heart failure -- and what's important, of course, is that all of these were the most common reasons for cardiovascular hospitalization other than atrial fibrillation.

There is a dilutional effect, Jim. There are a whole bunch of cardiovascular hospitalizations here for things that are cardiovascular but never form the end points for major clinical trials, and they were equally

distributed in the two treatment groups.

So the reason that you see in ATHENA a point estimate of .85 is because, for the major events -- which I tried to summarize in a separate slide -- it's really .75. For the -- and I'll call it clinically less important events, the ones that don't make it as end points, it's 1. It comes in between at .85. But the truth is there's something clinically really important in the .85 which has an association of a 25 percent reduction in risk.

DR. NEATON: I agree with you. I probably would have defined the end point differently. What I'm trying to get at is kind of some kind of bound on what the -- your primary end point was for your trials and for what your claim is here if you look at the collective evidence of all the studies you did. And so that's where I'm going.

DR. GURAL: A work in progress.

DR. HARRINGTON: Let's go on to Emil, and then Dr. Calhoun and Dr. Kaul, and then McGuire and Nelson.

DR. PAGANINI: I've been holding my urine all day while the heart settles down here with their arrhythmias. But let me go towards the renal response that we've seen.

In clinical medicine, any hospitalized change of .3 of serum creatinine has a dramatic increase in mortality in hospitals. Elderly thin females have the worst outcome. People who have chronic kidney disease prior

to anything afterwards have a worse outcome. And we're also becoming aware that, specifically in congestive heart failure, but overall, that increasing diuretic doses are associated with worse outcome.

I have a couple of questions on the renal effects, if I could, please, since that's a big issue for almost any drug.

The first is, were there any reviews of other renal injuries, such as a NAG or an NGAL or a KIM-1 or anything that would tell me about injury to tissue? And, second, is there any other functional evaluation beyond just a simple serum creatinine? Was there a cystatin C? Was there an effective GFR done? Something along the lines that would get me away from just a simple creatinine change?

And then, finally, in your CC-110, you listed the differences, and you put it together as a -- as a system, I guess, renal disease and urology. And within that I'm wondering whether or not the spray of patients having various CKD levels were equally distributed in your randomization.

DR. GURAL: Thank you. I believe that Dr. Chew in his presentation, as you so correctly pointed out, started to discuss on some of the renal effects, so if I could ask Dr. Chew to come and we can have a further discussion on those effects. Dr. Chew?

Perhaps, before we have Dr. Chew present the safety studies, I'm going to call Dr. Newton to come to the podium and discuss some of the studies that we have done on a pharmacokinetic basis to evaluate further those

effects. Dr. Newton.

DR. NEWTON: In clinical pharmacology studies, we've looked at the effect on glomerular function with Sinistrin, and we've shown the drug has no effect on glomerular function. The effect on creatinine is primarily at the tubular level. It's due to inhibitor of OCT2. And this is the -- slide on.

So this shows the effect of dronedarone on Sinistrin, placebo and dronedarone on the first line, creatinine on the second line, and then creatinine over Sinistrin -- you can see the effect on dronedarone in the third line, reducing the ratio.

DR. PAGANINI: Did you have any other -- for example, giving people cimetidine or something to totally flush that sort of secondary secretion question out to see what happens? Specifically in the congestive -- I'm not too concerned in the non-congestive heart failure patients. But in the congestive heart failure patients, there is a whole series of clinically significant interventions that people do, and one of them is diuretic use, a whole bunch of things that may or may not have effects on either electrolyte balance or creatinine change or affect an outcome. And I'm just wondering if you have any of those as subanalytical reviews.

DR. GURAL: Perhaps we could ask Dr. Berl to address some of those concerns, and then we can have Dr. Chew. Dr. Berl.

DR. HARRINGTON: While we're waiting here, for the committee's perspective, if we have any hope of getting through Norm's extensive list of

questions, I'm going to ask you to forego your break, but if you need to just get up and use the restroom, grab some coffee, et cetera. So just so that we can keep going here.

I'd like to turn to the questions in about 10, 12 minutes.

DR. BERL: Thank you. I'm Tom Berl from the University of Colorado, MLA. Cimetidine would do exactly what the drug does, and giving it on the background of the drug, I'm not so sure we would learn much more than we learned from the Sinistrin clearances that clearly showed that the drug does not affect glomerular filtration rate in 12 healthy volunteers.

You're correct that in heart failure there's so many other events that can affect glomerular filtration rate, both volume-related and changes in heart function, that can produce larger changes in creatinine. I think that the data shows that the drug was equally effective in those that were on diuretics and not on diuretics. But there were so many random increases in serum creatinine because of comorbid conditions, frequently completely unrelated to administration of the drug and in large measure almost always reversible when the drug -- even when the drug was continued, suggesting that the effects on serum creatinine were unrelated to the drug.

There are no other markers of renal injury that were monitored in the study, such as NGAL, KIM-1 or even cystatin Cs.

DR. PAGANINI: Tom, while you're there, there was one person that had an interstitial nephritis, and that was obviously -- was it biopsied or

not biopsied and, if not, how did they come to that diagnosis?

DR. BERL: I'm not so sure. I don't remember reviewing the case. I reviewed 19 patients that were designated had serious adverse effects for serum creatinine elevations. And in a great majority of those, the elevation in the serum creatinine that led to such a designation was temporarily completely dissociated from the initiation of the start of the drug. And in 15 the creatinines reversed while the drug was still continued.

DR. PAGANINI: So all of the effects, then -- the renal effects, quote/unquote, were based on an analysis of what happened to serum creatinine?

DR. BERL: That's correct.

DR. PAGANINI: Thank you.

DR. HARRINGTON: Are you satisfied, Emil? Are you okay?

DR. PAGANINI: That's the analysis they did. I mean, you know, maybe there would have been other analyses, but that's fine.

DR. HARRINGTON: Okay. Next up is Dr. Calhoun and then Dr. Kaul.

DR. CALHOUN: Thank you. So my question is going to turn on the reality that measures of heart failure are actually not static but rather dynamic and change over time. And given the fact that there may well be a safety signal in individuals who have acute heart failure, the question that was alluded to earlier I'd like you to maybe address more formally, and that is, what happens if someone develops acute deterioration? I just rescanned the package label, and I don't see anything in there about discontinuing the

drug if that occurs.

So it would be interesting to take a look at some of your data with respect to morbidity and mortality in patients who, during the trial, while on therapy, developed acute deterioration and to stratify that by treatment status.

DR. GURAL: Okay. Perhaps -- yes, Dr. Packer.

DR. PACKER: We have exactly what you've requested. Can I have the first slide, please.

This is just background. Let me just -- this is the hospitalizations for heart failure. You've seen this slide before. Now, what I'm going to show you in the next slide is an analysis from the point of time when they were hospitalized for heart failure. It's the only way we know of that we can address the question, but I do want to emphasize, this is an analysis based on the post-randomization variable, which is hospitalization for heart failure, and therefore does not have the protection of randomization.

Next slide, please.

Here is the data on the occurrence of events afterwards. And you can see on the primary end point you've got 72 and 59. On all-cause mortality, you've got 26 and 12. Let me emphasize, it is very hard to compare these numbers and these curves because the point of departure here is the point of heart failure hospitalization, not the point of randomization. So

please -- I mean, this is what you asked for, but we don't have any other way of addressing it. But this is a confounded analysis.

The next slide, just to complete the concept, is -- you could have asked the same thing about what happened in people who developed class IV symptoms, irrespective of whether they were hospitalized or not. And the next slide gives you the corresponding analyses for after they hit -- they reach class IV heart failure. Again, this is a confounded analysis based on the post-randomization variable.

I think the limited data that exists which has to be looked at and viewed very cautiously is there does not appear to be an indication for an adverse signal in patients after they are hospitalized, whether they are maintained on dronedarone or not.

DR. CALHOUN: So is it your position then that the drug can and should be continued through these episodes of acute deterioration? The beta agonist experience is not informative in this regard, or the drug is different enough that -- what's your view?

DR. PACKER: Let me just say -- I just want to give you what I would consider to be just a personal view. It does not represent the view of the sponsor. To the degree to which you make an analogy with beta blockade -- which I don't think is far-fetched; I think that may be an appropriate way of looking at this -- please be aware of the fact that physicians who treat heart failure -- hospitalization for heart failure have totally unpredictable ways

of dealing with patients on beta blockers. We see cardiologists who the minute that someone is hospitalized for heart failure, they stop the beta blocker. We have some cardiologists who continue the beta blocker. We have some cardiologists who cut the beta blocker in half.

All of the above seem to be reasonably appropriate. I wouldn't -- I think if the -- if -- the cautious approach would be to, if someone comes in with worsening heart failure, may be to temporarily -- and the operative word here is temporarily -- stop the drug until they stabilize and then reinstitute therapy, but this is a personal opinion.

DR. CALHOUN: Okay. Thanks.

DR. HARRINGTON: Sanjay?

DR. KAUL: Yeah, I have two questions, one for the sponsor and one for Dr. Karkowsky. I was intrigued by 39 cancer-related deaths occurring in ATHENA, 15 percent of total mortality. And so my question is, is this a chance observation or does that reflect on the quality of screening?

And how do you explain the imbalance in these deaths, 25 in dronedarone versus 14 in placebo? And was there any particular pattern with respect to the types of cancers, sarcomas, vascular tumors?

DR. GURAL: Okay. For the sponsor first or for Dr. Karkowsky?

DR. KAUL: That's for the sponsor.

DR. GURAL: Okay. For the sponsor. Okay. Obviously, we have the -- reviewed this information. First I'd like to call Dr. Chew, who will review

the cases, and then Dr. Cohen, perhaps, to give a perspective of the findings.

DR. CHEW: Could I have the slide on, please.

This is the overview of the malignant neoplasms on-study, which we felt was the most conservative way, going up to 6 to 12 months beyond the actual end of treatment, depending on the study. And you can see, for adverse events, overall there was no increase. On the bottom you can see 16 versus 29 listed here.

Now, in this case, we've looked for, again, the standard MedDRA query, so our numbers may differ slightly. We applied a standard approach, looking for all the neoplasms that could possibly be there.

So -- slide on, please.

This shows the malignant neoplasms leading to death, the 16 and the 29, with the demographics shown here. The median time of onset -- what's meant there is that from the time of randomization to the diagnosis. So from the time of randomization to diagnosis was 31 weeks for the median on placebo and 22 weeks for dronedarone. And the total exposure, including temporary stoppages, are shown there.

And when -- you can see that the cumulative incidence over time is there, shown below.

On the next slide are the types of malignancies. And lung cancer was very common. There were pancreatic cancers. There was also metastases of unknown site, but no particular difference in the types of cancers that were

seen.

Slide off.

DR. KAUL: So what is your interpretation?

DR. GURAL: Perhaps -- Dr. Cohen?

DR. KAUL: I mean, 15 percent cancer mortality in an atrial fibrillation trial seems too high. So the question I have is that -- were patients being properly -- with a history of cancer being properly screened? And the reason why I'm asking this question is that there's a common theme here, that we have questions regarding the quality of the data that was collected, and so this reflects, in my opinion, the quality of screening.

DR. CHEW: What I showed you were diagnoses that were made after randomization. As part of the inclusion criteria, patients who were not expected to survive the duration of the trial for whatever reason -- not particularly cancer, but for whatever reason -- because it was an elderly population. The average age was 71.

So if they were expected to survive the trial, they were enrolled. These diagnoses were made approximately four or five months after randomization.

DR. KAUL: Well, given the time frame, this is certainly pre-existing neoplasm. In other words, it cannot be tumor-inducing or tumor-promoting. Is there any pre-clinical data to suggest that in your pre-clinical package?

DR. COHEN: I agree with you that the -- certainly these tumors must have been pre-existing. And I don't know the specific criteria, but I don't that cancer actually was an inclusion or exclusion criterion for the studies, especially at this age.

There is really no difference in the distribution of the tumors. There is no one specific kind of tumor. In many of -- I've served on other of these oversight safety boards, and generally, as you're suggesting, tumors that appear in the first year of the study are most likely pre-existing; in fact, almost for sure, based on cell kinetic considerations, other than leukemia.

So my guess is that this is due to chance, most likely due to pre-existing criteria, and certainly fits in with other types of studies that have been seen in clinical trials that do happen by chance.

DR. KAUL: What is the pre-clinical data?

DR. COHEN: Nigel, do you want to -- the pre-clinical data showed that there was only one type of tumor that was statistically enhanced, and that was in the mouse breast cancer -- the mammary gland tumors in the female mouse. It was not seen in the male -- in the female rat.

The increase was only up to 18 percent. The concurrent controls was 3 percent. Historical controls go up to 12 percent. This is a relatively common tumor in this strain of mice. And it's most likely related to prolactin increases that were seen with the mice -- and I won't go into that

in detail.

There was also some question raised by the FDA regarding some vascular changes that were seen in the male rat. This had occurred only in the male rat, not in the female. Did not happen in the mouse.

But most importantly is that -- what these legions were. They were benign hemangiomas and benign -- what are called angiomatous hyperplasia of the mesenteric lymph node.

Now, unfortunately, the term "angiomatous hyperplasia" can be misleading because, when you think of hyperplasia, you usually think of it as a pre-cancerous change. In this instance, angiomatous hyperplasia is more like granulation tissue, and it has nothing to do with malignancy, either in the animal or in the human situation -- and, actually, in the human, the counterpart is vascular transformation of the sinuses, and this is a clinically irrelevant diagnosis.

Hemangiomas are extremely common in certain strains of mice, like this one, as well as in humans, and they don't transform into malignancy.

DR. HARRINGTON: Sanjay, you had a question for the FDA?

DR. KAUL: Yes. This question was motivated by Dr. Karkowsky's bulleted point number 2 in the penultimate slide, slide number 52. If not for the results of the ANDROMEDA study, subgroup analyses would offer comfort.

So -- it's a two-part question. How would you characterize the risk of the population enrolled in ATHENA? Is it low risk, intermediate risk, high

risk?

DR. KARKOWSKY: The only information that I can see shows that, with respect to the heart failure, 75 percent of the people in the ATHENA study did not have any heart failure at all. So I would have to say they're a low risk population relative to heart failure.

Whether it's the instability or the presence of heart failure, I can't tell, because I don't have any data from another population that allows for discrimination between the two possibilities.

DR. KAUL: So low, probably intermediate risk.

DR. KARKOWSKY: Certainly based on the New York Heart Association baseline.

DR. KAUL: Right. So the follow-up question is that what constitutes -- and it's a philosophical question: What constitutes a clinically meaningful or unacceptable increase in death that one would like to exclude in a relative stable, non-high risk patient population?

DR. HARRINGTON: Sanjay, rather than having Dr. Karkowsky answer that, that's going to be one of the essence of the questions that we're going to deal with. But if you --

DR. KAUL: I certainly would like to hear his perspective before I'd like to hear the sponsor's --

DR. HARRINGTON: Oh, I don't want to hear the sponsor's perspective. I want to hear either from the panel or the FDA. If you like the FDA, I'm

okay with that.

DR. KAUL: FDA's perspective.

DR. HARRINGTON: Okay.

DR. KARKOWSKY: It's a hard question to answer. In the past, we've approved drugs that have an adverse mortality claim if the symptom benefit is worth it. For example, there was a drug called flosequinan that was approved despite what was a point estimate of adverse effect -- I don't know if we would do it these days, but that's been historically what we've done.

And we've asked people in general to rule out a 20 percent or so decrease in hazard ratio, but some of it depends on how frequent the event rate is. So 20 percent of a very frequent event may be a public health catastrophe, whereas 20 percent of a low event rate -- and Dr. Temple can probably answer that better than I can.

DR. HARRINGTON: Go ahead, Bob.

DR. TEMPLE: We're asking in a number of settings -- if you've seen our recent diabetes guidance, we're asking people to put upper bounds on these things. Actually, Ray Lipicky and others put out a proposal not too long ago that all cardiovascular drugs rule out a risk of 1.5.

But on the whole, unless there's a very good reason for it, you don't really want any increase in mortality. But you can't rule out any increase. What you can do is rule out some upper bound.

DR. KAUL: Well, that's the --

DR. TEMPLE: But the idea that's being presented to us is that in the right population, population in ATHENA, you have very high degree of assurance that you're not making increased mortality. That's why they keep emphasizing the 1.08.

So the point estimate is below, and the upper bound is 1.08, and then you're going to tell us how you think that plays.

DR. KAUL: Mind you, this is a comparison against placebo, not against active control. And so --

DR. TEMPLE: Yes.

DR. KAUL: -- relative low risk population, and there are certain subgroups in this population where the upper bounds -- for example, in patients with EF less than 35 is 1.21. Class III heart failure, it's 1.34. Patients who have history of AF and AL, atrial flutter, at the time of randomization but are stable, the upper bound is 1.51.

DR. TEMPLE: Well, I mean, it's inevitable if you start looking at small subsets of a population, your upper bound is going to be higher, so --

DR. KAUL: I understand. That's why I'm asking the question, the FDA's perspective.

DR. TEMPLE: Well, that's part of the judgment you have to make. And one thing just to note: I don't think we're going to like the idea of doing the ATHENA study in a very high risk population. I think, you know -- it may be just chance, as Jim keeps throwing out, but I don't think we believe

that well enough to actually ask people to study that. So you're sort of stuck, heading toward a relatively low risk population. I don't know how you test that.

DR. HARRINGTON: Sanjay, your question is an excellent one, and it's going to be that is, as you look through the questions, we're going to come back to and get the full panel input.

We've got to get to the questions. I have three people remaining: McGuire, Nelson and Swenson. If you could keep your questions brief, and if the person who is asked to answer could keep them equally brief, it would be appreciated.

DR. McGUIRE: I have a question for the sponsor regarding drug interactions. There's a fair amount of information about digoxin interactions, and in DIONYSOS digoxin dosing was cut in half, based largely, I assume, on the active comparator, amiodarone's, interaction.

The concern I have is with Coumadin interaction. The proposed label doesn't comment very much -- and Dr. Chew went very quickly through the ATHENA INR. But in the briefing document, there is a concerning signal from DIONYSOS with dronedarone where 10 percent of patients with ten days had an INR greater than 4.5 on dronedarone, and 25 percent of patients had a dose decrease within five days of Coumadin.

So I'm not so convinced that there's not a Coumadin interaction that's clinically relevant.

DR. GURAL: In fact, we did look at that, and the DIONYSOS study was not presented today, but obviously we do have the data available to us, and I'm going to ask Dr. Chew to present both the data from the DIONYSOS trial as well from the ATHENA trial on the interactions with Coumadin.

DR. HARRINGTON: And, again, if you could just keep it brief.

DR. CHEW: Just to keep it brief, maybe we could go to the DIONYSOS trial, because that's the one that was mentioned.

Could I please have the slide showing the INRs for DIONYSOS for dronedarone and amiodarone. This is a double-blind study. As you know, there's a 2C9 interaction with amiodarone, and one has to be cautious in the use of Coumadin because it interferes with the metabolism of warfarin. Slide on, please.

In this study, you can see the INRs over a course of time with the DIONYSOS study, with the amiodarone in orange and dronedarone across the bottom, up to 12 months.

Could I also have the odds ratios for bleeding.

That was associated, not surprisingly -- okay. We'll have the Kaplan Meier. Slide on.

In the DIONYSOS study, there was an excess of bleeding associated with amiodarone. And you can see that, over the course of the 12 months, that there was a 50 percent greater risk of bleeding with amiodarone versus dronedarone.

Next slide.

This is showing the information the same way.

Do we have the adverse events and serious adverse event ratios?

There was an increase in adverse events -- slide on.

There was an increase of adverse events of bleeding as well as serious adverse of bleeding with amiodarone, including one intracranial hemorrhage that was seen with amiodarone.

DR. HARRINGTON: Go ahead, Darren.

DR. McGUIRE: But the question is more specific. I guess maybe a shift plot or shift table would be more informative. I'm concerned, looking at figures 28 and 29 in the briefing document -- this is a clinically relevant number of patients, although not as bad as amiodarone. The numbers exceeding 4.5 INR, that's a clinically relevant --

DR. CHEW: Yes.

DR. McGUIRE: -- drug testing abnormality.

DR. CHEW: Can we go to the main presentation for the oral anticoagulants where we had that same sort of DDI. We also had that for hemorrhage.

DR. HARRINGTON: So your point, Darren, is it's not amiodarone that's the relevant comparator here; it's placebo.

DR. McGUIRE: Right, I'd like to see it against placebo. And also not necessarily bleeding, but my concern is the necessity, A, for a potential

dose reduction at initiation, but B, more forceful language in the product label, if this gets approved, about monitoring frequently within the first five to ten days.

DR. CHEW: Slide on, please.

Before I address this slide, certainly we will be working with the FDA. We're going to be reviewing the risk management plan, along with the other issues I mentioned. But this was the mean change in the INR in ATHENA for dronedarone versus placebo.

And do we also have the relative risk for bleeding in ATHENA? We're looking for that drug-drug interaction in terms of bleeding.

DR. McGUIRE: I hate to -- do you have any more granular data within those first 14 days from ATHENA? Because all of the action in DIONYSOS is five to ten-day --

DR. CHEW: Right. We don't have that available.

DR. HARRINGTON: Are you satisfied, Darren?

DR. McGUIRE: I guess I'll just say it would be nice to have those data. I'm not convinced completely that we don't need to address Coumadin interaction more completely.

DR. HARRINGTON: So one of the things you will be asked is that, if the drug were to be approved, are there recommendations that you would make relative to either labeling, further studies, et cetera? So it may be the time to bring it up.

Dr. Nelson?

DR. NELSON: I could defer my question and bring it up later.

DR. HARRINGTON: Perfect.

Dr. Swenson?

DR. SWENSON: Just because of the past history of lung toxicity with amiodarone, we've heard just very briefly that there were no major respiratory complications arising from the use of the drug, but can the sponsor discuss just very briefly whether pulmonary function studies and particularly diffusing capacities were followed in these patients because of the -- certainly with any condition like afib, probably there's a lot of people with COPD at least in our population.

And was it specifically tested in anybody with underlying lung diseases?

DR. GURAL: In fact, we did look at certain aspects of that, but not in a prospectively designed way, looking at repeated measures of liver function tests.

Dr. Chew, in his presentation on pulmonary, perhaps can readdress some of the findings that we've seen, not only in the studies that are placebo-controlled but also in comparison to amiodarone.

Dr. Chew?

DR. CHEW: The -- slide on, please.

This is -- as you said, there was no signal in the AFL pool for an

imbalance for dronedarone versus placebo. There were no periodic or surveillance type of pulmonary function tests done. And in DIONYSOS there were just no events. Slide off.

DR. HARRINGTON: Are you okay, Dr. Swenson?

DR. SWENSON: I think there will be some questions arising in the final session about what to do in the future.

DR. HARRINGTON: Perfect.

So in the spirit of openness here, I want to look around the table and make sure that everybody has had a chance to ask the questions. I want to thank the sponsor for providing answers much of the day, the FDA for -- Dr. Karkowsky for doing the same.

Okay. If there's no remaining questions that you have for either the sponsor or the FDA, this next hour and a half -- hour and 45 minutes, actually -- are devoted to our discussion. Again, in order to forego a break, if people want to get up and get some coffee, et cetera, feel free to do so.

We have a series of questions that, in typical Dr. Stockbridge fashion, sort of build one upon another, and I think logically lay out the issues that they're asking for our help with. We'll end with the final voting question, which I believe, Norm, is the only voting question. And before we vote, Elaine will remind us as to the voting procedure, which has changed over the years.

So let me read the first set of questions here, and we'll go through

these one by one, and I will make very sure that everybody has a chance to weigh in.

This advisory committee is being asked to opine on the approvability of and the appropriate target population for use to decrease the combined risk of cardiovascular hospitalization or death in patients with either a recent history of or chronic atrial fibrillation or flutter with associated risk factors, as has been pointed out, in quotation marks.

Dronedarone was originally submitted as an NDA in June 2005 based on the results of two placebo-controlled studies. It delayed the time to first occurrence of arrhythmia and decreased symptomatic recurrence of these events in a patient population with either a history of afib/aflutter who were in sinus rhythm at the time of randomization.

The application was not approved, largely because of adverse outcomes in ANDROMEDA. ANDROMEDA was a placebo-controlled study of the active agent in patients with New York Heart Association class II to IV and a recent hospitalization, as has been pointed out, for heart failure.

Intended to provide reassurance regarding safety in this high risk population, this trial was stopped after 627 patients were enrolled, out of a planned 1,000, because of an adverse effect on mortality. You've seen the data and the numbers today.

The sponsor then performed ATHENA, which was a placebo-controlled study of the active agent in patients who, during the last six months, had at

least one episode of afib or flutter, and at least one normal EKG during the same time period, in either order.

Patients with permanent atrial arrhythmias were precluded from enrollment. Those who were in afib at the time of enrollment were to be converted after a suitable anticoagulation interval, and the primary end point was timed to first event of cardiovascular hospitalization or death from any cause.

You can see the primary data presented in the table on page 2 of your questions.

There were 25 percent fewer such events on the active agent relative to placebo, a difference that was highly statistically significant. The groups separated early and remained separated throughout the 24 months of follow-up. The results were largely homogenous across a variety of planned subgroups, including the United States versus outside the United States.

The sponsor now believes that adverse effects in ANDROMEDA were related to clinical instability of the ANDROMEDA population.

So the first question for discussion -- and I'll have you look at the question followed by the table of deaths on the next page -- is, does the committee find this explanation plausible and are there differences -- are these differences consistent with the sponsor's hypothesis?

So does the committee find that ANDROMEDA and the follow-up study different, based on this clinical instability hypothesis? So who wants to

begin the discussion? Go ahead, Mike.

DR. LINCOFF: I think -- essentially there's two options, either that it's due to the instability of the patients or that it's spurious, and I continue to believe that we have to operate on the assumption that it's real. I think it's a very reasonable -- and the data supports the idea that this patient population was unstable, had recent instability, and that that is a potentially good explanation for the mortality difference, particularly given the lack of an apparent mortality hazard in a lower risk, or less acute, perhaps, population in the ATHENA trial.

And certainly the breakdown of the deaths in the table are all consistent with the types of deaths that you'd expect a clinically unstable population of patients with heart failure.

DR. HARRINGTON: So you believe, Mike, that the finding of increased mortality in ANDROMEDA may well be a real finding, that we should -- we might treat it as such, and if we treat it as such, clinical instability is a reasonable explanation?

DR. LINCOFF: Yes.

DR. HARRINGTON: Does anybody have a counter belief to that? Let me go to Dr. Wolfe and then to Dr. Calhoun.

DR. WOLFE: It's more of a supplement than a counter belief. I mean, obviously blaming the patient as a cause of a problem is reasonable -- in this case, these people were clearly much sicker. But we do have a drug

that is a negative inotrope, and one can postulate that, in addition to their own clinical condition, and maybe particularly because of it, they were more susceptible to being given a drug that was a negative inotrope. So I would just add that to what is otherwise a patient-focused explanation.

DR. HARRINGTON: So would it be fair, Dr. Wolfe, if I amended our statement to -- you're putting forward the statement that this may well represent a deleterious effect of the drug in a clinically unstable patient population. Would that be a fair summary?

DR. WOLFE: Yeah, they would be particularly more susceptible to it because of their instability, yes.

DR. HARRINGTON: Mike did you want to follow up?

DR. LINCOFF: Yeah. That doesn't differ from what I -- I was not blaming the patient. We're not comparing this patient population to another population. We're saying this drug, in a high risk population -- I'm making the assumption that this drug does indeed result in a higher mortality because of the drug, but because of the population. It's not blaming the patient.

DR. WOLFE: Because of that particular characteristic of the drug. Right. Agree.

DR. HARRINGTON: Dr. Calhoun, Jim and Henry.

DR. CALHOUN: Not to discount Dr. Neaton's careful analysis, I think that his suggestion that this might, in fact, be a statistical variant is fair, and the data that the sponsor provided suggesting that this could be a

false positive as much as 20 percent of the time is something we can't discount.

However, in that patient safety is really paramount, I agree that we really do have to treat this as a real finding and, in that regard, the hypothesis seems to be consistent.

DR. HARRINGTON: And you're -- just for the reminder of everybody, you're referring to 20 percent based on the simulation testing that was done.

DR. CALHOUN: Based on the simulation testing and the multiple comparisons.

DR. HARRINGTON: Henry, and then Jim.

DR. BLACK: I also agree. The only potentially plausible explanations are that it is by chance -- which I think Jim and they have shown us -- or that this is a population, because of its negative inotrope effect or because of something else, would be at risk, and we have to be careful when we use it.

DR. HARRINGTON: You know, Milt brought up, I thought, an interesting point this morning when he showed the table of prior studies in heart failure where small numbers yielded one effect; bigger studies were done and the opposite effect was found.

But what's really different here is that an observation was made, and then the study was totally changed, whereas in those previous examples, everything was done possible to keep the same population because you wanted to

see the same result. So that analogy fell apart for me a bit, and I think that your comment is well-but.

DR. BLACK: Yeah, but for ethical reasons, you probably could not have continued this, and so this was a reasonable alternative.

DR. HARRINGTON: Agreed. I think we have Jim and then Mori and then Sanjay.

DR. NEATON: I think it's certainly plausible, but I think you can't rule out chance. I mean, I just -- the data don't add up to me. When you look at the subgroup analyses that were done, the change in eligibility -- none of that kind of adds up, in my mind, that this was just a totally, quote, unstable population.

Maybe another variation of what was said earlier is that if you give a drug to a group of people largely for whom little help is going to be kind of achieved with it, which was kind of a dumb thing to do to begin with, all you're going to see is the bad effects of the drug, and there's no such thing as a risk-free drug.

And so what we're seeing here is basically a balance of kind of -- it's been tipped totally the way, in terms of the risk instead of the benefit.

But I'm willing to accept that it's a plausible reason for it, and for reasons of safety concerns, that might guide our future discussion, but I still come back to the chance because it leads to the other questions in terms of how we kind of view the totality of evidence in these studies for their

impact on cardiovascular morbidity and mortality.

DR. HARRINGTON: So let me -- again, one of the things I'll try to do is refine the committee's perspective as we go through the question. Would you -- are you willing to say, Jim, that it's a plausible explanation that there is a deleterious effect of the drug in an unstable population, but you would not discard the notion that the play of chance is really paramount here?

DR. NEATON: There's more than one plausible explanation.

DR. HARRINGTON: I think we've got Mori, then Sanjay, then Erik.

DR. KRANTZ: I guess I would preface my comments by saying I think any type of post-hoc assessment of causality is speculative, and I think that's important just to get on the table.

But I think it's not definite that it's just clinical instability. How do you distinguish that, for example, from disease severity? And I think if you look at this population in terms of cardiomyopaths, there were 600 or so in ANDROMEDA and I think 170 or 179 with an EF less than 35 percent in the larger study of ATHENA. So I think really you can't really tease that out, and I think certainly for a clinician instability is, to me, a vaguer term perhaps than using objective measurements like New York Heart Association class or LB function.

DR. HARRINGTON: As Milton has pointed out, would a hospitalization for acute heart failure decompensation fit one of your categories of defining that patient population?

DR. KRANTZ: I'm just not sure -- explain to me where you're going with that.

DR. HARRINGTON: One of the things we're going to be asked to give our opinion on is that if we -- if we vote for approval, are there patient populations you would or would not recommend treating? What should be included in the label as a patient population to exclude from treatment? Et cetera.

DR. KRANTZ: And I guess my argument or my just sort of challenge would be that although you could say someone was in the hospital or they were feeling more dyspneic -- that's a looser thing to me, as a cardiologist, than looking at, let's say, the ejection fraction or trying at least -- with all the limitations of functional class, to sort of categorize them.

So I think -- you know, I think you run into sort of a perilous situation where people get well and better and worse --

DR. HARRINGTON: Again, in an attempt to try to provide the FDA with some perspective on each question, you sound, Mori, like you're falling more into Jim's camp, that you're willing to accept that there's a plausible explanation here of instability, et cetera, but there's maybe a bit more of a play for chance for you, because you don't believe that this instability is that compelling.

DR. KRANTZ: Or I would say that if you look at the robustness of the data, ANDROMEDA may be more robust because it has 600 patients with an EF

less than 30, and ATHENA only has 170.

And so in terms of -- to me, just from a safety perspective --

DR. HARRINGTON: Got it.

DR. KRANTZ: Again, I'm not saying I totally believe that, but it's something we want to sort of at least think about.

DR. HARRINGTON: And we're going to come back to that. Sanjay?

DR. KAUL: I pretty much agree. I think data that are stopped prematurely are notorious for their fragility. You could cast them at a random high or a random low.

But if I recall, I think most of the examples that Dr. Packer was too good be true early on and turned out the other way. But when you have a safety signal, ethics weigh in more than plausibility. So you are ethically obliged to terminate the trial. So...

DR. HARRINGTON: Erik?

DR. SWENSON: The other thing that might make it biologically plausible is I think we just don't have any data on the pharmacokinetics of the drug in this high risk population. And you would think that -- although maybe their absorption may be slightly different, and possibly depressed, I bet their excretion is also depressed, particularly if this may well have some hepatic elimination patterns.

And so, therefore, it could well have been the equivalent of using 800 milligrams BID in these lesser sick populations.

I think it's believable and would count it more that way, particularly with the real risk of entering a drug for a group like this.

The other thing is that even if this is an exclusion, those patients that are improved by further therapies and hospitalizations might yet might still be eligible for the drug. It's just that they won't be eligible with that early window of what we see as a safety problem.

DR. HARRINGTON: Okay. Let's go to Emil and then Henry.

DR. PAGANINI: The way I look at this, I need --my new drug needs to look at mortality for my new drug, so I'm just going to go choose a population that has a, quote, high mortality rate to see if my drug has any difference from placebo or other drugs or something. And so we're going to put it in these patients and we're going to evaluate the outcome and -- oops -- we have a higher rate of mortality here, and it probably is related to this patient population that has a high mortality.

And so, in effect, I've defined a patient who should not receive this drug. That's a positive thing rather than a negative thing.

So if you look at it from that point of view, while you're looking for an answer on one side, you got a very positive and strong class of patients that perhaps should not receive this drug. So that's a good thing.

DR. HARRINGTON: And perhaps that was one of the ways that Professor Camm was trying to lay it out for us this morning.

Henry?

DR. BLACK: I have a slightly different concern, which we sort of talked about, but what I'm not sure what to do is if somebody were on this and came in unstable, not a disease -- was having an event -- whether that means I should stop it or not, and --

DR. HARRINGTON: So, Henry --

DR. BLACK: -- when I would restart it.

DR. HARRINGTON: I'm going to ask you to hold that, because I actually have that on the list of things I specifically want to talk about when we give advice as to what else is needed, if that's okay.

Other comments on this first question? Norm, have you gotten a sense of how people think about this one? Okay.

Now, of course, in cardio-renal parlance, we never go to question 2 after 1; we got to question 1.2. In ATHENA, during the prespecified period of follow-up, there were 135 drugs on placebo and 115 drugs on dronedarone. It gives you the absolute rates, the risk ratio and the confidence intervals. Are these results compatible with the mortality seen in ANDROMEDA when you compare, one, confidence limits, two, populations, and three, patient management?

So now we're being asked to take the observation from ANDROMEDA and compare it with the observation in ATHENA and give our perspective on, are those just totally different things, and why? Or is there some perhaps consistency there because of the level of uncertainty, patient differences, et

cetera?

So who would like to start this discussion? Jim, do you want to tackle it?

DR. NEATON: I'll just say a couple of things. One is that I think the goal they set out with in ATHENA was to rule out a 50 percent higher mortality. They achieved that. And so I think the data there speak for themselves.

The analysis that they showed where they pooled the data from the AF trials support that. So the -- and the data we saw this morning, after we requested it, even when you include ANDROMEDA, the upper bound -- some might concede that -- think this is a bit conservative, but I would probably do the fixed effects analysis -- so that's what I would have done. It would be about 1.17, 1.18.

And so from a statistical point of view, they're not dissimilar. We heard the P-value this morning for the test of heterogeneity, which probably is about right, around .25. They certainly look different in the two populations -- but we're dealing with small numbers in ANDROMEDA. But I think that we have a situation where the sponsors have done what they set out to do, is ruled out a mortality benefit that's certainly less than 50 percent and appears to be less than 20 percent.

DR. HARRINGTON: You mean mortality risk?

DR. NEATON: Mortality risk, right.

DR. HARRINGTON: So, Jim, since you brought it up, Sanjay had brought up the two different methods to look at things in a meta-analytic fashion, the fixed effects, the random effects model. Could you, for the rest of the committee who are not statisticians, just opine on that a little bit to make sure that people understand?

Because the risk ratio does change fairly substantially, as Sanjay points out, and -- which would be more appropriate in this setting.

DR. NEATON: Well, I think you could argue here most of the afternoon on that. I mean, it seems to me that if you -- and I think Sanjay said it right. If you really view these as distinctly different populations, kind of random draws from different populations that you're comparing, maybe the random effects model would be the appropriate way to go.

The data suggest here that, you know, there's at least kind of from a statistical point of view these are poolable, and so you might look at ANDROMEDA and kind of think, with the small numbers, come to a different impression. But if, collectively, you look at the six studies that are involved there, that's not the case.

And so another way of looking at this is that each of these studies is essentially providing an estimate, some more reliable than others, of the same effect. And in that case the best estimate is a simple, appropriately pooled combination of the six studies, which would be the fixed effects approach.

DR. HARRINGTON: Sanjay, do you want to comment on that?

DR. KAUL: I agree with Dr. Neaton, but I am concerned that the point estimates are in two different directions. Typically when we do fixed effects and random effects, the point estimates don't change that much. It's usually the width of the confidence interval. So that is bothersome to me, with all the caveats enunciated by Dr. Neaton.

DR. HARRINGTON: So before I get to Bob, then, would you care to weigh in on the way the question is specifically asked, which is, are the results from ATHENA compatible with the mortality seen in ANDROMEDA?

DR. KAUL: Well, the way I interpret that result is that, is there an overlap in the confidence intervals? And I don't see any overlap, as was described by Dr. Karkowsky.

DR. HARRINGTON: So you would call these distinctly different results?

DR. KAUL: Right.

DR. HARRINGTON: Bob?

DR. TEMPLE: Well, that's why I was going to ask, too. The hypothesis is that you describe two different populations with different results. Why would you want to pool them all and -- in any one of those ways?

The question that you're asking -- that the question is asking, maybe not in the most perfect language -- I can say that because I didn't write it -- is whether there's a plausible difference between these two

results, and I think that's what Sanjay was saying. That seems to me a relevant question.

DR. HARRINGTON: Other comments on this question? I know you guys are tired, but this is what we're here for. The rest was all just asking questions. Go ahead, Mori.

DR. KRANTZ: Can you just remind me of the upper tail of the confidence interval for one study and the lower for the other? Because I thought they were pretty close, if I remember, and I can't remember if they actually overlapped.

DR. HARRINGTON: If somebody has it, just read it out.

DR. KAUL: 1.08 in ATHENA and 1.10, the lower tail, for ANDROMEDA.

DR. NEATON: But if you pool all the AF studies, it's also 1.08. And so there's some information in the other studies as well. I mean, I think the difference we were talking about were the two results you cited, the random effects, the upper bound was about 1.5 or 1.6.

DR. KAUL: 75, yeah.

DR. NEATON: 1.7.

DR. HARRINGTON: Other comments? Is it a plausible explanation for the group that these are really distinctly -- as Bob has pointed out, these are distinctly different patient populations and different mortality findings within those populations?

Dr. McGuire?

DR. McGUIRE: You know, I think they are compatible. I think these are two very distinct patient populations. I think Dr. Packer's comments in regard to the beta blocker field are relevant here, that beta blockers are deleterious in the acutely unstable patient, and beneficial in the stable ones, and we know that dronedarone has some beta blocking properties.

And also what hasn't been discussed today is that the beta blocker, as the victim interaction studies suggest, increased area under the curve of beta blocker exposure, especially for metoprolol which was measured, and presumed for carvedilol -- and we know a 30 percent increase in beta blockers in the chronic ambulatory stable heart failure patient is a clinically reasonable idea, and in the acutely unstable patient, it's not.

And so I think we have lots of plausible mechanistic explanations, all of them completely theoretically, but certainly compatible with the results from the two trials.

DR. HARRINGTON: Dr. Nelson, and then -- Dr. Wolfe, you were shaking your head; do you want to weigh in?

DR. WOLFE: I'm agreeing.

DR. HARRINGTON: Okay.

DR. NELSON: So I'm not sure that this really answers the question, but maybe it's just a perspective. You know, obviously these are two separate patient populations -- I think we would all agree. One of things I'm a little bit concerned about is that there might be a third patient population that we

haven't really looked at, which are people who have even less risk, perhaps, than these folks who were just in atrial fibrillation. And we really don't know what the risk-benefit ratio is in that group.

And when happens to a drug when it gets marketed, obviously, is that it gets distributed more widely than the initial patient population to whom it's been studied.

Now, we know it's very dangerous in people who are quite ill. We -- based on what we've already talked about, taking the studies at face value, it has some benefit in people with moderate degrees of illness, and, you know, there's a risk-benefit ratio that has to be applied, perhaps kind of theoretically and conceptually to this other patient population, which may turn out to be a very large patient population, depending on how the drug becomes generalized once it's being used.

DR. HARRINGTON: Well, I think your point, Dr. Nelson, is an excellent one because we've heard all day from either the patient representatives or from the sponsor this is an enormous pool of patients with atrial fibrillation. So I think your point is well-taken, that while the label may say one thing, the usage of it may be much broader than that, which I think is your point. And we don't know -- we might not have information about that group.

Norm?

DR. STOCKBRIDGE: Yeah. Aren't you then at least fairly reassured

by the fact that, within ATHENA, people who presumably, you know, weren't -- weren't unstable, the people who were sickest appeared to do best?

DR. NELSON: I mean, obviously, you could be assured, but there are a lot of other issues that we haven't really even touched upon, such as the fact that these people will be on this drug for the next 20 or 30 or 50 years. You know, we really don't have long-term safety studies.

I mean, we briefly discussed the pulmonary toxicity issues, for example, which is the risk part of the risk-benefit equation. You know, amio's pulmonary toxicity often doesn't manifest for quite a long time. Mechanistically, we don't really know why that happens, why amiodarone produces pulmonary toxicity.

This drug is structurally very similar. If there is some structural reason that this happens, this may very well be -- because, I mean, I think we could feel comfortable that the thyroid effects won't occur, just based, again, on the mechanism, you know, the iodination issues. But there's just a lot of those issues.

So, you know, even though there might be some very short-term, you know, risk-benefit balance, as this progresses out in time, all bets are off.

DR. TEMPLE: So you're expressing a concern about -- I mean, this was studied in people whose heart failure wasn't so bad, but who otherwise were a relatively high risk population, and the proposed labeling talks about high risk population. But you're worried that it would spread to people whose

risk for whatever we're talking about is not so very large. That could suggest a number of possibilities, such as additional studies in low risk population, or at least following people for longer term to look at pulmonary function, which I gather the company is planning to do, and I'm sure we're going to be interested in that.

DR. NELSON: You know, my clinical practice is not in cardiology, and I practice in emergency medicine; I work in an emergency department -- I see a lot of people with atrial fibrillation. Not all of them are 75 years old. Many of them are 40 years old, and there's a thousand reasons people have atrial fibrillation.

It was whispered in my ear I thought that I had had as well, which is that, you know, the benefit may change, but the risk is going to be persistent. I mean, the risk to a 75-year-old, you know, in terms of its pulmonary or hepatic or other effects may not be any different than the risk to a 20-year-old except for the fact that the 20-year-old is going to be on it for the rest of his or her life.

So these are very, very hard questions to answer with the limited data that we have.

DR. TEMPLE: There are ways of tracking a cohort looking for pulmonary fibrosis, and we'll certainly think with the company about that. Anything you suggest would be of interest to us too.

DR. HARRINGTON: And I think, Bob, it's fair to say -- and Sanjay

was getting at this earlier -- in terms of the risk of the population, the criteria for entry into the study, which are the associated risk factors, are largely risk factors associated with the complications of atrial fibrillation per se and -- you know, hypertension, increased size of left atrium, et cetera.

So I think -- you're absolutely right. These are no high risk heart failure or high risk coronary disease patients per se.

Go ahead, Henry.

DR. BLACK: I just want to support what Lew is saying. As someone who treats a lot of hypertensives and a lot high risk people, when they get on in years, and even if they haven't had afib -- and if this were out, I'd be really tempted to think about using it.

DR. TEMPLE: Before they get afib.

DR. BLACK: Before they get afib, right.

DR. HARRINGTON: You're a dream doctor.

DR. BLACK: I said tempted.

DR. HARRINGTON: All right. I think that's been a good discussion on this question. Let's go to the next one, which I meant to ask today because it's -- and I assumed it had to do with either one of two things, so let's see what else other people come up with.

But ATHENA's planned enrollment was 4300, but the actual enrollment was 4637. Why was that?

And at least two explanations -- I thought about this while I read the briefing books. One might be in these studies of a chronic care, one sort of banks patients and sponsors don't like to stop enrollment on a dime, but in fact, give people some time to get those patients that they've had lined up into the study.

The other is the event-driven nature of things, and was it -- but it's not quite clear in what we've read as to what the explanation is.

So those are two explanations I've come up with.

DR. LINCOFF: Why don't we ask the sponsor?

DR. HARRINGTON: Well, I meant to do that earlier today, but I just didn't do it. Good suggestion, Mike.

DR. GURAL: We can, indeed, answer the question. I'll ask Dr. Gaudin to come up on the operational aspects, but it was the former, rather than the latter.

DR. GAUDIN: Yes, as you mentioned, the plan was for 4300 patients. By the end of period of enrollment, there was a decision made by the steering committee in order to finish the enrollment in a proper way, and the final data for enrollment was set up as the last day of 2006, 31st of December of 2006. so this is the way it happened, and we got the evidence one year later, of course.

DR. HARRINGTON: Norm, why did you ask the question for the panel as opposed to -- did you not know that, or was there something else nefarious at

play that you were concerned about?

DR. STOCKBRIDGE: Oh, I doubted that we were expecting a big difference in outcome, at least as far as the primary end point is concerned. But it's a fairly big discrepancy in the planned and actual enrollment, and it's a fairly -- fairly deep, important aspect of the way people conduct a trial. You've got to wonder about anything you think is marginal under circumstances where somebody is diverged in that fashion.

DR. HARRINGTON: Okay.

DR. STOCKBRIDGE: And although the primary end point isn't a very marginal P-value, some of the other things are.

DR. HARRINGTON: Other -- so you were wondering if -- while things are sitting at the margin, do just a few more patients help push you over the edge? And that raises all sorts of other questions, doesn't it?

DR. STOCKBRIDGE: Right, like who knew what and when?

DR. HARRINGTON: Exactly.

Jim, and then Emil.

DR. NEATON: I'm a little bit less concerned because I think the issue should be -- as I understand it, they amended the protocol and were going for 262 deaths. I would be concerned if what we were looking --

DR. STOCKBRIDGE: Which they didn't get.

DR. NEATON: They came close to -- so you make an estimate of, and you come as close to it as I presume that you come -- can, for logistical

reasons, choosing a closing date. I'd be more concerned if this was 350 deaths as opposed to 262 deaths.

DR. HARRINGTON: Emil?

DR. PAGANINI: I wonder if you could just take a look at the first 4300 enrolled and then look at the whole group, with the 4637, and see if there's any meaningful statistical difference between the two. And that would answer your question of who knew what, when, where and whether or not this was bad or good, or it was already, you know, some sort of subversive thing that was going on.

On the other side of the coin, any large trial like this I think always likes to stack the deck and have a few more patients, for just that reason, to have more power for whatever analysis they're doing.

DR. HARRINGTON: Sanjay?

DR. KAUL: The end point that needs scrutiny is cardiovascular mortality.

DR. HARRINGTON: I think that was what Norm was getting when he made the comment that it's not the primary end point; it was some of the defined secondary end points.

Dr. Karkowsky, did you do the analysis of the first 4300 patients enrolled?

(No response.)

DR. HARRINGTON: Did the sponsor do an analysis of the first 4300

patients enrolled?

DR. GURAL: Yes.

DR. HARRINGTON: And can you share that with us?

Dr. Karkowsky, did you guys do it?

DR. KARKOWSKY: We could.

DR. HARRINGTON: It sounds like there's a recommendation that you do, and let's see what the sponsor is going to show us.

DR. GAUDIN: Yes, we performed this analysis -- slide on, please -- and these are the results for primary end point, death and cardiovascular death. Relative risk of 0.7 -- so you have to look at the analysis on the right side of the slide which represents the first 4300 patients enrolled and follow up to one year after the enrollment of these 4300 patients.

And the primary end point is 0.751, not much different from the one of primary analysis. For death, it is 0.904 with boundaries of 0.7 and 1.167. And for cardiovascular death, it is 0.747, with boundaries of 0.54 and 1.04.

DR. HARRINGTON: So this is -- gets at Norm's point, that the secondary end point, which is obviously to you an important one, cardiovascular death -- one would argue that it moves perception-wise in a different direction, that -- with the upper bound above 1 versus below 1.

Remind us -- you made a comment about who was the DSMB statisticians. Who actually had access to the database at the sponsor and -- prior to the lock and unblinding of the data.

DR. GURAL: All the data was locked -- was blinded to the investigator until the unblinding date, which was March 2008.

The DSMB statistician was indeed Tom Fleming, and he was the only one that access to the information.

DR. HARRINGTON: So Tom held the randomization codes, and those were not held within the sponsor?

DR. GURAL: We don't have that information. It's done by a centralized randomization.

DR. HARRINGTON: So the sponsor did not hold the randomization codes. They were held by an outside group; is that correct?

DR. GURAL: That's correct.

DR. HARRINGTON: Dr. Karkowsky, are you comfortable with that?

DR. KARKOWSKY: The answer is yes. The point is I have no information to add to what the sponsor says. But it seemed reasonable what they did, but there's always that question when things occur late, after an interim look. And even though you believe that everybody is honest, it's still uncomforting.

DR. HARRINGTON: Okay. Fair comment. Sanjay?

DR. KAUL: Well, I'd like to thank the sponsor for sharing those data, and I'd like to remind the chair to keep that in mind because these data will be very instructive on the language of labeling.

DR. HARRINGTON: Yes. It's one of the things I think we'll probably

bring back up.

Other comments on -- so, Norm, you got a lot more action out of that question than I thought you might have.

(Laughter.)

DR. HARRINGTON: Other comments or questions on this question from the panel?

Okay. Let's go on to question 3. Some analyses categorized the hospitalizations and deaths as cardiovascular or non-cardiovascular. Please comment on the categories of events that were considered cardiovascular and non-cardiovascular and the adequacy of the information on the case report form to support that categorization.

So this gets to some of the issues, I think, that Dr. Karkowsky had brought up in his presentations. Again, who would like to start? Go ahead, Mike.

DR. LINCOFF: I think the -- Dr. Karkowsky's analysis and the general information about the way that the deaths were categorized -- not adjudicated -- really throws a lot of concern in terms of making a distinction between cardiovascular death and death as a whole. And I think that -- so I feel very strongly, based on the data that we've seen, that we cannot make conclusions regarding cardiovascular death, that the categorization is flawed, but intrinsically so, not intentionally on anybody's part, but just there's insufficient information that was collected in this trial, and that no comment

-- no statement can be made regarding cardiovascular death, and that that consideration should be part of when we have later discussions regarding what the label should reflect.

DR. HARRINGTON: Do you want to comment, Mike, on the adequacy of the case report form? Obviously, you haven't seen the whole case report form, but parts of it that Dr. Karkowsky provided.

DR. LINCOFF: We did see the pages, but again -- so, I mean, I think an investigator can say, you know, a patient died from such and such. But when you're trying to talk about cardiovascular death versus not cardiovascular death, particularly in the context which I believe you have to have -- in the context of the type of agent you're testing, you need more information than that.

So I don't believe that the form provides enough information. Even if it had, I think the right way to have done this, if you wanted to make a statement regarding cardiovascular death, would be to adjudicate with source documentation. And that was not done.

So there would only be so much you get from a case report form. You'd have to have additional information.

DR. HARRINGTON: Go ahead, Bob.

DR. TEMPLE: Let me just follow that up a little bit. So what I heard is you don't think there's a claim in there; there are other reasons that were given, you know, it was the third end point, among the secondary end

points, and they weren't entitled to look at it anyway, but leaving that aside, remember I said earlier that we would ordinarily put the nature of the combined end point at least somewhere in the labeling, without P-values, without claims and stuff, but as part of what you do when you win on a combined end point.

Ordinarily, that's what we would do. There wouldn't be a P-value next to it, wouldn't say it's been shown, or anything like that. Any thoughts about that? It seems odd not to put it in, but I'm just curious.

DR. LINCOFF: No, and that's why I said we would discuss it later, because I think that's a very interesting question. I am -- you know, I firmly understand the rationale behind composite end points. We've certainly used them in investigations of our own. And you would hope that if everything is consistent, that the end point be looked at as a whole, with the proper caveats that we don't have enough information for some of the components to say definitively whether or not there's an effect.

I think that why -- the reason that this deserves consideration at least about whether or not a death claim can be made as part of the composite is because there was another trial that suggested increased mortality.

So I think that that's a point that should be discussed specifically, but to answer this question specifically, I believe the information is clearly inadequate to show an effect on cardiovascular --

DR. TEMPLE: Okay. So that goes to whether there's a separate claim

for cardiovascular mortality.

DR. HARRINGTON: And getting into the composite question, Bob --

DR. TEMPLE: Okay. Fine. Maybe that was premature.

DR. HARRINGTON: No, no. I think we can certainly have part of that discussion now. I had said earlier, when we were discussing this, that we frequently use composite end points, because any one event is infrequent enough that, to have a reasonable sample size, in a sense, you have to. And to your point earlier that death just seems like it should always be in there, and cardiovascular disease.

This seemed to me, in the composite -- and I thought that the presenters did a nice job of saying they really had two separate points here, one of which was to demonstrate an effect of the drug on cardiovascular hospitalizations, and this trial was way overpowered to do that.

And then they were trying to set up some boundary of risk for the mortality part of the component. And I view, therefore, this composite a bit different than you might see of a death, MI, stroke, rehospitalization for acute coronary disease. That's my opinion. I think it is a bit different in this setting.

DR. TEMPLE: That's fair. We also, although I'm sure we make our biostatisticians uncomfortable, tend to say something about the composite, even if it's not as rigorous as you want, because how can you not, in some sense?

DR. HARRINGTON: I feel uncomfortable advocating against it, but I think that there might be a special situation here. Jonathan?

DR. FOX: Just a comment for clarify -- and I feel a bit responsible because I think I threw the first hand grenade into this one, but anyway, if I read the documentation correctly, the claim is for cardiovascular hospitalization or death, not cardiovascular death. And so this question is sort of really a mix of two questions. It's around the adequacy of the documentation to categorize hospitalizations as cardiovascular, and then it's just death, which is, as someone else said, counting the bodies. But maybe if there's then a subsequent claim for, specifically, a cardiovascular flavor of death, that's a different debate.

DR. TEMPLE: But just to say what I sort of said before, it would not be unusual if we thought that most of the action was on cardiovascular hospitalization, which it self-evidently is here, to say the composite end point was driven largely by cardiovascular hospitalization, atrial fibrillation hospitalization, whatever one decided to do, sort of downplaying the mortality component.

But, you know, it's fairly obvious you're going to say something about the mortality component because, as Bob is saying, it was there not necessarily to win, but to be a little reassuring, if you could. So it's hard to avoid commenting on it.

DR. FOX: I think we're in violent agreement here. I think Bob's

point -- Bob Harrington's point was a good one, which is this wasn't a composite of two shades of the same kind of benefit; it was really an overall benefit risk, really, assessment of -- you know, an efficacy end point versus a show no harm kind of end point.

DR. HARRINGTON: That's fair. We've got Dr. Wolfe, followed by Dr. Nelson.

DR. WOLFE: Part of the next one --

DR. HARRINGTON: Dr. Nelson?

DR. NELSON: I'll just go back to my original question earlier from the morning, but this was just an opportunity to collect pharmacokinetic data on patients, and the objectivity of a blood level in a patient who's had an adverse event or had died is very important.

So just -- to me it's unfortunate when you try to categorize people to not have that kind of objectivity, particularly the deaths. I mean, all of these deaths should have had, I imagine -- or many of them might have actually had post-mortems done, and perhaps there could have been more than an investigator assessment of the actual cause of death.

You know, the comment before about this intracranial bleed -- you know, the word "subarachnoid hemorrhage" has a lot of meanings to a lot of people, and I think the implication that I heard before was that this was an aneurysm that had bled, but it doesn't necessarily mean that. I mean, the person could have syncopized, fallen down, hit their head and developed

subarachnoid blood.

So, you know, that's why you really want to have more objective data than what an investigator thinks the outcome is, and that's my understanding as to how this was done. So, I mean, in addition to the objectiveness of a post-mortem or something equivalent, I think, you know, pharmacological data would be important as well.

DR. HARRINGTON: Jim?

DR. NEATON: I just was going to say that -- I mean, it's not too surprising to me -- I mean, I appreciate what you're saying, Bob, about kind of this all-cause mortality here has its own special place in the ATHENA trial, but it's not too uncommon in these trials where your expectation is that a high percent of the deaths are going to be cardiovascular, just to go with all-cause mortality, to avoid all the problems with cardiovascular kind of classification and everything else.

And so I totally support not drawing attention to cardiovascular mortality. But I think Bob -- I agree with Bob that I think somehow when you -- when you lay this out, you need to describe the components of this, both the hospitalization components and what fraction were due to all-cause mortality.

DR. HARRINGTON: I don't disagree with that.

Emil?

DR. PAGANINI: Just a quick -- I think adjudication would have

resolved a lot of the non-homogenous classifications that we're seeing, and it's too bad it wasn't done. The forms were inadequate for stratification of admission severity, and so that's a problem.

One quick question. ICD-9 groupings and DRGs, does that have anything to do with anything at all?

DR. HARRINGTON: In what sense?

DR. PAGANINI: Well, you know, was the entire hospitalization paid for by the study or was this paid for through standard DRGs? And it depends on what your ICD-9 is as to what you're getting back. And is that -- was that data utilized for any of the outcome studies at all, or were these just brought up by the investigator with specific diagnoses specific to the study and be damned with the DRGs?

DR. HARRINGTON: So are you trying to get at the --

DR. PAGANINI: I guess what I'm looking for, is there any influence of reimbursement on classification of what people had?

DR. HARRINGTON: You mean if you were going to get a couple of thousand bucks every time the patient was hospitalized --

DR. PAGANINI: Or two more days in the hospital with one ICD-9 versus another ICD-9, so influence -- you know --

DR. HARRINGTON: My guess is that that would be pretty hard to tease out, but I don't know if the sponsor has a brief comment on that.

DR. GURAL: As I mentioned before, the predominant number of 1400

patients were conducted in the United States. The remainder of those were done outside the United States, so they would not be subject to the DRGs.

DR. HARRINGTON: I think we're going to actually come back to some of that question, Emil, so let me keep going here. The major -- because a lot of the same themes will emerge.

The major categories of cardiovascular hospitalization are shown in the table below -- page 5, for those of you who have it -- which is the categorization of CV hospitalizations in ATHENA. Then there's three questions. We'll go through them one by one.

Is the effect on cardiovascular hospitalization more than an effect on symptomatic atrial fibrillation?

Dr. McGuire, do you want to start us off?

DR. McGUIRE: I guess my gut reaction to the question is yes. It was, I think, best illustrated by Dr. Packer's demonstration of the afib admission censured time to first event where a consistent monotony across the other cardiovascular indications.

DR. HARRINGTON: So you believe that the effect is not limited --

DR. McGUIRE: I think it is not limited to --

DR. HARRINGTON: -- to symptomatic afib?

DR. McGUIRE: -- afib, symptomatic improvement, yes.

DR. HARRINGTON: Okay. Michael?

DR. LINCOFF: I'm not sure that slide answered the question. I

think it's clearly not limited to hospitalizations strictly for atrial fibrillation, but I don't know that the -- it wasn't clear to me -- and maybe I'm just misinterpreting -- I mean, because there was a big change in heart failure and a big change -- but those may have been heart failure due to atrial fibrillation. So I just don't know if the mechanism is anything other than atrial fibrillation. But I do believe that it's more important causes of hospitalization than simply because they were in atrial fibrillation.

DR. HARRINGTON: Well, let's just --

DR. LINCOFF: But maybe I'm interpreting --

DR. HARRINGTON: Let's just look at the data that's been provided us here on page 5. There were approximately 850 cases of CV hospitalization in placebo versus 675 in the dronedarone. And you have the majority of them, but not all of them, in the AF or SVT realm. And then you, though, have -- numerically, anyways -- fewer heart failure hospitalizations in favor of the active drug, fewer cases of unstable angina or MI. And then you have some numbers that are either very close to each other or, you know, some going back and forth.

Do you find the heart failure or unstable angina compelling? Yes?

DR. PACKER: If I could just clarify, this is a breakdown of the first --

DR. HARRINGTON: We got that.

DR. PACKER: -- hospitalization.

DR. HARRINGTON: We got that, yeah.

DR. PACKER: Right. So that the committee had previously asked about, if you censured the atrial fibrillation, what would you see? And I showed that slide earlier.

DR. HARRINGTON: Correct.

DR. LINCOFF: But what I don't understand is -- so if a patient came in with severe pulmonary edema and was also in atrial fibrillation and the primary reason for hospitalization was pulmonary edema --

DR. HARRINGTON: It depends what the investigator ticked the box.

DR. LINCOFF: Yeah. So would that be under pulmonary edema? Could some of these, under worsened heart failure, be also patients in afib?

DR. HARRINGTON: Sure.

DR. LINCOFF: That's the part I don't understand.

DR. HARRINGTON: Sure. It depends upon what the investigator felt was the primary reason -- let me go to Darren, then Sanjay.

DR. McGUIRE: I guess the other thing in my mind that suggests that this may go above and beyond just symptomatic afib improvement is this drug has relatively modest effects at afib recurrence -- in the 15 to 25 percent range, depending on if you look at time to event or absolute numbers of events -- and a fairly modest effect on heart rate, with an average of eight to ten beats per minute.

So it's hard for me to believe that those relatively modest --

they're real; they're better than placebo, but they're relatively modest -- would translate into a 25 percent reduction in hospitalization. It's very -- it's an indirect consideration.

DR. HARRINGTON: And they're not as robust as amiodarone for keeping you out of afib.

Dr. Wolfe, then Sanjay.

DR. WOLFE: May I just -- with a little calculator here did -- if you take off the AF cases, you wind up with 16.5 -- if the numerator is everything but afib and the denominator is the number of patients, it's 16.5 percent versus 17.3 percent for dronedarone as opposed to placebo.

So the point is that there is really no difference, in terms of the overall numbers, between the two as you just alluded to.

There are some going one way, as was pointed out, some going the other. There are over three times more pulmonary emboli in the dronedarone group than there are in the other one.

So I think that, at least from my perspective, looking at this table, the full table in the handout or the part of the table here, subtracting off the AF, I think it almost entirely overall accounted for by AF hospitalizations. And again, as has been pointed out many times -- I raised this this morning -- we don't really have a clue as to exactly what those AF hospitalizations were like, other than someone ticked off AF, and the spectrum of what they were is just all over the map, and we don't know what it is, and

that's unfortunate.

DR. HARRINGTON: So just to be clear, and in fairness, this is dealing with the primary end point, and of the primary end point -- I think Dr. Karkowsky pointed this out as well. In the primary end point, the hospitalizations are largely accounted for by afib or supraventricular arrhythmias.

Bob, and then Sanjay?

DR. TEMPLE: Well, but that's the crucial question. If you just looked at these numbers, you'd say, oh, there's not much else going on. But when you look at the total hospitalizations, you get a somewhat different picture, which Milton showed us before.

So I guess the question is, which should we be looking at? I mean, there's a good reason for doing first event. You know, it leads to a nice clean analysis, but other things happen when the study goes on, so...

DR. HARRINGTON: And certainly in other areas -- total days out of the hospital is an important analysis. There's a lot of sort of AUC-type analyses that can be done to look at freedom from something bad happening to you, so your point is well-taken.

Sanjay?

DR. KAUL: I'm seeking clarification from Dr. Stockbridge. I'm assuming that by symptomatic atrial fibrillation you mean atrial fibrillation leading to hospitalization?

DR. STOCKBRIDGE: Yes.

DR. KAUL: Because we really don't know what drove the hospitalization.

DR. STOCKBRIDGE: Right. That is --

DR. KAUL: Okay. So in order to answer the question, is the effect on cardiovascular hospitalization more than an effect on atrial fibrillation-induced hospitalization, I've done the breakdown here. The overall hazard ratio is .75. And for the AF population -- or AF indication -- the hazard ratio is .63. And for the non-afib hospitalization, the hazard ratio is .86.

So the answer is yes, it is driven -- the effect on cardiovascular hospitalization is driven by the effect on atrial fibrillation-induced hospitalization.

DR. HARRINGTON: Does anybody want to comment on what Bob brought up, that we did see some data, that there are other -- second hospitalizations, for example, which include things other than atrial fibrillation? Do people want to comment on that? Go ahead, Sanjay.

DR. KAUL: Of course there is an overlap.

DR. HARRINGTON: That's fair.

DR. NEATON: I actually think the other data that we saw is more appropriate to look at than this. I think this is a very useful descriptive table. The top line is clearly important. And then this basically tells you what contributed to that first event.

If you want to ask the question, does dronedarone versus placebo differ for different types of cardiovascular hospitalization, I think we want to refer to the analyses earlier.

Now, actually, it gives you a very similar number. So that for AF hospitalization, what we saw was roughly a 38 percent reduction in risk, and what we saw for non-AF hospitalization was a 15 percent reduction in risk.

Now, that's just ATHENA. And so that -- you know, those numbers -- I think the non-AF hospitalization, if you kind of are of a mind that we should incorporate the other studies, and particularly ANDROMEDA, that's going to be shoved up. And so it seems to me the answer here, at least in my mind, is it's primarily driven by AF hospitalization. But in ATHENA, we see a modest effect that is barely significant.

DR. HARRINGTON: On other --

DR. NEATON: On other hospitalization besides AF.

DR. HARRINGTON: I think that's actually well-summarized. Other comments? Mori?

DR. KRANTZ: I just think it's a challenge, you know, to tease out when you have a rhythm disturbance and you're tachycardiac with -- or troponin -- little troponin leak, someone comes in with angina, all these things, worsening heart failure -- they're all so interconnected that I think it's really hard to posit anything really more than the arrhythmia as the main driver.

DR. HARRINGTON: Okay. Norm, are you content with that discussion?

DR. STOCKBRIDGE: Yes. So let me see if I've got that right. You know, the description in the label will say something about the composite. It will say the composite was essentially all cardiovascular hospitalization. And then I say what exactly about whether the cardiovascular hospitalization was mostly -- largely AF-related?

DR. HARRINGTON: I think you can take a queue from -- Bob had made the comment earlier when we were talking about the overall composite -- here you'd say, in the cardiovascular hospitalizations, which is a composite, that the effect is largely driven by a reduction in hospitalization for atrial fibrillation. And you can certainly provide the data, as Jim I think is indicating, on the other cardiovascular components.

DR. STOCKBRIDGE: Let me phrase it a little bit differently, then. Would you expect to see an advertisement that says the effect on hospitalization -- it's more than AF?

DR. HARRINGTON: Go ahead, Mike.

DR. LINCOFF: I think there's actually a distinction here in the wording here. It's hospitalizations related to atrial fibrillation -- related to, not necessarily -- because many of these events, heart failure, unstable angina, et cetera, are likely the result of atrial fibrillation. In the absence of data, which I haven't seen, to show that events other than atrial fibrillation -- that patients were hospitalized with events that did not have

a concurrent atrial fibrillation -- in the absence of data to say that these were absolutely independent of afib, which we don't have, but we don't have -- I think it's reasonable -- what we have is evidence that it reduces hospitalizations related to afib where either afib is the primary reason, or some complication of atrial fibrillation.

And I think that's a very reasonable claim that is pathophysiologically -- I mean, it fits with the proposed mechanism of action of the drug.

DR. HARRINGTON: Sanjay?

DR. KAUL: The chicken or the egg debate can go on.

DR. HARRINGTON: Henry?

DR. BLACK: Norm, I was going to ask you whether you're secure putting the word "symptomatic" in when we have so little information about why people got admitted.

DR. STOCKBRIDGE: As I said earlier, I think that was just the assumption -- something drove people to the hospital. It presumably wasn't the detection of arrhythmia at some regularly scheduled visit.

DR. HARRINGTON: I think Mike's comment is a fair one, Norm, that primarily what you're seeing here is a reduction in cardiovascular hospitalizations related to atrial fibrillation, and then it gets to Sanjay's -- you don't know, did the heart failure come first, or the afib? Afib followed by the heart failure? That seems reasonable, related to.

Bob?

DR. TEMPLE: In some sense this is not so different from the dual purpose you described earlier. What probably is important is you take reassurance from not finding a huge excess of heart failure hospitalizations, and it doesn't really matter that much whether it was slightly reduced or dead even, but it's not way up. And given the ANDROMEDA study, that's somewhat reassuring.

DR. HARRINGTON: Jim?

DR. TEMPLE: So maybe it doesn't have to be --

DR. NEATON: I think it is -- the wording helps a little bit, but I go back to kind of what we heard this morning where there's really an unmet need for drugs that do more than reduce hospitalization for afib, recurrences of afib. And I don't think the data here are real convincing on that.

And so I would hate to see an advertisement or a claim made for that.

DR. HARRINGTON: So to answer Norm's question directly, you would not like to see something that said, it's more than an effect on afib.

DR. NEATON: Exactly.

DR. HARRINGTON: Do other people -- does anybody disagree with that?

(No response.)

DR. HARRINGTON: Let's go to part 2. Same issue, cardiovascular hospitalization. Are the study results on cardiovascular hospitalizations

applicable to U.S. practice?

I'm going to look to the sponsor, but about 1400 patients enrolled in ATHENA from the United States.

Sanjay?

DR. KAUL: Well, you know, hospitalization for atrial fibrillation varies according to individual, institutional, geographic practice patterns. And I think that's what Darren was trying to get at, is that what is driving these patients to get hospitalized? I can tell you about our experience.

We see three times as many patients in the ED only with atrial fibrillation than are hospitalized. So I like to get that information as to what prompted these individuals to be hospitalized. I think that addresses the crux of the matter.

DR. HARRINGTON: So that may be a question that they have to come back to, because as Dr. Karkowsky and others have pointed out, they are limited by what they collected -- and I'm going to look to Dr. Karkowsky over there. I think you did say -- and I do remember reading in the briefing book -- that the effect in the U.S. 1400 was very consistent with the overall effect.

DR. KARKOWSKY: If I may, the definition of a hospitalization was two calendar days either in the ED or in the hospital; that is, if you came in at 11:59 p.m. and stayed till 12:01, that was a hospitalization, whether they did anything for you.

And as far as the primary end point, Dr. Freidlin did the analysis and looked at both a scatter plot of various sites and also various countries. And the U.S. was not heterogeneous with respect to that, nor was there any one site that drove the outcome.

DR. HARRINGTON: Dr. Nelson, and then Darren.

DR. NELSON: I was going to support Sanjay's last comment. And working at things from the other end, I have people with atrial fibrillation all the time, and you could just toss up a coin to try to figure out whether they're going to be admitted or not. It sometimes seems just like a random event, based on individual practitioners, you know, time of day, weekend or weekday -- and there's so many variables.

So I'm not really sure there's just a simple -- applicable to the United States, because there's probably no real rule here.

DR. HARRINGTON: So this may be something that you would want to see more data on as to the reason for these patients getting hospitalized?

DR. NELSON: (Nodding head.)

DR. HARRINGTON: Hold on, Dr. Wolfe. Darren, then Dr. Wolfe.

DR. McGUIRE: I just will make the caveat comment a striking omission from the registration data set are ethnic minority representations, and if you want to talk about the U.S. population applicability, there are only 50 African-Americans in the entire registration data set, by my count, 300 Asians and, to my count, no Hispanics are represented. So it's probably

applicable across these races, but we don't have those data, and those would be something on the to-do list.

DR. HARRINGTON: Very good point.

Dr. Wolfe?

DR. WOLFE: Just a 20-second comment. Start your watches. I think -- we can't answer the question. I mean, the answer to the question is you can't answer it because, A, we've already heard that there's huge variation for hospital to hospital within the United States, and, B, we have no idea what the reason for the hospitalization was in the study. So if we don't know that, we can't know whether it's applicable. We don't know what the "it" is to be applicable.

DR. HARRINGTON: Okay. Fair comment.

Other -- go ahead.

DR. STOCKBRIDGE: Wait, wait. You know, if you give up that ground, you can't come back later and say, we should approve this. If you don't believe this is clearly applicable to U.S. practice, you won't be able to vote to approve it.

DR. WOLFE: I was simply saying that the study itself doesn't have enough definition -- I mean, let's assume that the study is randomly representative of the United States, which -- I don't know what the sites were or whatever else. All I'm saying is that since we don't know what the spectrum of cause is for hospitalization for cardiovascular reasons in the

study were, we just can't answer the question.

You can say, if it, in fact, represents the whole United States, then it is representative. But we don't have the data. And, you know, points have been made many times today: It is unfortunate and I think, to some extent, inexcusable that there weren't these kinds of data collected at the time of hospitalization for cardiovascular reason.

DR. HARRINGTON: But let me try one other thing, Dr. Wolfe. I think we agree -- and Henry had commented on this -- that the population that was enrolled in this trial, with the risk factors, the associated comorbidities, appear to be the type of population that has atrial fibrillation in the United States. Would you grand that?

DR. WOLFE: Absolutely.

DR. HARRINGTON: The use of concomitant medications, with beta blockers, anticoagulants, anti-platelet agents, et cetera, appears to be consistent with the population in the United States. So then the question becomes, do you believe that the treatment behaved in the United States as it did in the overall study? And we heard from the FDA that the point estimate was very consistent.

Does that sway you at all or --

DR. WOLFE: I'm just making a finer point about not knowing the nature of the hospitalizations for AF handicaps answering the study -- answering this question. That's all.

DR. HARRINGTON: I won't disagree. Let me go to -- let me go to Mike, Henry and Bill.

DR. LINCOFF: I actually will disagree. I mean, this is a study of a -- of practice. It's a large-scale study of practice. Granted, being in a trial always has some subtle influence on the way you take care of patients -- and you may be more attentive and more likely to hospitalize -- but it's a blinded study, and that influence should affect both arms.

So as long as we have point estimates in the U.S. that are similar to outside U.S. that suggest a similar practice pattern, I don't think we need to know, to answer this question, what the reasons were for all the hospitalizations. We have clinician judgment across a broad spectrum of countries, a quarter of whom -- a quarter of the patients were in the United States -- who had similar medications in other practices.

So, you know, to answer this question, we don't need to know necessarily why the physicians hospitalized the patients. We just need to know that clinical judgment was used to hospitalize the patients and that there was a relative difference between two blinded arms.

DR. HARRINGTON: Henry, and then Dr. Calhoun.

DR. BLACK: Yeah. I want to support that. I think we can say there was an adequate representation of U.S. volunteers. How they're treated exactly, I don't think you could get two doctors in the same hospital or the same division to agree with everything and treat every patient the same way.

But it wasn't as if we had 6,000 people and only a hundred came from here. I think we had enough to be able to say it.

DR. HARRINGTON: Dr. Calhoun?

DR. CALHOUN: I at least, and perhaps some of the rest of the committee, misunderstood the take of your question. It was good for you to clarify it, Dr. Stockbridge. Because I think with the limitations that Dr. McGuire noted with respect to minority -- ethnic minority representation, I think it is reasonably clear that the results don't differ in U.S. versus non-U.S. sites. And so it would be generally applicable, again, to Mike's comments.

DR. HARRINGTON: Dr. Temple.

DR. TEMPLE: I was just going to point out that I'm aware of at least three meetings coming up in the next few months on what are called pragmatic clinical trials which hew to the idea that too much data collection gets in the way of ever learning anything.

And this, of course, is the model for a pragmatic trial. Just ask if they're hospitalized; don't worry so much about why they were.

And there is a substantial movement in that direction, partly coming out of Duke and other places, that maybe you don't learn that much when you get all these details. I just want to mention the tension that's going on about that.

DR. BLACK: I'm a fan of large simple trials. I just don't like

large sloppy trials.

DR. TEMPLE: Right. But, I mean, everybody likes the concept of large simple trials, but then you go probe the data to find out what happened, and you can't. And then you get irritated.

DR. HARRINGTON: That's well-summarized.

Let's do 4.3. While heart failure hospitalizations -- again, refer to the table -- trended lower on active drug, other potential signs of worsening heart failure trended adversely -- peripheral edema, for example, fatigue, dyspnea -- and you can see the absolute rates given here. How do you reconcile these findings?

Anybody want to start?

DR. CALHOUN: I don't think one can interpret numbers that have such a small absolute variance. I think it's just a variance of the signal.

DR. HARRINGTON: Darren, you're shaking your head.

DR. McGUIRE: Yeah, I would agree with that. I have some confidence that the cardiovascular hospitalizations captured clinically relevant incident and worsening heart failure. These are signals that are of some note, but I don't think undermine the overall cardiovascular hospitalization, so...

DR. HARRINGTON: Does anybody want to disagree with that, that these are relatively small differences in investigator appointed [sic] events, and that the harder end point, if you will, of hospitalization is not different -- or, rather, is lower in favor of the drug?

Okay. I'm sorry. Dr. Wolfe.

DR. WOLFE: I just wanted to amend -- Dr. Karkowsky pointed out that although there were more patients -- slightly more patients in the placebo hospitalized with heart failure, that they required, at least generally, less serious treatment than the ones that were hospitalized with heart failure with dronedarone. So, I mean, I -- these are small numbers here. They're not quite as small, but they're still small numbers. And the treatment -- again, we've got this idea that it is a negative inotrope, and it might be that when it is related to heart failure, the heart failure itself, even though the cases are different, the severity of it is more.

So I think that the whole package of the treatment of these patients and the difference in the percentage of symptoms may make some sense.

DR. HARRINGTON: And I think it's a theme that's come up from a number of you -- certainly Mori brought it up, I think Jim brought it up -- a number of people have brought up this notion that if -- Dr. Nelson brought it up -- that if the drug were to be approved and on the market, understanding its effects in this group of patients with significant left ventricular dysfunction or heart failure -- which may not be systolic dysfunction, but just -- but an element of diastolic dysfunction -- is going to have to be worked out. And so certainly more investigation is going to be warranted.

All right. Let me go to question 5. Is there an effect of dronedarone on atrial flutter?

Now, I asked this question and -- based on some of the comments that were discussed in terms of the infrequency, overall, of pure flutter versus fib combined with flutter. And we did -- the sponsor did show us odds ratio plots which suggested that the point estimate -- although the group was smaller, the point estimate was consistent across the categories.

Norm?

DR. STOCKBRIDGE: We probably need to get some clarification about exactly what data were that you saw. I thought we heard that those were people who were in aflutter at baseline. Was that really the people who had aflutter as their qualifying arrhythmia?

DR. GURAL: Yes.

DR. STOCKBRIDGE: It was, okay. All right.

DR. HARRINGTON: Dr. Karkowsky, were you able to reproduce that analysis?

DR. KARKOWSKY: My understanding is there were, I think, 500 patients -- I don't recall them being specifically the qualifying ECG within six months prior. But if the sponsor says that is indeed what that number came from -- I couldn't tell from the description where those ECGs came from.

DR. HARRINGTON: Does the sponsor want to clarify that?

DR. GAUDIN: This information was based on reported ECG at baseline by the investigator.

DR. HARRINGTON: So if we -- go ahead, Dr. Karkowsky.

DR. KARKOWSKY: I'm still confused. Baseline occurred six months after the -- could have occurred six months after the event. As far as I could tell, there was no ECG appended to the case report forms. So how was that data collected?

DR. HARRINGTON: Does the sponsor want to comment?

DR. GAUDIN: This was based on the information reported by the investigator. So baseline ECG was most recent ECG at the time of randomization. But it was not based on a reading of ECG, but on the information reported by the investigator.

DR. HARRINGTON: So was there a tick box on the case report form that said the reason for entry into this study is afib, aflutter, or the combination thereof?

DR. GAUDIN: Correct. This is the way it was collected.

DR. HARRINGTON: So that's the way it was collected. And then, in your analysis, what we're seeing is those three categories providing a baseline variable.

DR. GAUDIN: Yes.

DR. HARRINGTON: Dr. Karkowsky, are you comfortable with that?

DR. KARKOWSKY: If that's what they did, that's perfectly reasonable.

DR. HARRINGTON: Norm, are you comfortable with the response?

DR. STOCKBRIDGE: Yes, I am.

DR. HARRINGTON: Any additional comments on the fib/flutter question? Don't fade on me yet, guys. We've got some questions to go.

DR. KRANTZ: I would just say that, clinically, we don't want to make a distinction. I mean, they are really a continuum of the same disease, and so I think, as we apply therapies, I think this would be an instance where we -- we don't want to split; we lump.

DR. HARRINGTON: But certainly it's reassuring to see all three categories with, directionally, the point estimates lined up.

DR. STOCKBRIDGE: And it's worth saying not everything that's got an afib claim has an aflutter claim. And they haven't tracked very well with one another.

DR. HARRINGTON: I think that's fair.

All right. Now we're going to start to get into some of the juicy questions here. So -- the secondary end point were arranged to be analyzed sequentially. The first secondary end point was all-cause mortality, which, as noted above, trends nonsignificantly -- P equals 0.25 -- lower on active drug. Thus, one is not entitled to evaluate subsequent end points of cardiovascular hospitalization alone -- it gives the nominal relative risk and the P-value -- or cardiovascular death.

However, there was no possibility of getting a claim for all-cause mortality -- the qualifier says, too broad to be meaningful. Can you ignore all-cause mortality because it should never have been in the analysis plan

and, if so, is there a reasonable basis for a claim on cardiovascular death?

Now, that is a -- this, like, offends the English major in me, Norm. This is --

(Laughter.)

DR. STOCKBRIDGE: I don't know about the English majors, but I almost got lynched by the statisticians behind me, too.

DR. HARRINGTON: So why don't you tell us what you're looking for here.

DR. STOCKBRIDGE: Well, I mean, the question is -- I mean, I -- the -- the thing to explore here is whether somebody is tied to an analysis plan that we may have bought into, but doesn't really make a lot of sense. It was not a sensible thing to stick all-cause mortality in as the first primary -- first secondary end point. Look, if they thought -- if they thought that it was only worth talking about because it was reassuring that, you know, overall it would carry the day on all-cause, it shouldn't have been a named secondary end point at all.

There isn't any likelihood -- there isn't any plausibility that a drug really affects all causes of mortality. So we weren't going to give them an all-cause mortality claim, even if they appeared to earn it.

(Laughter.)

DR. STOCKBRIDGE: And if that's true, then why is the chain broken by this end point? And I'd say the same thing about the cardiovascular

hospitalization thing. We were going to look at that whether it was part of the formal analysis or not. And if, in fact, it drove the overall analysis, as it did, that's going to be the nature of the claim they get at the end of the day too. So that one shouldn't have been in there either.

DR. HARRINGTON: So what you're saying is that you'll try to help protect them from themselves if they don't pick the --

DR. STOCKBRIDGE: Well, that's the question that's put to you: Is there any rational basis for reaching down into the third secondary end point and saying, you know, that has some plausibility to it; you know, we should pay attention to the actual numbers.

DR. TEMPLE: Or would, if you didn't already express reservations about it.

DR. HARRINGTON: I was going to bring that point up.

DR. STOCKBRIDGE: I think that's right.

DR. TEMPLE: Can I just add one other thing? I mean, taken literally, this sequence says you cannot test for cardiovascular hospitalization when we all know, from the primary analysis, that's the only thing that there was.

So we're sort of asking about these group sequential analyses and pestering Jim about it, just like we're pestering our own statisticians.

DR. NEATON: I think that the answer to your question is that they probably shouldn't get a claim on cardiovascular mortality for reasons that

are totally different than what you've kind of laid out. And so that -- I mean, I think if we were in a different situation where there was a more cohesive body of evidence across these studies and the events were -- we were more confident in the classification, I probably would be inclined to kind of go along with your idea that this sequential plan perhaps was illogical to begin with, and we should kind of look at the data and make a common sense decision.

DR. HARRINGTON: Mike?

DR. LINCOFF: I won't -- I've already stated my skepticism regarding the veracity of the finding. But in terms of the methodology here -- first of all, I think they were trying to counter the perception in ANDROMEDA of increased mortality, which was all-cause mortality.

Secondly -- so I can understand why they would prioritize that end point, because that's what they had to overcome to get approved for anything.

DR. STOCKBRIDGE: But they didn't say, you know, we're going to -- the hypothesis that was tested was against zero effect. It wasn't against some upper bound.

DR. LINCOFF: That's true. So maybe had they defined that we would show non-inferiority by this -- or not an excess by this boundary, we could then go on to look for superiority, and that may well be true.

But I'm curious -- you know, there have been a lot of trials that have not tried to adjudicate causes of death, particularly over relatively

short periods of time -- which two, three years actually is -- where you would simply assume that the majority of the mortality events are going to be related to cardiovascular; the rest is noise, but it means you lose your power -- but so what? And you get, if not a claim specifically for that, the word "mortality" -- maybe not, you know, all-cause: We're going to stop you from getting hit by a car, but you just say mortality.

So I'm kind of curious -- you know, it's not irrational if you just want to test mortality -- if you think most of your mortal events will be something that you could affect.

DR. TEMPLE: It's very common to have all-cause mortality be an end point or part of a combination end point. But when we actually -- we try, if it's at least possible, to look at the subgroups and see if all the action is, in fact, in the cardiovascular mortality. And my bias -- although, you know, you can debate this with a lot of people because that wasn't the primary end point, after all -- my bias is you put them in cardiovascular if that's were all the action is because you're sort of misleading people otherwise.

But this is all sort of outside the realm of ordinary biostats. It's, you know, clinicians fooling around with -- but, I mean, if I were doing this, I would have put cardiovascular hospitalization as my first secondary end point, because that's where all the action was.

DR. HARRINGTON: So I think what you're saying, Bob and Norm, is that it's still most appropriate for the sponsor and the investigators to lay

their nickel down on what they believe in terms of their sequential testing plan. You would hope that they would do it with a degree of logic that reflected both the disease and the therapy that they were giving, but it would be reasonable for you -- and, by proxy, us -- to, if they don't do that, for us to peel back the onion a bit and try to find out where the predominant effect is. That's what you're asking.

DR. TEMPLE: It's sort of permission to noodle around for good reason, right.

DR. NEATON: I have to --

DR. TEMPLE: That's probably offensive to Jim.

DR. NEATON: Well, I mean, I have to say I definitely disagree with putting cardiovascular hospitalization as the first one. I mean, I don't think you should look at that without looking at cardiovascular deaths along with it.

DR. TEMPLE: No, no, no. As the first secondary end point.

DR. NEATON: I'm saying, if you kind of incorporated cardiovascular, right --

DR. TEMPLE: But that was the primary end point.

DR. NEATON: No, it was all-cause mortality.

DR. TEMPLE: Oh, okay. Fine. Fine. Fine. Right. That would have made sense, right.

DR. HARRINGTON: Bill, then Sanjay.

DR. CALHOUN: So we're here to try to do the best thing for patients in the U.S., and it strikes me that this is a little bit process-oriented when we worry about looking at these secondary end points and ignoring information that's in those secondary end points simply because -- for whatever reason. There might be valid reasons for having done that. Someone wrote them down in the wrong order.

You know, it's clear, when you look at the primary end point and then you look at some secondary end points -- I agree that the -- for the reasons that Mike has kind of outlined that the cardiovascular death claim is on shaky ground. That does not look to be a robust outcome.

But there probably is important signal in cardiovascular hospitalization. And, again, I understand the biostatistical process. But it seems to me perhaps focusing too much on process as opposed to outcome if we worry about the order that somebody wrote these things down first and trying to get -- instead of trying to get to what's best for the patients.

DR. TEMPLE: Well, that's why we're asking for your input on this. I don't want to devalue the rigor our biostatisticians bring to things. It's worth a lot. And, you know, you can be misled by being careless and by groping the data too much and all that stuff. We're just trying to look at the parameters of all this.

DR. HARRINGTON: Sanjay, do you want to comment?

DR. KAUL: I'm not going to make any comment about the statistical

methodology. What I will say is that I will reiterate what Mike said, is that the quality of the data regarding cardiovascular death are suspect to me. And the original sample size determined analysis on cardiovascular death fails to meet -- fails to exclude a -- a risk ratio of 1.

So, to me, that should be the basis for any decision we make here today.

DR. HARRINGTON: And I think we've heard from a number of people that there's some concerns about the -- as Mike said, the veracity of the -- or the robustness, as Dr. Karkowsky said, of the cardiovascular death end point. I think that largely I'm hearing that we agree with that statement.

Question 7. If you favored a mortality claim -- which we did not -- are placebo-controlled trials still ethical in this setting?

Would you like us to explore that, Norm, or because it seemed as though no one was in favor of a mortality claim --

DR. STOCKBRIDGE: Right. I don't think you have to worry about it.

DR. HARRINGTON: Okay. Great question coming next -- and, Dr. Nelson, we'll look for your pharmacology help here: Have the dose and the regimen been adequately studied and, if not, does further study need to be done prior to approval, or is there a second question which is, or post-approval?

So, Dr. Nelson, do you want to kick us off?

DR. NELSON: Well, I mean, you can tell from my previous response I

don't think it's really been adequately studied or, if it has been studied, it certainly has not been presented and well-documented. And there's many different levels of study I think that need to be done.

I mean, the most obvious is going to be dose-ranging studies -- or at least the relationship between a dose and a blood level -- because it seems kind of incomprehensible at some level that every single human being in the world can get the same dose of a drug.

We all have different, you know, metabolisms and we're different sizes, et cetera, so it seems wrong to think that it can be done.

We know that the bioavailability differs dramatically between people, among whether they're, if I remember correctly, men or women, Japanese or not, and some other things.

So it's just -- I think we need a lot more data because I think at some level you have to say a blood level is going to equal an effect and a blood level is going to equal an adverse effect. We may not be able to put real parentheses around each of those numbers and what they're going to be, but there's going to be some concept that we could put around it. So I really do think we need to have that information.

I also think we need some good drug interaction studies. I mean, I've seen a little bit mentioned in -- you know, some, again, conceptual -- you know, based on 2D6 and 3A4 and other things and how dronedarone will affect other drugs and how it will be affected by other drugs. But this is

critical information, and I don't see how, without really good quality data, the drug could be set out on its own and given to people on a broad scale.

So I would be very concerned, without better data, to market something like this.

DR. PAGANINI: Are there any other questions about --

DR. TEMPLE: I don't understand the dose question. The problem with outcome studies, as a general matter, is it's hard to study more than one dose, and it's almost never done. So think of all of your post-infarction beta blocker studies. Think of any heart failure study you care to think of. They're all single-dose studies. Even though what you just said here is equally true, people get different blood levels.

What are looking for? Effects on outcome? Or how blood level varies from one member of the population to the other, even though you have no idea how that's going to link to the outcome? What exactly do you want them to do? They have some interaction studies; maybe they should present them.

DR. NELSON: They do.

DR. TEMPLE: Yes, they do. They've done 3A4 interaction studies. They know what happens to simvastatin and stuff like that. That's fairly predictable stuff. Maybe they'd need to do more. I'm not -- I'm not fully aware of it all.

But what can they do on dose response to answer the questions we're really interested in? This comes up all the time with outcome studies. What

are you supposed to do? What could they do?

DR. HARRINGTON: Go ahead, Dr. Nelson.

DR. NELSON: If it's a question for me, I don't know that it necessarily has to be done in a large, you know, randomized trial. But I think there has to be some good pharmacokinetic data and some pharmacodynamic data on what we can expect with a given type of human being -- not a 74-year-old white man, you know. And I think that we need to be able to at least semi-quantify what a given drug will give you as a blood level and what that blood level means.

Beta blockers are interesting as an example because, I think from a blood level relationship to effect, it's a fairly -- I guess the word would be broad. I mean, beta blockers tend not to be very toxic, ironically, right. I mean, at least in healthy people they tend not to be very toxic. In people with poor hearts, they could be a little bit more of a problem, but you tend to do fairly well with a wide range of beta blocker doses in terms of getting a clinical adverse effect -- maybe not necessarily a clinical benefit. I mean, you still need a minimum dose -- a minimum blood level to get an effect.

I just think that we have such limited data from these studies on the potential for what's going to happen when the drug is marketed. I mean, it could be left to post-marketing studies, but we know the history of getting post-marketing studies done, and it's been pretty poor.

DR. TEMPLE: Well, a couple of things. They studied, in at least

one modest-size study, a two-fold dose range, 400, 600, 800, and clearly showed that 800 isn't tolerated; everybody got sick to his stomach and so on, so they weren't planning to use that.

I'm sure, given the poor bioavailability, that people get a reasonably large range of doses, and it's perfectly conceivable that if they shaped -- you know, they did a concentration-controlled study and actually measured concentrations, which no one ever does, they could get a better effect because then everybody would be in the same place.

But what I'm asking is, as a practical matter, with outcome studies -- this had 4,000 people; it's not the biggest one ever done -- but what are we supposed to do? I mean, ever drug you can name, whether it's clopidogrel or whatever it is, it's studied at a single dose in the large outcome studies, maybe two doses once in a while -- hardly ever.

So, I mean, I'm asking because --

DR. NELSON: I just think --

DR. TEMPLE: -- because we don't know what to do about that.

DR. NELSON: You're looking at efficacy, and I'm probably focusing more on safety, you know. And this is a drug with really potential safety issues, you know, both QT issues -- we don't know about pulmonary toxicity and other issues, especially based on the analogs of the other drugs we have out there. I mean, there are other people looking to answer this question, so perhaps I shouldn't usurp all the time.

DR. HARRINGTON: Go ahead.

DR. WOLFE: I think what's different about this in at least many, if not all the things you're talking about, Bob, is that this is a drug that killed a lot of people in this first trial, and so there is a huge amount of concern.

The nature of the inclusion and exclusion criteria for both ANDROMEDA and ATHENA have -- and I think different people have said it in different ways -- almost non-overlapping populations. In the real world, there is no question -- there is no question that you're going to have people on the in-between group that are sicker than they were in ATHENA -- and maybe merging into some of the characteristics that caused the deaths in ANDROMEDA.

And on the other side that Dr. Nelson mentioned, you may be having some people who are less sick, don't have the risk factors that were in ATHENA, and yet have a constant level of risks, as in various kinds of possible toxicity, or the actual toxicity, and they may, at their low end of benefit, be having risks that outweigh the benefits.

So I just -- I think there is a huge dilemma here, largely, if not entirely, caused by this ANDROMEDA study, because we know this drug is toxic. We know this drug, in certain kinds of circumstances, has killed people, and we know, from every marketing experience we've ever looked at, that off-label use is guaranteed -- and it's guaranteed all over the lot, the ability to assess initially and in a dynamic way the changing status of failure in a

patient is just not that great that we're not going to expect this.

So I am very concerned about that, both in terms of -- and I think it's not so much the dosing. I think it's the kinds of people that are going to get dosed.

DR. HARRINGTON: So two questions, one of which is -- comments, one of which is we're going to get to exactly your question in question 9, which gets into both the restriction of use plus the feasibility of that, which I think you're both getting at.

And second, Dr. Wolfe, we saw an analysis this morning, based on simulation, that there may be upwards of a 20 percent type I error in the ANDROMEDA findings. So to say that we know it kills people -- a little harsh?

DR. WOLFE: Well, I think that unless one believes that it is by chance -- I think people have, at least around the table -- the company may be stronger, for obvious and understandable reasons, in thinking that it's a chance finding -- I think that is enough of a likelihood that it is probable -- probably the case -- and there are plausible biological explanations for it -- that the people with the more severe unstable recently changed heart status actually had an increased rate of death with it.

And the concern is that you're not going to draw these tight circles around the ATHENA group and the ANDROMEDA group in the real world, and that's a serious reason for me to wonder whether this drug should be approved.

DR. HARRINGTON: Okay. Let me go here, and then to you, Jim.

DR. PAGANINI: I agree with more pharmacodynamic studies than anything else, especially in the changing population. We have already a signal in the population with congestive heart failure at a specific dose. And we know that congestive failure can alter liver function. And so there has to be a pharmacodynamic issue here. At one specific dose -- perhaps the blood levels of that particular dose, no matter how aberrant it was -- are much higher, which creates some problems.

And also in the patients that are primarily focused, as the ideal patient for this -- we've heard all this morning and this afternoon that they vary through. So you have that transition group that may go in and out. And I think there's where you need to look at pharmacodynamics. What happens as somebody goes from one thing to another as the primary organ of removal varies, and what happens to the levels and their effect?

So I think the pharmacodynamics are extremely important.

DR. HARRINGTON: So let me answer the second half of Norm's question, which is, does it need to be done prior to approval? Let's make the assumption that approval is the way people vote. Does this have to be done prior to that?

DR. PAGANINI: Well, you know, that's a good question. I think it depends -- you guys can tell me better than I can. The population that it seems to be settling in on -- how frequently does that population move into that sort of vague shadow of transition? And if so, and if they're going to

be given the same drug dose, without knowing what the levels are, then perhaps that's the population that you might want to look at before you release the drug.

DR. HARRINGTON: Bob?

DR. TEMPLE: So you're describing pharmacokinetic data. What pharmacodynamic data did you want?

DR. PAGANINI: Well --

DR. TEMPLE: What measure -- what? What measures, I mean? What are we talking about? QT?

DR. PAGANINI: Just the idea that a drug which has a predominant removal rate by way of liver -- looking at liver function and the effect of the liver on its removal as the liver is more or less congested.

I'll give you an example. Someone with acute kidney injury that has renal and liver dysfunction -- liver perhaps mildly dysfunctional, but not really that bad, but acute kidney injury -- is given a drug. As soon as -- something like vancomycin. As soon as you do that, you dialyze that person. During that dialysis period, you affect the renal aspects, et cetera, et cetera, but you also affect the function of the liver such that vancomycin has a totally different kinetics and dynamics after dialysis than it did before, with no real big change, so --

DR. TEMPLE: So you'd be interested in pharmacokinetics and clearance in people with varying degrees of heart failure; it could be even a

single-dose study.

DR. PAGANINI: Correct. Correct. And -- yes. Correct.

DR. TEMPLE: Okay. They may have data on various degrees of renal failure. I think they do.

DR. PAGANINI: It's not just renal failure, though, Bob --

DR. TEMPLE: And hepatic dysfunction, too.

DR. PAGANINI: Right. With congestive failure and various -- because that's the area that we've had the strong mortality signal at a specific dose --

DR. TEMPLE: Right. Remember, this is a -- I don't know -- mostly cleared by 3A4, right, which is predominantly intestinal, not really liver, although there's some liver. I don't know, but --

DR. PAGANINI: It's very quick.

DR. TEMPLE: But we're talking about kinetic studies here.

DR. HARRINGTON: We're talking about kinetics, not dynamics.

DR. TEMPLE: I don't think. Yeah. That's why --

DR. NELSON: But kinetics and dynamics go together. Right? I mean, it's hard to --

DR. TEMPLE: No. I don't know what to -- what would they measure, pharmacodynamically? QT prolongation? What?

DR. NELSON: Yeah. I mean -- yeah, that's one of -- you know, and some of these things are going to be much harder to measure in terms of -- and

I'll just use, you know, pulmonary, you know, problems as a measure. It's -- I would imagine -- and this is unknown to me. But I imagine that if you have a blood level of X, your likelihood of getting pulmonary damage is whatever it is. If your blood level is 2X, it's more likely than not that your likelihood of getting pulmonary damage is greater, right, assuming that -- because it's typically a dose response relationship to anything, to all of these issues.

And I use the word "dose" again to mean serum concentration, not necessarily the amount that you take by mouth.

DR. TEMPLE: So what I hear is that you want to know all the things that can give you greater blood levels than are typical, which --

DR. NELSON: Oh, yeah.

DR. TEMPLE: -- could be renal failure; it could be cardiac failure; it could be --

DR. NELSON: But there's a lot of other -- as they would define, I guess, as intrinsic reasons. You know, if you looked at the -- the briefing documents, we know that eating food can double or triple your level, eating it with food, you know. And we know people don't do very well with taking their medications, you know, at the right times and with the right types of foods. Fatty food may be worse than non-fatty food. You know, drug interactions are clearly important. And there's a lot of over-the-counter drugs that would have drug interactions, not even things that a physician would give you.

So I just get very nervous -- when you think -- see things that have

real serious adverse effects --

DR. TEMPLE: They should probably summarize, which they have not done, their drug interaction studies. I was just looking at the labeling earlier. There have been a lot of them. It's metabolized in a fairly well-understood way, 3A4 and 2D6 -- those are not mysterious things.

It also affects other drugs by turning on 3A4. So those things plainly have to be done, but --

DR. HARRINGTON: So let me --

DR. TEMPLE: There's a lot of --

DR. HARRINGTON: Let me try to move us along. If there's a single piece of data you want to show us --

DR. GURAL: Single piece --

DR. HARRINGTON: Okay.

DR. GURAL: Single piece of data to share with you what we already gave -- presented --

DR. HARRINGTON: Earlier today, right.

DR. GURAL: -- was on congestive heart failure, I through III, the level was about 122, and the congestive heart failure patient was around 80.

So, if anything, at the higher levels, it was lower. Class IV. Class IV. Only had four people in class IV, right.

DR. HARRINGTON: Right. Okay. Henry?

DR. BLACK: I just -- I think this is a little late in the game to

ask for some of these things. We had 1500 pages worth of things to read where a lot of this was done. And we have a 4,000-patient outcome study, and many others, where we didn't see the pulmonary toxicity. Sure, we may see it in five years, but we haven't see it yet.

And I think there's benefits that this drugs, at least seems to me to have, where I think we can potentially meet an unmet need. And I would hate to see it held up while we're looking for things that are clearly going to be needles in haystacks and we'll probably find out later.

We can't ever, as Dr. Wolfe has said and others have said, really put that tight circle around people who ought to get it and different one for -- that's going to have to happen later on, and we've got to watch very carefully.

DR. HARRINGTON: Okay. And we're going to give you a chance to cast a vote in a little bit there.

Mr. Dubbs?

MR. DUBBS: I'd just like to reiterate what I asked earlier, or commented on earlier, which is I don't find the indication statement appropriate, and I'm becoming more convinced that it's not appropriate in light of the discussions about the distinct populations and the fact that there's deleterious effects on some of those populations and positive effects on others.

DR. HARRINGTON: So hold that thought. If you read ahead to

question 11, depending upon how you vote, you will have a chance to comment on whether or not you would narrow or broaden some of those statements.

So let's move on to question 9, which is going to have two parts to it, and then it sort of bleeds in a bit to question 10, before we vote. And question 9 is who should not receive dronedarone? And for each -- so when you comment, if you say a group should not receive it, talk about how important it is to restrict that.

And then something I think Dr. Wolfe was bringing up, how feasible it is to restrict that. Mike?

DR. LINCOFF: This is the time that I'd like to challenge the assertion that was made that this is strictly an issue of acuity. I recognize the data and the overlap, but the probably is if you look at the Kaplan Meier curves or the time to event curves in ANDROMEDA mortality, many of these deaths occur after 30 days.

So if you simply say that after a patient gets past their acute phase, we'll wait 30 days and then start it, then, you know, it's hard to -- granted, this is not the same as -- you know, it's not exactly the same as having started. They got 30 days of therapy. But it's hard to believe that 30 days of therapy is responsible for their death over the next six months.

So you could interpret the data from the Kaplan Meier curves as saying that population of patients, even after 30 days, continue to die on the therapy. So I wonder if it's strictly the acuity. And I recognize the

difficulties in grading heart failure and grading ejection fraction, et cetera, but I think that we ought to take the data and look at it in terms less of acuity and more of severity of disease, and so a level of ejection fraction and perhaps an assessment of heart failure class.

DR. HARRINGTON: So you're following Mori's train of logic, if I remember, from earlier. Are you not comforted, Mike, in ATHENA that there were a group of patients with heart failure who received the drug and, in fact, seemed to derive benefit?

DR. LINCOFF: I am. And -- but, again, you know, we're talking subsets. I think you need to -- we cannot -- we're never going to be able to set aside ANDROMEDA. It may be spurious, but at least on the data we have now to start this drug out into clinical practice, I think we have to operate on the assumption that ANDROMEDA is real -- and I just don't think that the time to event data is consistent with strictly an acuity issue.

DR. HARRINGTON: So who do you want to restrict its use in? Question 1, who should not receive it? Is it class III heart failure? Is it EF less than 35? Who is it?

DR. LINCOFF: I think that's probably where I would -- yes, at this point. And then, if subsequent studies show safety in a more refined way in that group of patients, you could extend it. But I think, to start off, you would say, pick an ejection fraction -- probably around 35 percent -- and a class.

DR. HARRINGTON: So let's go over here to Dr. Krantz. Then I'll go down to you, Bob.

DR. KRANTZ: I don't want to overstate it, but I agree with Michael. I think you had over three-fold the number of patients in ANDROMEDA with LV systolic dysfunction, so I think to sort of not call that out as a potential source of risk is a little bit risky, I guess.

I think that -- you know, it's not like we haven't had other drugs, like TZDs or metformin where we can then make that distinction and, you know, when using the drug, not use them in heart failure. So I don't think it's the -- to answer the second part about feasibility, it's challenging with the overlapping Venn diagrams of afib and heart failure, but I think it's still conceivable that it can be done thoughtfully.

DR. HARRINGTON: So there's at least two considerations for avoiding it in people with advanced -- we'll call it advanced heart failure symptoms, class III, or low ejection fraction.

Bob, did you want to comment on that?

DR. TEMPLE: Well, I just wondered if the ability to decompensate to the point that you need to be hospitalized is one way to define who might be at risk --which doesn't mean you're going to die tomorrow, but it means that, over a period of time, you might be at high risk -- as some sort of integrated measure of how sick you are. I mean, I wondered what you thought about that.

DR. LINCOFF: So that might mean that a patient who has been

hospitalized recently, a year, whatever, but within the relevant past, with decompensated heart failure, then becomes not a candidate for a non-defined period of time.

DR. TEMPLE: It's also possible that we could list several things that make you not a candidate, one of which is recent decompensation, another of which is very low EF, you know.

DR. LINCOFF: I'm just uncomfortable with the beta blocker analogy where -- we often start beta blockers, you know, in the seventh day of hospitalization after -- and they do fine. I mean, you know, there it's a very short period. Get them out of the decompensation, and then you can usually start it, if you do it carefully.

I'm a little afraid, from the data that we have, that it's not the same with this.

DR. HARRINGTON: So let me maybe rephrase it. So the case has been made that perhaps clinical instability, as a recent thing, as a marker for patients not to treat -- you're saying, Mike, extend that to patients with some degree of heart failure; you might avoid until you have more data because you're not willing to just say, you know what, ANDROMEDA is not just a fluke.

DR. LINCOFF: That's right. And it's just -- not just time. And I don't know that today we have to say exactly what those limits are, but I would say that limits should reflect severity rather than strictly acuity.

DR. HARRINGTON: So, Dr. Calhoun --

DR. CALHOUN: So I guess I was somewhat reassured by the data that were presented that individuals who had new onset of heart failure during treatment still did better while on active therapy versus placebo.

DR. HARRINGTON: In fact, the point estimate was greater than the other group's.

DR. CALHOUN: Was better than -- yeah, it was better than the other. So it seems to me that, although that's post-hoc and there are lots of potential problems with that data, it's reassuring enough to me that I probably wouldn't restrict it quite so severely.

I think the acuity issue is a big one, and I would be amenable to a restriction on acuity, and I think that's both important and feasible.

DR. HARRINGTON: So let's go to Dr. Wolfe and -- Jim, are you waving your hand over there? So let's go to Dr. Wolfe first; then we'll come over.

DR. WOLFE: Just to comment on Bob's suggestion about using hospitalization as a criterion, the variability around this country, or anywhere else for that matter, on what threshold Dr. A versus Dr. B uses for hospitalizing a patient with failure is such that I just think that that would be reliable at all.

DR. HARRINGTON: Let me push you a step further.

DR. WOLFE: If someone has been hospitalized --

DR. HARRINGTON: So you would prefer a more objective measure that both Mori and Mike have pointed out --

DR. WOLFE: Yeah.

DR. HARRINGTON: -- active heart failure, low EF, et cetera.

DR. WOLFE: If I were to think the drug should be approved.

DR. HARRINGTON: Understood. Understood.

Jim.

DR. NEATON: I guess I'd like to ask a question to my clinical colleagues on the committee. So we've gone through this logical progression of questions that Norm put together, and so one study we haven't talked about is DIONYSOS.

And so if you believe kind of -- and I think we kind of addressed these questions -- that's there not an excess risk of mortality, but there's no mortality benefit, and we're -- kind of to say it kind of in the best possible way -- have substantial uncertainty about a cardiovascular morbidity/mortality benefit, and you get substantially greater reductions in AF with amiodarone -- I mean, it's of the same order of magnitude that you get with placebo versus dronedarone -- why would you use this drug before amiodarone?

DR. HARRINGTON: Go ahead, Sanjay.

DR. KAUL: Well, I was just going to make a statement here, if that's all right with you, Bob. I think that -- if I understood from the briefing document, the whole premise behind ATHENA was to overcome the adverse mortality observed with the drug in the ANDROMEDA trial. And when one

combines all the placebo comparator studies, as was suggested by Dr. Neaton, conducted with this drug, so far I'm not sure -- this is my personal view -- a clinically unacceptable increase in mortality has been excluded. And by that I mean a hazard ratio upper boundary of about 1.10 to 1.15.

The only reason the result of the ATHENA trial provides some reassurance about long-term use is a much lower risk population was studied.

And the efficacy appears to be very modest with respect to normal sinus rhythm maintenance and rate control. And coupled with the fact that the patient population enrolled does not reflect the spectrum of AF patients typically observed in clinical practice -- at least in my practice -- and the lingering controversy about the primacy of rhythm versus rate control strategy -- I'm struggling to find a proper role for this drug in clinical practice.

And, finally, the drug was ostensibly designed to offset the adverse an extra-cardiac toxic effects associated with amiodarone. And even for this objective I'm not sure if superior tolerability has been demonstrated with some degree of confidence. I mean, we saw that there is 50 percent loss of efficacy compared to amiodarone, and it was only 22 percent better tolerability, which was statistically non-significant.

On the other hand, ATHENA is the largest outcome trial in patients with a history of current AF/flutter with demonstrable effects in reducing cardiovascular hospitalization, admittedly not the most robust of end points.

However, this end point is somewhat clinically relevant, especially

if it leads to reduction in ICU admissions. And I don't know whether we -- I may have missed the data, but I didn't see the data in the slides, but it's available somewhere.

There's a possibility of a quality of life advantage, which we obviously did not get to see. And the reduced hospitalization rate may also have the potential for significant cost saving.

But I agree with Dr. Neaton is that for patients at risk, including class III heart failure -- by the way, I don't think this drug should be given to patients with class III or LV ejection fraction less than 35 percent. But for patients at risk, amiodarone should be the -- the treatment of choice. And dronedarone can be considered in these patients if they become intolerable to amiodarone.

But I would like to see a larger comparative study, if feasible, with longer follow-up to demonstrate superior tolerability without unacceptable loss of efficacy. And I haven't seen the data.

DR. HARRINGTON: Okay. So we're going to -- as I told Dr. Black, we're going to come back to exactly what you're saying when we actually vote. What I'd like to do, is on question 10, which is, how concerned are you about adverse effects of dronedarone on a variety of things -- renal function, bradycardia, QT, heart failure -- we've talked about most of these today. Emil has talked extensively about renal function. Dr. Nelson has talked, I think extensively about QT prolongation. We've talked about heart failure.

Does anybody want to bring anything else up in this section that we haven't discussed? Darren?

DR. McGUIRE: Just a couple of very quick points. I don't think we've heard anything about defibrillation thresholds for patients with ICDs. Amiodarone is a common offender for DFT abnormalities, so we'd need to know that as this population -- it may be less of an issue --

DR. HARRINGTON: Do you have that piece of data?

DR. GURAL: Yes.

DR. HARRINGTON: So while you're -- I'll let Darren talk while you're lining that up.

DR. McGUIRE: A couple of other -- I would like the issue with Coumadin interactions better addressed subsequently. I don't think it has to be done before approval, but I think there's a signal from DIONYSOS that can't be ignored. Despite the fact that bleeding hasn't been a signal, the INR measures have been.

Liver -- throughout the registration program, LFTs greater than two times the upper limit of normal have been excluded. And I think, unless there's compelling data otherwise, we should probably hold the product label to that, if approved.

And I'm most concerned about the duration and cumulative toxicity, as Sanjay and others have mentioned. The fundamental premise for this drug development was to overcome the toxicities of amiodarone, and to this point,

that hasn't been tested. The cumulative toxicities are both dose and time-dependent. And having median duration follow-up of one year doesn't completely convince me. Although I don't see any signals I'm concerned about, I think that surveillance has to systematically go on.

DR. HARRINGTON: Bob, do you want to weigh in?

DR. TEMPLE: Well, can I just be sure people -- I mean amiodarone pulmonary toxicity certainly can occur in less than two years, and none was seen here. You've got to evaluate whether it was looked for or not.

I'm a little puzzled by the enthusiasm for amiodarone. All the trials that have led to the conclusion that rate control is better than rhythm control are because amiodarone was the rhythm control drug and lethality was greater in those trials. That doesn't seem -- I mean, those aren't data we've reviewed, but just what you read doesn't make it sound like much of a bargain.

I must say, I was struck by the very modest effect in delaying recurrence of atrial fibrillation in the two early studies and was somewhat surprised by the reduction in hospitalizations, but that is sort of what they found.

And all I can say is we've -- we and others in a lot of places have found decreased hospitalization to be something of value. So if people really don't think it's of value, I guess I'd like to hear a little more. Most of the heart failure trials and most of the -- you know, have shown decrease hospitalization -- death plus hospitalization, but always driven by

hospitalization.

DR. HARRINGTON: Henry?

DR. BLACK: When it comes to using amiodarone, I'm not different than Bob here. The cardiologists I know were afraid of it -- and that was a while ago, since I worked intimately with them. I certainly wouldn't start it or change it on a patient. And I just wonder, with my cardiology colleagues who are much more experienced with this, am I biased against amiodarone or is my concern about the toxicity reasonable or not?

DR. HARRINGTON: Let's show the piece of data about -- is it defibrillation thresholds? And while you're -- and then we'll answer this question about how people feel about amiodarone.

DR. RADZIK: We conducted a study in patients with an ICD -- slide on, please.

This study looked specifically at the defibrillation safety margin defined as the maximum energy of the device minus 10 joules. We looked at very high doses. You see there 1200 milligrams, 600 milligrams and 2 grams per day -- so much higher than the recommended dose.

The proportion of patients with a safety margin of less than 10 joules is shown here. You see that at 1200 milligrams there were no patients with a safety margin below 10 joules.

DR. McGUIRE: But that doesn't really answer -- do you have shift data? You know, if you pick a particularly healthy cohort with a particularly

low baseline DFT, then you may or may or not see greater than 10 joule excursions.

What I'd be more interested in is the more common heart failure patient with a defibrillation threshold of 23 joules.

DR. RADZIK: What we did do is study defibrillation threshold in animal model where you can give a lot of shocks.

DR. GURAL: Would you be interested in seeing that?

DR. HARRINGTON: Do you want to see more, Darren?

DR. McGUIRE: A summary of the findings would be fine if you --

DR. GURAL: We have that.

DR. McGUIRE: -- have detected no --

DR. GURAL: We have the animal data to --

DR. HARRINGTON: Let's hold off on that, because I don't think that this is going to be a make-or-break question here to get that piece of data.

Sanjay, could you keep it brief?

DR. KAUL: I'd just like to respond to Dr. Temple's comment. If you were unimpressed by the efficacy of amiodarone in preventing recurrence of atrial fibrillation, I'm interested to hear your thoughts about a drug that has 50 percent efficacy of amiodarone.

DR. TEMPLE: No, I'm not unimpressed. Amiodarone is fantastic at preventing atrial fibrillation. It's just not very good at preventing death.

DR. KAUL: So the follow-up is --

DR. TEMPLE: Because it does things that kill you.

DR. KAUL: Okay. So the follow-up is, in this particular population, does the efficacy of a drug trump safety or does the safety of the drug trump efficacy?

DR. TEMPLE: I mean, they did a study with 4,000 people, and it evaluated both efficacy and safety. What are you interested in?

DR. KAUL: The comparative trial in the DIONYSOS.

DR. TEMPLE: Oh, no. Amiodarone -- I mean, we all know amiodarone is better at preventing recurrence.

DR. KAUL: But superior tolerability was not demonstrated -- now, it's conceivable, with a larger patient size and a longer follow-up, that that would be evident. But that's the kind of study they didn't need to do.

DR. TEMPLE: And I don't know who would enter that study. I wouldn't. And I have atrial fibrillation sometimes. You wouldn't get me on long-term amiodarone.

DR. BLACK: If I can understand what practice would be, to practicing cardiologists -- and you're much closer to them -- what this drug would replace, if approved, would be amiodarone. And you would accept it wasn't quite as good, but you wouldn't have pulmonary toxicity, I don't think, to worry about. We haven't seen it. You wouldn't have the thyroid problems for sure. And I think it would be better tolerated.

I agree it would be an impossible job to recruit somebody to a study

where you told them all the things that were going to happen with amiodarone.

So it seems to me that this drug, I think, has been shown with ATHENA it's probably not killing people. And I would think the tolerability would be better. Whether or not we can undertake a long-term tolerability study to look at some of those things, I don't think that's feasible.

I think the people who were in ANDROMEDA should not be getting this drug. We can describe them -- and with some other things. But I think as far as that goes, I think, at least in my point, to talk about common sense -- which I was happy to see statisticians talk about today -- that this is a drug which overall is going to be helpful.

DR. HARRINGTON: Okay. People are starting to weigh in on how they want to vote. Darren, Mori, Mike. Very quickly.

DR. McGUIRE: I'm wondering if someone could -- to your question, Henry, about cardiologists using amiodarone, we all learned about its toxicities at a time we were using 800 or 400 milligrams a day, and it's clearly dose and time-dependent toxicity. At 200 milligrams a day, I'm very comfortable, as a cardiologist, using it. As a patient, I'm not completely convinced I'd be comfortable taking it, but I think I would be because I think the toxicities have been minimized with the lower dosing.

I would like to see the best estimate at 200 milligrams a day of the pulmonary and hepatic toxicities of amiodarone, if the sponsor or the FDA would have those data, so we can put this safety concern in clinical context.

DR. HARRINGTON: Mike and Mori.

DR. LINCOFF: I mean, I think this drug would certainly be used. First of all, I agree that the amiodarone toxicity is relatively low, and we certainly use it -- and although the big trials comparing rate control to rhythm control have suggested no benefit of rate control -- rhythm control, there may be issues regarding less anticoagulation in those patients, leading to more of the mortal or morbid events.

And so we individualize based on patients who have symptomatic frequent atrial fibrillation, and I think we often use amiodarone with comfort.

But if there were a potentially less toxic alternative, I think that this would certainly be used, and if it turned out not to be effective in a specific patient or if that patient was high risk, by on, say ANDROMEDA -- these characteristics here, then we would, you know, preferentially use amiodarone.

So I think that there's certainly a big role -- and also my understanding is that the regulatory obligation here is to show it's better than placebo, not necessarily better than amiodarone, since amiodarone isn't the standard of care.

DR. HARRINGTON: Go ahead, Bob.

DR. TEMPLE: Well, just to comment, if we thought for some really important end point something was clearly inferior to other therapy, we might

have reservations about approving it. We don't have that kind of data. What we have is that it's superior to nothing.

And you could decide whether hospitalization for atrial fibrillation is the sort of end point where we would worry about whether it was as good. If it were mortality, we definitely worry about that sometimes. But we're not in the presence of a lot of controlled data on amiodarone.

DR. LINCOFF: And you don't have an approved standard of care for whatever end point --

DR. TEMPLE: Right.

DR. HARRINGTON: Mori?

DR. KRANTZ: I'll just quickly go with question 10. I think for QT prolongation I don't think it's a real big concern. Certainly it's less potent on the QT interval than amiodarone. I think digoxin and Coumadin are concerns.

But I think at the end of the day the question that Bob was raising was -- really, is this the same as amiodarone in terms of safety for structural heart disease? Because we're taught, as you mentioned, that, you know, this -- amiodarone is the only safe drug for patients with structural heart disease. And by comparison, can we say the same thing about this drug? And I don't think we can say that yet.

And I look back at the AFFIRM trial, and I remember the subgroup analysis in people with cardiomyopathy, and it wasn't statistically

significant, but actually amio was the predominant drug, and it actually trended in the right direction for rhythm control. So I agree amio is not safe, but at the same time it's kind of the best we have and it's the current teaching -- the standard of care.

So I think we have to be really cautious in that context.

DR. HARRINGTON: But Sanjay's comment is not inappropriate, which is that there needs to be more work done here to figure out when you would -- this should not be -- however one would vote, this would not be a wholesale abandonment of a pretty good drug that has been worked out over a fair bit of time with a dosing regimen that's not pretty well tolerated in favor of something for which we have a lot of uncertainty about things like effect on heart failure; is that a fair statement?

DR. KRANTZ: That's exactly right, but I think what happens in practice and what we say here are different things, as I think was pointed out by the panel earlier. I just would hate to see that sort of broad brush stroke result happen.

DR. HARRINGTON: Well, I think that that's an important message to deliver to FDA because, as they craft the label, an enthusiastic, you know, we can't wait to see this out on the market; get it out tomorrow -- versus, hey, they've met the obligation, but there's still a lot of holes here -- those are sort of two different messages that they take away from a meeting like this.

Jonathan?

DR. FOX: Just a very short reminder that what we're all describing as current standard of care is, in fact, an off-label use.

DR. HARRINGTON: But in the guidelines.

DR. FOX: Exactly.

DR. BLACK: Could I ask one other thing? Again, from -- this is for my own information: You could put this drug as something that you gave people who couldn't tolerate amiodarone, or you could put amiodarone as a drug for people who didn't respond to this. Which do you think would be the better way to go?

DR. HARRINGTON: The challenge you'd have is that that's not the question that was studied, which would be the first --

DR. BLACK: Oh, I understand.

DR. HARRINGTON: Right.

DR. BLACK: I'm just trying to collect some opinions from people I respect.

DR. HARRINGTON: I mean, you could -- I think that would be difficult to implement.

Go ahead. Last comment before we vote, Jim.

DR. NEATON: I just was going to say that I think the answer to my question is more study is needed.

DR. GURAL: Do you want me to comment --

DR. HARRINGTON: No. I think we've -- I appreciate you looking, but

I think that we've gone round and round on issues, and -- I appreciate it, but I think that it's probably come time to get to question 11, which is the vote.

And there is a new method of voting that I'm going to read about. And this says, we will be using the new electronic voting system. Each of you have three voting buttons on your microphone: Yes, no and abstain. Once we begin the vote, please press the button that corresponds to your vote. After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen, and I will read the vote from the screen into the record.

Next, we will go around the room and each individual who voted will state their name and vote into the record, as well as the reason why they voted as they did.

So that helps us get to the second part of the question, which is asking about whether, if you voted for approval, should the claim be broader or narrower -- this is what I was pointing out to you earlier, Mr. Dubbs. So this is your chance to both vote on approval as well as vote on should the claim be broader or narrower than it currently exists. So --

DR. KAUL: Sequentially?

DR. HARRINGTON: We're going to just vote on approval, and then you'll comment on the other.

DR. SWENSON: So are we voting on the approval for the indication of atrial fibrillation prevention and this --

DR. HARRINGTON: I'm going to read you the question that you're going to vote on.

DR. SWENSON: Okay.

DR. HARRINGTON: And it may not -- remember, the question does not necessarily read exactly as the proposed indication does. So vote on the question that I ask, correct, Norm?

DR. STOCKBRIDGE: Yes.

DR. HARRINGTON: So the question that we've been asked to vote on is, should dronedarone be approved to treat patients with non-permanent atrial fibrillation?

So vote yes, no or abstain. And you can go ahead and vote.

Do you have us logging -- they'll tell us over here.

MS. FERGUSON: They'll let me know if you guys have registered your vote.

DR. HARRINGTON: You've got everybody's vote? Everybody has voted?

MS. FERGUSON: Everybody has voted.

DR. HARRINGTON: Okay. If you could display it on the screen.

So I'm asked to read the vote into the record. The vote is 10 yes, 3 no, and zero abstains.

And now the procedure is to go around the table, state your name and how you voted. And I would ask you to just briefly summarize why you voted as you did. If your reasons are similar to someone else who has already spoken,

you can certainly defer to that -- or refer to that.

DR. KRANTZ: Mori Krantz, cardiology in Denver, Colorado. I voted to approve this drug. I think it adds a nice advantage for our patients, particular with atrial fibrillation and flutter. I do think I have some significant concern in the setting of severe LV dysfunction and heart failure and suggest a boxed warning label in that regard.

I don't think that the indication should be very broad, although I understand the desire to include mortality reduction, since it was part of the primary end point, but I think we should be fairly circumspect.

DR. HARRINGTON: Darren?

DR. McGUIRE: Darren McGuire. I voted to approve the drug. I think the outcomes data, as circumspect as some of the features of them are, is a great step forward in atrial fibrillation management where we have real meaningful clinical outcomes evidence for patients with this disease.

I would not be in support of supporting the claim for mortality. I believe it would be for prevention of heart failure -- I mean cardiovascular hospitalization driven primarily by atrial fibrillation.

I think I would be in favor of expanding the claim towards also reduction of recurrent atrial fibrillation and reduction in heart rate response to atrial fibrillation as evidenced by the prior NDA.

I think there should be product labeling, at least cautionary, with regards to particular drug interactions with amplification of the present

proposal for digoxin and possibly Coumadin.

And I would not -- I would consider even a black box warning to restrict its use from class III to IV heart failure with a recommendation that additional studies in that patient population be considered by the sponsor.

DR. HARRINGTON: Dr. Wolfe?

DR. WOLFE: Sid Wolfe. I voted against the approval. Part of it is a statement in the FDA briefing package which says, quote, we feel that the safety of dronedarone presents a problem that the label alone may not be able to cover. I agree with that, and I add the things I said earlier, that it doesn't work as well as amiodarone, A; B, we have no idea, because of the lack of data, on what these people were hospitalized for, and C, I don't think it is possible to get this nice, clean clinical trial, but not real world separation from the ANDROMEDA patients and the ATHENA patients.

DR. HARRINGTON: Dr. Swenson?

DR. SWENSON: I voted yes, and for some of the reasons that have already been stated. I can't add anything more.

DR. HARRINGTON: Dr. Lincoff?

DR. LINCOFF: I voted yes, and for many of the reasons that Dr. McGuire expressed. I think this is an incremental agent that has attractive -- potentially attractive side effects profile. So although it may not be as effective as amiodarone, it's still a useful addition to the armament.

And I also agree that the -- the claim should be for cardiovascular

hospitalization, not for mortality.

DR. HARRINGTON: Robert Harrington. I voted yes. I would like to make sure that the claim is narrow in its scope, that we are very careful about the inclusion of heart failure patients -- or the exclusion of heart failure patients in the labeling.

I also would support not including the mortality claim at all in the label, though obviously at some point we need to refer to the clinical study results.

I would not include claim for cardiovascular death. I think that a number of things need to be done post-marketing, including expanding the ethnic minority treatment with the drug. I think that we need to explore further comparisons against amiodarone. I think we need more long-term data.

I think that that's a number of things that are needed in the post-marketing phase, so I would support a cautious yes.

DR. PAGANINI: Emil Paganini. I actually voted yes as well. I think it's a little bit less effective than amiodarone in certain areas, but it is an alternative medication which should become available.

I think it should be restricted and strictly restricted to those less sick population, and in the sicker population -- that is congestive heart failure, ejection fraction less than 35 percent -- that those folks should have further characterization and perhaps some further kinetics in that population.

DR. BLACK: Hi. This is Henry Black. I also voted yes. I agree with the restrictions. I think they should be tight. I think we do need some more information about the tolerability compared to amiodarone, and I'm -- much of what I had to say has been said.

MR. DUBBS: I voted no for many of the reasons that Dr. Wolfe stated. But, in addition, I'm not sure, based on what we've seen today, that the verbiage that can be added to the indication statements would overcome the deleterious effects and differentiation among the patients that would take the drug.

DR. HARRINGTON: Dr. Calhoun?

DR. CALHOUN: This is Bill Calhoun. Dr. Harringon has articulated my reasons for voting yes very well. The only things that I would add is that the differential safety profile looks just marginally cleaner for dronedarone as opposed to amiodarone, and so that provides me a little impetus.

The patients who are like the ANDROMEDA patients should clearly be excluded, and the label needs to be, I think, fairly explicit about that. And the notion of a black box warning is not inappropriate, I think.

DR. HARRINGTON: Dr. Kaul?

DR. KAUL: I voted a very cautious yes. The claim should be for reducing cardiovascular hospitalization in low to intermediate risk patients with current or previous history of non-permanent afib/flutter, and who do not have contraindications, including, in addition to the ones listed, class III

congestive heart failure or LV dysfunction, as assessed by ejection fraction of less than 35 percent.

Specifically, the claim for a tolerability advantage over amiodarone should not be allowed. And the sponsor should be urged and encouraged to do a long-term larger comparative study to look at the benefit-risk profile between dronedarone and amiodarone.

And amiodarone should remain the treatment of choice for patients with structural heart disease, including those with left ventricular hypertrophy, as per the guideline recommendations.

DR. HARRINGTON: Dr. Neaton?

DR. NEATON: I guess you could classify mine as a cautious yes too. I think the claim -- I would make it even narrower: Hospitalization for atrial fibrillation or flutter.

And I think the data are pretty convincing about the safety risks with regard to all-cause mortality with the ATHENA trial, and in the collective evidence of all the studies. They are ambiguous in my mind still for the non-AF cardiovascular hospitalizations, and more work on that is needed, as well as head-to-head comparisons with amiodarone.

DR. HARRINGTON: I've been told that I need to read Dr. Nelson's vote into the record, and he voted no, and he had indicated it was for many of the safety issues that he had brought up earlier in the conversation.

Dr. Wolfe?

DR. WOLFE: Just one quick comment, which is, for those that voted yes, and if that's what the FDA decides, I think, as just mentioned before, that as one possible way of trying to separate out these two populations, there definitely should be a black box warning. That is clearly within the FDA's authority, and that certainly raises this to a much higher level of concern.

I mean, the company has already said they would do a medication guide, which would be an FDA-approved medication guide. But I think that this drug, because of ANDROMEDA, clearly needs a black box warning.

DR. HARRINGTON: Bob?

DR. TEMPLE: I merely want to say that it's not a black box warning. It's a box warning.

(Laughter.)

DR. WOLFE: Sorry.

DR. TEMPLE: Black box implies to the world that you mustn't ever use this. We're trying to remind people that a box warning is to tell you things you're supposed to know.

DR. WOLFE: You should put a different colored border on it, then.

DR. TEMPLE: I know. I know. It's a box warning, and I can tell you we're very sympathetic to what people are saying about that. I mean, you had a trial in which there was a terrible outcome. You should tell people about it.

DR. HARRINGTON: So, Norm, I hope that you've gotten the kind of information that will be useful to you today. I will thank the panel. I apologize for running over in terms of people's time.

Any final remarks, Norm?

DR. STOCKBRIDGE: No. That was very helpful, and I appreciate everybody's input.

DR. HARRINGTON: Great. Thank you very much, and the meeting is adjourned.

(Whereupon, the proceedings at 5:32 p.m. were concluded.)