FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE (CRDAC)

Tuesday, December 10, 2019

8:00 a.m. to 2:53 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Yinghua Wang, PharmD, MPH, RAC
Division of Advisory Committee and
Consultant Management
Office of Executive Programs, CDER, FDA

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

John H. Alexander, MD, MHSc
Professor of Medicine
Department of Medicine, Division of Cardiology
Duke University School of Medicine
Durham, North Carolina

Jacqueline D. Alikhaani, BA
(Consumer Representative)
Volunteer and Advocate
American Heart Association
Los Angeles, California

Barry R. Davis, MD, PhD
Guy S. Parcel Chair in Public Health
Professor, Department of Biostatistics and
Data Science
Director, Coordinating Center for Clinical Trials
The University of Texas School of Public Health
Houston, Texas

C. Michael Gibson, MD, MS
Professor of Medicine
Harvard Medical School
President
Combined non-profit Baim and PERFUSE
Research Institutes
Boston, Massachusetts

Julia B. Lewis, MD
(Chairperson)
Professor of Medicine
Division of Nephrology
Vanderbilt Medical Center
Nashville, Tennessee

John M. Mandrola, MD, FACC

Electrophysiologist

Baptist Medical Associates

Louisville, Kentucky

David J. Moliterno, MD

Professor and Chairman

Department of Internal Medicine

University of Kentucky Medical Center

Lexington, Kentucky

Milton Packer, MD

Distinguished Scholar in Cardiovascular Medicine

Baylor Heart and Vascular Institute

Baylor University Medical Center

Dallas, Texas

Paul M. Ridker, MD MPH, FACC, FAHA
Eugene Braunwald Professor of Medicine
Harvard Medical School
Director, Center for Cardiovascular Disease
Prevention, Division of Preventative Medicine
Brigham and Women's Hospital
Boston, Massachusetts

David G. Soergel, MD
(Industry Representative)
Global Head
Cardiovascular, Renal and Metabolism Development
Novartis Pharma
East Hanover, New Jersey

TEMPORARY MEMBERS (Voting)

James Floyd, MD, MS
Assistant Professor of Medicine and Epidemiology
Cardiovascular Health Research Unit
University of Washington
Seattle, Washington

Nedra Hazlett, MSN, CRNP

(Patient Representative)

Women's Health Nurse Practitioner

Administrator, Atrial Fibrillation Support Forum

Murrysville, Pennsylvania

Jenna M. Merandi, PharmD, MS, CPPS

Medication Safety Officer

Nationwide Children's Hospital

Columbus, Ohio

Matthew Needleman, MD, FACC, FHRS

Commander, Medical Corps, U.S. Navy

Program Director, Cardiovascular Diseases

Fellowship, National Capital Consortium

Director, Arrhythmia Services

Walter Reed National Military Medical Center

Associate Professor of Medicine and Pediatrics

Uniformed Services University of Health Sciences

Bethesda, Maryland

FDA PARTICIPANTS (Non-Voting)

Ellis F. Unger, MD

Director

Office of Drug Evaluation I (ODE I)

Office of New Drugs (OND), CDER, FDA

Norman Stockbridge, MD, PhD

Director

Division of Cardiovascular and Renal Products

(DCaRP), ODE I, OND, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. LEWIS: Good morning. I'd first like to remind everyone to please silence their cell phones, smartphones, and any other devices if you have not already done so. The FDA press contact for today's meeting is Jeremy Kahn. If you're present, please stand. I don't think so. If he's not at the meeting, which he appears not to be, his contact information is available on the press handout at the check-in table.

My name is Julia Lewis. I am the chairperson of the Cardiovascular and Renal Drugs Advisory Committee in this meeting. I will now call today's meeting of the Cardiovascular and Renal Drugs Advisory Committee to order. We'll start by going around the table and introducing ourselves. I will take a moment to thank the people who had a particularly difficult time getting here for doing so.

We will start with the FDA on my left and go around the table. Dr. Unger?

DR. UNGER: Good morning. I'm Ellis Unger. I'm director of the Office of Drug Evaluation I, in the Office of New Drugs, CDER FDA.

DR. STOCKBRIDGE: Good morning. I'm Norman Stockbridge. I'm the director of the Division of Cardiovascular and Renal Products.

DR. RIDKER: Good morning. I'm Paul Ridker, a cardiologist at the Brigham in Boston.

DR. GIBSON: Mike Gibson, interventional cardiologist and trialist, professor of medicine, Harvard Medical School.

DR. PACKER: Milton Packer, cardiologist, Baylor University Medical Center in Dallas.

DR. DAVIS: Barry Davis. I'm a biostatistician at the university of Texas School of Public Health in Houston.

DR. MANDROLA: John Mandrola. I'm a practicing electrophysiologist at Baptist Health Louisville, in Louisville, Kentucky.

DR. WANG: Yinghua Wang, designated federal officer, FDA.

DR. LEWIS: Julia Lewis, nephrologist,

Vanderbilt.

DR. ALEXANDER: John Alexander, cardiologist and trialist from Duke University.

DR. MOLITERNO: Good morning. David Moliterno, cardiologist and chairman of medicine at the University of Kentucky.

MS. ALIKHAANI: Good morning. I'm Jacqueline Alikhaani. I am a heart survivor, volunteer patient advocate, and ambassador with the American Heart Association, and the Patient-Centered Outcomes Research Institute, and other patient support organizations.

MS. HAZLETT: Good morning. I'm Nedra Hazlett, Women's Health nurse practitioner, Pittsburgh, Pennsylvania.

DR. FLOYD: James Floyd, general internist from University of Washington.

DR. NEEDLEMAN: Good morning, Matthew Needleman, practicing cardiac electrophysiologist at the Walter Reed National Military Medical and USUHS.

DR. MERANDI: Hi. Good morning. Jenna Merandi. I'm a medication safety officer at Nationwide Children's Hospital.

DR. SOERGEL: Good morning. I'm David Soergel. I'm the head of cardiovascular renal metabolism development at Novartis.

DR. LEWIS: I'm now going to read the Conflict of Interest Statement.

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 recognized by the chairperson. 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 the 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, the FDA will refrain from discussing the details of this meeting

with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunches. Thank you.

Yinghua, my colleague, will now read the further Conflict of Interest Statement.

Conflict of Interest Statement

DR. WANG: 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 of the committee are special government employees 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 that 18 U.S.C. Section 208, 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 federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, 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 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of new drug application 022034, for vernakalant hydrochloride solution, for intravenous injection, submitted by Correvio International Sarl, for the proposed indication of rapid conversion of recent onset atrial fibrillation to sinus rhythm for non-surgery patients; atrial fibrillation less than or equal to 7 days duration; and for post-cardiac surgery patients, atrial fibrillation less than or equal to 3 days duration.

This is a particular matters meeting during which specific matters related to Correvio International Sarl's NDA 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. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that

Dr. David Soergel, Jr. is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Soergel's role at this meeting is to represent industry in general and not any particular company. Dr. Soergel is employed by Novartis.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. LEWIS: We will now proceed with the FDA's opening remarks from Dr. Norman Stockbridge.

FDA Introductory Remarks - Norman Stockbridge

DR. STOCKBRIDGE: Good morning, again, and thanks in advance to all of the committee members for their participation in the first advisory committee

meeting we've held since 2015. The agency has acknowledged that vernakalant is an effective agent, and so the issue today is mostly about safety.

The drug appears to be a negative inotrope in dogs and in humans. This has implications for some patients who can be readily identified as being at risk of having a problem with this, but it also appears to be a risk to some patients who cannot be reliably identified prior to administration of the drug. If it were true that you could reliably intervene in somebody who got into trouble because of the negative inotropic effects, that also would be okay.

So the main interest here is to have you folks look at the available safety database that comes from both controlled trials and some postmarketing registry data, and opine on this.

You should understand that part of the reason why we don't have very many advisory committee meetings is if we're pretty well convinced something should be approved, we're not likely to bring it here and have you try to talk us out of it. We also, I think, don't bring things to you where the answer is so clearly

known, that there's no way you can talk us into an approval.

So the fact that we're having a meeting here today is an acknowledgement that there is a case that can be made, and we want you to hear it and opine on it, and give us your best advice. Thank you.

DR. LEWIS: Thank you, Dr. Stockbridge.

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 advisory committee meeting, the FDA believes that it's important to understand the context of an individual's presentation.

For this reason, the FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, an interest in the sponsor, including equity interests, and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do

not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the presentations from Correvio International Sarl.

Applicant Presentation - Mark Corrigan

DR. CORRIGAN: Good morning. I'm Mark Corrigan, employee of Correvio and the CEO, and I'm a physician by training, with 25 years of drug development. I'd like to thank the FDA and the committee for your time today.

Vernakalant is an atypical application for this committee and the FDA to consider. The path has not been straightforward. Let's set the stage. In 2007, the Cardiorenal Advisory Committee voted in favor of approval. The two dissenting votes and the FDA requested additional safety data. We now return with a revised NDA.

This NDA has addressed the issues in the approvable letter, and is further supported by larger preclinical and clinical databases, along with the

substantial post-approval safety study in which no deaths occurred, and over nine years and greater than 58,000 treatment episodes in the post-approval experience.

Vernakalant is a pharmacologic treatment option for recent onset atrial fibrillation, a common condition affecting thousands of patients in the U.S.. While many patients can be treated with ECV, for some, pharmacologic conversion is a more appropriate treatment approach. The data demonstrate that vernakalant is a safe and effective pharmacologic treatment option, particularly when contrasted with other medications used for cardioversion in the United States.

Vernakalant was approved in the European Union in 2010 and is currently approved in 41 countries, providing over 9 years of post-approval experience and more than the 58,000 exposures. Vernakalant is included in the Canadian Atrial Fibrillation Treatment Guidelines and in Europe as a class 1A recommendation for recent onset AF.

Here is an overview of our presentation.

Following my introduction, you will hear from the following speakers, who will summarize the data supporting the efficacy and safety of vernakalant. Because FDA and Correvio agree that efficacy has been clearly demonstrated, our presentation will emphasize our review of additional supportive safety information. The following experts are also here to help address your questions.

The indication we are seeking for vernakalant in the United States is identical to that currently approved in the countries depicted here. Since AF occurs both spontaneously in the adult population and frequently in the context of post-cardiac surgery patients, vernakalant was studied in the two populations, non-surgery patients with an AF for less than 7 days and post-cardiac surgery patients with AF for less than 3 days.

The overview of the regulatory history is shown here. Above the date line are the North American milestones, and below the line are the activities that occurred in Europe. The original NDA was submitted in March 2006 and included clinical studies of 475 AF

patients treated with vernakalant. In 2007, cardiorenal drugs were voted an approval.

In August 2008, FDA issued an approvable letter, stating vernakalant was clearly effective for cardioversion of recent onset AF, and requesting additional data to more fully characterize the safety of vernakalant and address 8 events, adverse events, of concern. The ACT V clinical trial was initiated in 2009, and the protocol was designed and agreed with FDA.

Vernakalant was approved in Europe in September 2010 for cardioversion of recent onset AF, with a commitment to conduct a post-approval safety study, SPECTRUM. In October 2010, ACT V was placed on clinical hold due to an SAE of cardiogenic shock and death, and that study was terminated.

In parallel, the European Medicines Agency requested revisions to the label to extend patient monitoring and to include the contraindication of IV antiarrhythmic drug classes 1 through 3. In 2012, we added a preinfusion checklist to guide physicians in the identification of appropriate patients for the use

of vernakalant, and in 2017, vernakalant was approved in Canada.

This brings us to today, with a well-characterized, antiarrhythmic medicine that has been thoroughly investigated, both preclinically and clinically. The NDA resubmission contains an additional 2,545 patients in clinical studies, including the 2009 exposures in the post-approval safety study, which was designed and agreed with EMA. Also included are data from exposures in over 2,000 patients in investigator initiated studies and periodic safety updates in the 58,000 patients exposed to vernakalant.

The studies conducted since 2006 have allowed us to more clearly define the target patient population. The SPECTRUM study confirmed the patient population and reflects patients in the U.S. who are appropriate for and who will benefit from vernakalant treatment.

Vernakalant is a valuable addition to the physician treatment armamentarium for the management of patients with recent onset AF. We are not recommending

vernakalant for every patient with recent onset AF or to replace electrical cardioversion. Vernakalant has advantages reducing patient time spent in AF and preventing hospitalizations.

The safety profile has been well-characterized both in research and clinical treatment settings. We have defined the population who can benefit and are committed to ensuring that those are the patients who will receive the medication. These data will facilitate the FDA's discussion question 1.

We're committed to patient safety, and we've listened to the FDA's concerns. We've not yet presented our proposal to the agency and are working with the U.S. physician experts to craft enhanced risk mitigation measures to ensure identification of appropriate patients through the label, the electronic checklist as part of a necessary component to drug dispensation, and a prescriber training program.

Secondly, we propose the healthcare setting certifications to reinforce the labeling and achieve two goals of the medication being delivered in appropriate treatment settings and optimal medical

management and monitoring.

We have confidence in the confirmed clinical efficacy and safety profile for a new atrial conversion agent. The totality of the pre and postmarketing global experience with vernakalant supports the committee's recommendation to allow U.S. patients and physicians to have access to this important treatment option.

Dr. Peter Kowey will now describe the clinical landscape in the United States and the need for a new pharmacologic treatment option, and comment on the second question for discussion, comparing vernakalant to existing treatment options. Thank you.

Applicant Presentation - Peter Kowey

DR. KOWEY: Thank you, Dr. Corrigan.

My name is Peter Kowey. I'm a cardiologist and rhythm specialist at the Lankenau Heart Institute and professor of medicine and clinical pharmacology at Thomas Jefferson University in Philadelphia. I'm here as a consultant to the company. I've been paid for my time and travel expenses, but hold equity interest in no pharmaceutical company.

I'm privileged to be here as an advocate for my patients and for my cardiology colleagues who seek better care for our AF patients. I also want to add that I'm extremely grateful to the FDA for convening this august group to render advice about the value of vernakalant to patients in the United States.

My task today is to outline the disease state we call atrial fibrillation, and then briefly review with you the unmet need for antiarrhythmic medications that we use to treat it. I'll return later this morning after you've heard about the safety and the efficacy of vernakalant to provide my perspective specifically on its clinical advantages.

Atrial fibrillation is by far the most common cardiac rhythm disturbance encountered in clinical practice, and its prevalence is expected to double by 2030. It's a complicated disease, with a myriad of etiologies, and it is responsible for significant morbidity and mortality in the United States.

Patients with atrial fibrillation deluge our emergency departments. A recent report stated that almost 600,000 emergency room department visits each

year in the United States are for atrial fibrillation. This number has increased 31 percent in 7 years. About a third to half of these encounters are for new or recent onset AF, and about 60 percent of these patients get admitted to the hospital. Surveys suggest that over half of these patients are candidates for pharmacological conversion. Since the patients have severe symptoms, prompt and efficient management of recent onset AF is important to prevent hospital admissions.

The currently available treatments in the United States each have limitations that influence their use. The FDA has implied that electrical cardioversion is the best method for this condition and that there's little need for an alternative. I hope in the following minutes to point out the need for alternative treatments; most importantly, a safe and effective parenteral antiarrhythmic drug.

In the guidelines from several of our professional organizations, pharmacological conversion is recommended for symptomatic patients, but we have not had a new pharmacologic agent for AF approved in

the United States for several years. Pharmacologic conversion is particularly useful in patients whose heart rates and symptoms are difficult to control, those with infrequent paroxysms of AF, for example, and particularly those with new onset AF who present within 48 hours, where efficacy of pharmacologic cardioversion is maximal.

The guidelines also state that rhythm control might be particularly important in younger patients and may prevent atrial electrical remodeling, and thus AF progression. The guidelines also state that the method of cardioversion should be at the discretion of the physician, based on clinical history, symptoms and signs, and what is optimal for the individual patient.

When encountering a symptomatic patient with recent onset AF, physicians think about relieving symptoms, reducing the chance of a stroke, and maximizing the efficiency of care. Cardioversion fulfills all three of these imperatives but is carried out in a relatively small percentage of patients in the United States.

Why? Currently used drugs are either not fast

acting and/or come with an unacceptable high rate of proarrhythmia. Electrical conversion in most settings requires the assistance of an anesthesiologist, sometimes additional cardiology consultation, and an additional and appropriate setting for performing and monitoring the procedure. It is not practical within the time constraints of an emergency department visit, and despite how symptomatic patients are in this setting, unless patients are severely hemodynamically compromised, most physicians pursue rate control and anticoagulation.

The end result is hospital admission in the majority of patients or, at minimum, recurrent emergency room visits and frequent office follow-up. Hospitalization is expensive, it's distressing to patients, and it is a terribly inefficient use of resources. Notably, this situation is not the case in many other countries where additional faster acting drugs such as IV flecainide and IV vernakalant are available.

There is one FDA-approved drug for cardioversion of recent onset atrial fibrillation.

Ibutilide, which I'll describe further in my next slide, is approved for recent onset AF and is a rapidly acting drug, but is not used because of its risk of proarrhythmia. Oral dofetilide; amiodarone, oral or IV; oral flecainide; and oral propafenone are not approved in the United States for acute AF termination.

Amiodarone is by far, nevertheless, the most commonly used drug, but has a long time to onset of effect, even when used in its intravenous formulation. Oral class 1C drugs are slow acting with only modest efficacy and are restricted to patients without any form of heart disease.

The FDA called out a pharmacologic therapy for the acute termination of AF that they believe has clinical value and ostensibly supplants the need for another agent. Ibutilide was approved in the United States over 20 years ago on the basis of 586 patients treated with the drug in phase 2/3 studies.

I presented the safety data set for IV ibutilide in 1996. The conversion rate within 70 minutes from AF to sinus rhythm was 22 percent for the 1-milligram dose and 43 percent for the 2-milligram

dose. Notably, ibutilide, unlike vernakalant, works better for atrial flutter than it does for atrial fibrillation. Its use has been sparse in the United States and practically nonexistent in the rest of the world. The safety limitations of ibutilide are in the explanation and are underscored by the boxed safety warning for life-threatening arrhythmias in the approved product label.

Specifically, ibutilide is associated with QT prolongation and a relatively high risk of Torsades. For all of these reasons, in our hospital is a niche drug used by electrophysiologists, the crazy electrophysiologists in the laboratory, for AF termination at the time of catheter ablation procedures.

The postmarketing reports for ibutilide give an important perspective on the safety profile of the drug. Remarkably, despite gross underestimation that we know occurs with spontaneous adverse event reporting, there have been 295 incidences of ventricular proarrhythmia and 16 deaths in the database since the drug was approved.

The FDA also references electrical cardioversion in their briefing document. Let me say, first, that electrical conversion is very effective, providing prompt conversion to sinus rhythm in several clinical settings. Though it works most of the time, it is not used in our emergency departments for early conversion on a high frequency, and it is simply not logistically feasible or practical to carry out this procedure in most emergency departments.

There are lots of other limitations. It's not ideal in patients following thoracic surgery, for example, or with respiratory disorders. The patients must be fasting, and it is associated with immediate and early recurrence of atrial fibrillation, which can occur in up to 25 percent of patients.

Accordingly, it is often used with pharmacologic agents such as am amiodarone to reduce the risk of immediate AF recurrence. But the greatest downside for the use of electrical cardioversion is the need for an anesthesiologist to provide complete anesthesia -- complete anesthesia -- and the potential for severe and life-threatening side effects.

Hence, in most cases, electrical conversion has to be scheduled, and this results in delays to cardioversion, which then needs to be done in a procedure room by an experienced physician or during a hospital admission; and there are no large randomized control trials which rigorously characterize the safety of electrical conversion when used in the emergency department to convert recent onset AF, and the most common adverse effects are shown in the last bullet.

I will continue this discussion on the available cardioversion options later this morning.

In summary, although pharmacologic conversion is recommended in appropriate patients with recent onset AF, it is simply not used in the United States. This is unfortunate since pharmacologic conversion has several potential benefits for a subset of patients with recent onset AF.

It offers immediate relief of symptoms so patients can go home. It normalizes the ventricular rate and improves hemodynamics and exercise tolerance. It can reduce the need for hospital admission and repetitive access to the healthcare facilities. It can

reduce the need for later electrical cardioversion and weeks of anticoagulation, and it may mitigate remodeling and its effect on progression of AF.

Pharmacologic conversion is a guideline recommended means of cardioversion in appropriately selected patients, but currently there is a dearth of effective and easy ways to use pharmacologic conversion in the United States. Vernakalant provides -- and I will emphasize, please -- an additional option for cardioversion.

Now, I'd like to introduce one of my colleagues, Dr. Peter Siegl, to speak to the pharmacology of vernakalant.

Applicant Presentation - Peter Siegl

DR. SIEGL: Good morning. I'm Peter Siegl, a pharmacologist and consultant working with Correvio. I have no financial interest relevant to the outcome of today's meeting.

Mechanisms of action and safety of vernakalant have been thoroughly characterized in nonclinical studies, and I will summarize these findings in my talk. On this slide, the molecular mechanisms of

action for vernakalant are summarized. On the left is a depiction of an atrial myocyte action potential and the ion channel currents which modulate it. On the right is a table of the relative potencies for inhibition of these cardiac ion currents, presented as IC50 values, obtained from voltage clamp studies.

As you can see, vernakalant has pharmacological activity on several cardiac ion channels at therapeutically relevant concentrations. This novel, multi-ion channel profile underlies the efficacy and safety of vernakalant. Briefly, the contributors of efficacy to vernakalant are decreased excitability and slow conduction; the inhibition of the peak sodium current, like flecainide and propafenone; in addition to delayed repolarization in the atria by inhibition of IKur and IKAch, activities that are unique to vernakalant; as well as inhibition of IKr, like dofetilide and ibutilide.

The low proarrhythmic risk with vernakalant is consistent with its ion channel pharmacological profile. First, sodium channel inhibition with vernakalant is greatest at faster rates and less

polarized cells. This translates into greater potency in the atria during atrial fibrillation. Second, IKur, or Kv1.5, and IKAch are located in the atria and not in the ventricle. As a result, there is a preferential effect of vernakalant on atrial repolarization. This has been confirmed in both nonclinical and clinical studies.

Now, a preferential effect on atrial versus ventricular repolarization cannot be achieved with IKr or sodium channel inhibition alone, and therefore IKur and IKAch inhibition contribute to the effects of vernakalant on atrial repolarization.

Lastly, inhibition of the late sodium current offsets the prolongation of the action potential due to IKr inhibition. The net result is both the magnitude of QT interval prolongation as well as the risk for Torsades de Pointes or less than with selective IKr blockers. These three attributes contribute to a lower proarrhythmic risk than sodium channel blockers, such as flecainide and propafenone, and potassium channel blockers such as dofetilide and ibutilide.

Hypotension has been observed in some

patients, which led us to explore the mechanisms of this effect. From the nonclinical studies, when present, the primary mechanism for hypotension with vernakalant is a decrease in cardiac output. There are no contributions of a decrease in vascular resistance or bradycardia, nor are there any off-target mechanisms contributing to the hypotension. When present, the hypotension occurs at peak plasma levels, which is at the end of the infusion.

Like other sodium channel blockers, vernakalant has a direct negative inotropic effect at or above therapeutic levels. This is not an off-target effect. And since it is mechanism based, it is dose related. The decrease in contractility occurs immediately after administration. It's reversible and has a short duration.

Now, negative ionotropic activity is not unique to vernakalant. Other drugs used in the management of atrial fibrillation decrease contractility at therapeutic levels, including flecainide, verapamil, and beta adrenergic blockers. So for all drugs with mechanism-based negative

inotropic effects, there is a risk for decreased cardiac output and hypotension in patients with significant uncompensated left ventricular dysfunction; and therefore, appropriate patient selection and monitoring are important to mitigate the risks associated with these drugs.

In conclusion, the ion channel profile of vernakalant has been extensively profiled and is ideal for the conversion of atrial fibrillation and reduced likelihood of proarrhythmia. The cardiovascular safety of vernakalant has been fully characterized in nonclinical studies, including effects on hemodynamics, cardiac contractility, and importantly, risk factors for and mechanism of hypotension.

The information from the nonclinical studies has helped to inform the selection of appropriate patient populations who can benefit from vernakalant and guide the exclusion of subjects who should be contraindicated for vernakalant.

I'll now like to introduce Dr. Andrew Tershakovec, who will discuss the clinical efficacy of vernakalant.

Applicant Presentation - Andrew Tershakovec

DR. TERSHAKOVEC: Good morning. I'm Andrew Tershakovec in clinical development. I'm a paid consultant to Correvio, but have no financial interest in the outcome of today's meeting. I will present an overview of the clinical efficacy of vernakalant for rapid conversion of recent onset atrial fibrillation or AF.

The 2006 NDA filing in the U.S. for vernakalant included two phase 2 studies and three pivotal phase 3 studies. The 2019 resubmission includes new efficacy data from four additional phase 3 studies, SPECTRUM, a phase 4 post-approval study, and a postmarketing experience over 9 years and 58,000 treatment episodes, some of which have been described in the post-approval literature.

Here are the studies in the 2006 submission. The phase 2 were CRAFT, a dose-ranging study, and Scene 2, a study in AFlutter. Regarding the three pivotal phase 3 studies, ACT I enrolled AF subjects; ACT III enrolled subjects with AF and AFlutter; and ACT II was a study of AF and AFlutter in post-cardiac

surgery subjects.

On the bottom row, you can see the original NDA included 872 subjects of whom 537 received vernakalant. The resubmission is supported by substantial additional clinical data. The top row shows the subject numbers from the original NDA. Below it are the additional clinical studies in the resubmission and the related exposure numbers. These include the placebo-controlled AF trials, ACT V and Asia Pacific study; an active comparator AF study with amiodarone, AVRO, conducted to meet EU filing requirements; ACT IV, a single-arm AF trial; and SPECTRUM, the large post-approval safety study conducted in the EU.

Thus, the 2019 resubmission includes clinical data from over 1600 subjects, over a thousand of whom received vernakalant. Together with SPECTRUM, these numbers increased to over 3600 subjects, over 3,000 who were treated with vernakalant, shown in the bottom row.

Note that some studies included subjects with AFlutter, or with longer duration AF or AFlutter. As efficacy was not demonstrated in AFlutter or in AF for

a duration longer than 7 days, the requested indication excludes these subjects, and the efficacy presentation will focus on AF with duration of 7 or fewer days.

The study design for the pivotal efficacy trials, ACT I, III, and II, was similar. At baseline, subjects were screened, and then randomized to either placebo or vernakalant. The first infusion was infused over 10 minutes, then there was a 15-minute pause. If subjects did not convert, a second infusion was given from 25 to 35 minutes.

Subjects were then followed for 90 minutes for the primary endpoint period and had close clinical monitoring, including telemetry for 2 hours after study drug administration. Subjects also had continuous Holter monitoring over the full 24-hour period, and frequent 12-lead ECGs were recorded at prespecified intervals over these 24 hours. This multipronged monitoring plan supported a very detailed assessment of the efficacy and safety of vernakalant.

Note the design feature on the bottom right. Electric cardioversion or other therapies for cardioversion and ongoing AF were allowed beginning

2 hours after study drug administration. Finally, subjects had a follow-up visit as 7 days and a phone follow-up at 30 days.

The dose used in the phase 3 studies is the dose recommended in the proposed label. This is an initial infusion of 3 milligrams per kilogram over 10 minutes, with a maximum of 339 milligrams. This is based on a body mass of 113 kilograms or 250 pounds. The 15-minute observation period allows full distribution of the drug while monitoring for safety and conversion. If there's no conversion to sinus rhythm and no other important clinical issues are observed, the second dose of 2 milligrams per kilogram is infused over 10 minutes to a maximum of 226 milligrams.

Here are the patient populations enrolled in the pivotal phase 3 trials. We will focus on the short duration AF population, defined as 3 hours to 7 days in ACTs I and III, and as AF less than 72 hours in ACT II.

The primary endpoint for the pivotal ACT I and III studies was the proportion of subjects with short duration AF, who converted to sinus rhythm for at least

1 minute within 90 minutes of the first exposure. As the durability of the conversion is generally strong, this endpoint represents a clinically relevant milestone.

Secondary endpoints were timed to conversion, and the maintenance of sinus rhythm at 7 days. Exploratory endpoints included relief of AF-related symptoms. Also, for the evaluation of efficacy, the ACT I and ACT III study data were combined, as subjects had similar clinical backgrounds and the studies had similar designs.

In the ACT I and III studies, the subjects were about two-thirds male, the average age was 60, and they were predominantly white. About 40 percent were from North America and about 60 percent from western Europe. The baseline characteristics are generally consistent with what would be expected for an AF population. About 10 percent of the subjects had a history of congestive heart failure; about 40 percent had hypertension; 5 to 7 percent a history of MI; 11 to 14 percent with ischemic heart disease; just under 10 percent with valvular heart disease; and overall, 25 to

30 percent with a history of structural heart disease.

Three-quarters of the subjects were on rate control medications, most of these beta blockers, and smaller proportions receiving calcium channel blockers or digoxin. Twenty-seven percent were receiving rhythm control medications, predominantly class 3 antiarrhythmics. Importantly, the median duration of AF was 28 hours.

Here are the results for the ACT I and III studies shown side by side. On the X-axis is the time for first infusion, starting at zero and then going out to 90 minutes. On the Y-axis is the proportion of subjects who convert. The first and second infusions are shown by the shaded areas.

A significantly greater proportion converted in the vernakalant group, 51.1 percent, versus 3.8 percent in the placebo group, with a p less than 0.0001. About 40 percent of the vernakalant treated subjects convert after the first dose. An additional 20 percent of subjects who received the second dose convert. The median time to conversion for vernakalant responders was 10 minutes.

Now, let's turn to ACT II, the pivotal trial that supports the second part of the proposed indication, rapid conversion of AF in post-cardiac surgery subjects, where electric cardioversion is generally not recommended.

The ACT II study enrolled subjects who had AF with duration from 3 hours to 72 hours, which occurred between 1 and 7 days after valvular or coronary artery bypass surgery. The primary endpoint was the proportion of subjects with AF or AFlutter who had conversion to sinus rhythm within 90 minutes. Other endpoints include an assessment of conversion for AF and AFlutter individually, symptom relief, and maintenance of conversion.

In ACT II, the average age was 68, slightly older than ACT I and III, and about three-quarters were male. About two-thirds had coronary artery bypass surgery, about 20 percent had valvular surgery, and about 10 percent both. Further baseline characteristics are generally as expected in post-cardiac surgery subjects. I can provide more details in the question and answer period if you'd

like.

Here are the primary results in the post-cardiac surgery subjects with AF, 47 percent in the vernakalant group and 14 percent in the placebo group converted within 90 minutes of treatment, with a p equal to 0.0001. The higher placebo conversion rate and variability in the treatment response were potentially related to postoperative injury and inflammation. The median time to conversion for the vernakalant responders was 12.4 minutes. Again, this is overall evidence of efficacy and rapid conversion.

Before reviewing the other efficacy data, let me again review the other studies included in the 2019 refiling. Here are the phase 2 and phase 3 trials in the 2006 filing, and shaded in blue are the new studies added to the refiling. Recall these additional studies include ACT V and the Asia Pacific placebo-controlled studies; the AVRO study with amiodarone as an active comparator; the single-arm ACT IV trial; and the large post-approval safety study, SPECTRUM.

A large portion of the new information in this resubmission comes from the SPECTRUM study. This

European post-approval safety study was designed in conjunction with the European Medicines Agency or the EMA. It was conducted from 2011 to 2018, with study sites in the countries listed here. The full report was submitted in November of 2018 to the EMA and was recently approved.

As this was a safety study, Dr. Weaver will describe more fully the details of SPECTRUM in his safety presentation. I will provide a brief overview and describe the efficacy results. The primary objective was to estimate the incidence of prespecified medically significant health outcomes of interest, or HOIs. Subjects could be enrolled more than once if they had independent events of AF. So overall, 2,019 treatment episodes were captured for 1,778 patients.

Over 1500 subjects were enrolled prospectively. To ensure timely completion of this study, with consent from the EMA, an amendment was implemented to allow the retrospective enrollment of subjects from chart reviews. This added about 400 treatment episodes.

The demographics of the study population was

similar to that in the phase 3 clinical trials. However, the baseline characteristics reflected the refined patient selection criteria in the European label, consistent with treating physicians applying the labeled guidance to select lower risk subjects for vernakalant treatment. Also, the duration of AF was 8 to 12 hours, shorter than the meeting time in the clinical trials. This is important, as shorter term AF duration is associated with higher conversion rates.

Here is the proportion of subjects who converted to sinus rhythm in SPECTRUM and the phase 3 studies, vernakalant in blue, placebo in gray, and amiodarone in light blue. Across the full development program, we observed generally consistent conversion rates, about 50 percent with vernakalant.

The higher conversion rate in SPECTRUM, about 70 percent, is likely related to the study design, the lower rate of structural heart disease, and the shorter duration of AF in this study population. Also, across these studies, we saw consistency in time to conversion for vernakalant responders. The median conversion times were between 8 and 14 minutes and slightly longer

in the SPECTRUM postoperative subjects.

Here are the results for the maintenance of sinus rhythm at 24 hours and at 7 days in the phase 3 studies. Across the development program, we generally see approximately 90 percent maintenance at 7 days. The one exception is ACT II in the post-cardiac surgery subjects, which may be related to postoperative injury or inflammation.

Vernakalant treatment is also related to AF symptom relief. Sixteen symptoms were tracked. Here are the proportion of subjects with any AF-related symptoms on the left and then the five most commonly reported symptoms: chest tightness or pain; dizziness; irregular pulse; palpitations; and rapid heartbeat. For each, the blue bar represents symptoms at baseline and the green bar represents symptoms at 90 minutes, the end of the primary endpoint monitoring period. There was a significant decrease in all of these symptoms in the vernakalant group.

In summary, vernakalant supported effective and rapid conversion of recent onset AF with generally consistent conversion rates observed across the

development program. That conversion was accompanied with lower rates of AF-related symptoms, and sinus rhythm was maintained in the vast majority out to 7 days. The efficacy demonstrated in the phase 3 studies was confirmed in the post-approval experience.

Thank you, and Dr. Weaver will now review the data supporting the safety of vernakalant.

Applicant Presentation - Douglas Weaver

DR. WEAVER: Thank you, Dr. Tershakovec.

I'm Dr. Doug Weaver, past president of the American College of cardiology, and my academic career has focused on both pharmacological and medical device development. I have been a consultant to the sponsor and studying the findings and characteristics of this drug for the past 11 months. I have no financial interest dependent on the outcome of today's meeting.

I will present to you the evidence that provides an in-depth understanding of the safety profile of vernakalant. My overall conclusions of safety are different from those in the FDA briefing document. We identified some data discrepancies in there listed topics, and all of these will not be

detailed in my presentation due to time limitations. However, we have some backup information if they come up in your questions.

One very important difference that I will discuss is the ACT V patient, whose condition at the time of enrollment I would not consider to be otherwise healthy, nor to be a representative case of hypotension, arrhythmia, and conduction findings associated with drug administration. I also have backup information available regarding the 43 patients subpopulation, which is highlighted the QRS and QTc prolongations and blood pressure differences that provides more clarification of these differences.

We will begin where this submission left off 10 years ago, by presenting the 8 events of concern outlined by the agency in 2008. Then I'll discuss any deaths that occurred in the trials, including details about the one that led to a clinical hold. After careful review in each, the sponsor does not believe that the 8 events and the ACT V death warranted a clinical hold, and I will explain why.

The presentation will then cover the safety

findings from the 9 trials using several different methods to identify events. We will then look at the analysis of risk factors for developing hypotension and bradycardia, and this helped to identify a target treatment population with a positive benefit-risk profile.

I will present a lot of data, but for the sake of time will limit my comments to key clinically important details important to decision making. I'd be happy to provide additional ones later. The EMA approved the drug and target population in 2010, with a proviso that the company obtain additional safety information in a large post-approval study. I'll end with that, along with other post-approval information.

To begin, there were 4 cases of hypotension, 3 events of bradycardias occurring at the time off or following cardioversion, and one nonsustained ventricular arrhythmia identified as concerning. The 4 hypotension events are shown here. I have highlighted key details about each. The first three would now be contraindicated under the proposed label, as shown in the right column.

The first event occurred in a patient with a dilated cardiomyopathy and it resolved spontaneously; the second in a patient with severe aortic stenosis and an acute coronary syndrome, who required fluid resuscitation for symptomatic hypotension before receiving the study treatment. He received two full infusions of drug despite recurrent hypotension, which ultimately led to a loss of blood pressure and cardiac arrest.

The third patient, with heart failure and an ejection fraction of 25 percent, became hypotensive; blood pressure was 110, dropped to 70; then had a short run of sustained VT, which reverted spontaneously to sinus rhythm, and then hypotension also resolved after salient infusion and Trendelenburg positioning.

The fourth, admitted after several days of orthopnea, had a transient 15-minute drop in blood pressure during the first infusion, which resolved with fluid administration. He did not convert and later was electrically cardioverted. He developed shock 12 hours later in the middle of the night, a time when the drug concentration would not be detectable, and this

occurred following multiple doses of sedatives and haloperidol. And the shock was preceded by mental disorientation, and then shortly thereafter a respiratory arrest, which led to intubation and to his recovery. This event of shock at 12 hours was not considered by the sponsor to be related.

The next three events were bradycardias, which kind of occur with all forms of cardioversion, as well as may unmask both sinus and AV nodal dysfunction. The first, at the time of cardioversion, was associated with hypotension and resolved with atropine. The second, transient bradycardia and sinus arrest post-cardioversion; no treatment was given.

The third, in an elderly woman who did not convert with vernakalant, but developed complete heart block with hypotension after electric cardioversion, and she received atropine, Isuprel, and days of temporary pacing for persistent bradycardias and presumed sick sinus syndrome.

The last patient had short runs of non-sustained, monomorphic and polymorphic ventricular tachycardia and transient hypotension, most likely

associated with GI bleeding. These same rhythms were recorded prior to treatment, however, this particular patient with known moderate to severe reduction in LV function, would also be contraindicated today.

Of these 8 cases, 5 had poor LV function, a current contraindication and 3 transient Brady arrhythmias, which can occur with all forms of cardioversion. These events and additional findings have guided the current EU label.

I'll now present the findings surrounding any death that occurred within 30 days in the trials, that includes one that led to the clinical halt. There were 9 in all, 1 in the placebo group and 8 in the twice larger vernakalant group. Only one was considered by the investigator to be treatment related. The sponsor, however, judged two to be treatment related.

None of the seven here were considered by both the treating physician and the sponsor to be treatment related. Most were associated with comorbid conditions; for instance: stroke, lung cancer, heart failure, unrecognized aortic dissection, and pneumonia.

The first patient that was deemed related is

the aortic stenosis case that I just highlighted. He had severe aortic stenosis known by the treating physician, a gradient of 120 millimeters, a dilated ventricle, and an ejection fraction of 40 percent. He was admitted with AF, chest pain, and an elevated troponin.

He became hypotensive and nauseated following a small dose of IV beta blocker, and he required fluid resuscitation even before receiving the drug. Despite that, he had recurrent episodes of hypotension during the initial infusion. He received full to 2 infusions, lost blood pressure, and that was followed by VF, and he died after a short resuscitation attempt.

In the sponsor's assessment, he was not a candidate for any form of pharmacologic cardioversion. In addition, even in this early trial, the finding of acute MI was a study exclusion, as was the failure to discontinue treatment if hypotension occurred. Severe aortic stenosis, however, then became an explicit exclusion criteria in the later trials.

The second death occurred in the ACT V study and was considered related to treatment by the sponsor,

but for unknown reasons, not by the treating physician, it led to the clinical hold. After thorough view of the source documents, our reassessment differs from that of the FDA briefing book, in which he is described as a representative case of hypotension, arrhythmia, and conduction disorders, and deaths.

The patient was a 77-year-old man with a history of hypertension, chronic alcohol abuse, and otherwise was stated as unremarkable. He had a 1-week history of dyspnea, orthopnea, fatigue, which the investigator classified as class 3, meaning symptoms with minimal exertion. He had palpitations for 2 or 3 days before admission. He also gave a history of palpitations a month earlier.

He had vesicular breast sounds, and notably his respiratory rate was 20 to 28 throughout the prescreening plus baseline measurements. His heart rate was fast, 150 beats per minute or faster. The treating physician did an echo before initiating treatment, and the medical record states, and I quote, "Moderate systolic dysfunction, diffuse hypokinesis, left ventricular hypertrophy, and estimated ejection

fraction to be 44 percent. The left atrium was also dilated."

As you are aware, an accurate assessment of EF measurement is difficult to determine during rapid AF. Thus, most physicians, when assessing functions in patients such as this, instead base their assessment more on the overall observed semi-quantitative wall motion findings than a single EF number.

At the end of the first infusion, the patient developed severe hypotension; then at tonic posturing, a seizure; lost consciousness; cardiac with initial pulseless rhythms; then he had VF and other arrhythmias. The resuscitation notes in the record, first, 2 IVs were started and then multiple large doses of epinephrine given. There was a long, 40-minute resuscitation, and the patient died 29 days later from multiorgan failure.

At the time of this study, the exclusion criteria that was relevant was heart failure, which was defined in the protocol by either a prior history, or by current symptoms and signs, or evidence of LV dysfunction, which are suggested by the 1-week history

of dyspnea, the marked limitation of fatigue, the rapid respiratory rate, as well as the echo findings.

In addition, the protocol also required the investigator to assess the risk of thromboembolism prior to enrollment and to anticoagulate if needed before considering treatment in patients with AF for 48 hours or longer. With AF present in this patient for at least 2 days, and possibly a month, and a CHADS 2 score of 3, the suggested guidelines at that time called for full anticoagulation with warfarin for weeks before considering cardioversion. However, because of this event and because functional class is an inexact measure of LV function, the proposed label has been narrowed to also exclude those with known moderate or severe left ventricular dysfunction.

This patient should not have been treated then, per the protocol, nor would such patients be treated today given their clinical findings, the duration of AF, and the CHADS 2 risk score. His inclusion was a clear protocol violation, as well as the finding of moderate LV dysfunction would also exclude him today.

I'll now show the safety data available from all the trials with special emphasis on the adverse events of ventricular tachycardia, bradycardia, and hypotension. The data set, now 6 times larger than the initial NDA, includes over 3,000 treatment episodes.

Here are the baseline characteristics in the all-patient population, those from the original studies plus the 4 additional ones they've done since 2009: the average age 62; heart failure in 16 percent; 30 to 35 percent had a history of MI or ischemic heart disease; a little over 10 percent with valvular heart disease; 40 percent had structural heart disease; half the patients were on beta blockers; 4 to 5 percent received class 1; and 12 to 13 percent class 3 antiarrhythmia drugs prior to enrollment. The immediate post cardiac surgery patients represent about 10 percent of this entire cohort.

AEs were captured for three time periods: 0 to 2 hours; 2 to 24 hours; and 0 to 24 hours. The 0 to 2 hours captures a time of Cmax, which occurs at the end of the infusion. The 2-to-24 hour period will be that in which the placebo cohort may undergo electrical

cardioversion, and the findings in the vernakalant group will also be confounded by additional treatments.

As a reminder, following discontinuation infusion, the drug is rapidly distributed at 30 minutes, the concentration has dropped to less than half, and by 2 hours to about 20 percent, and at 24 hours, the drug is barely detectable by the assay.

Here is the overview of the adverse events. There were more in the vernakalant group, though were non-serious. SAEs were about 1 percent higher in the vernakalant group, 4.8 versus 3.9 percent for placebo. Drug discontinuation for adverse events was also higher in the vernakalant group.

I'm first going to describe these events in the all-patient population, and then later in my our proposed target population. We performed detailed searches to identify and characterize the adverse events AE database and also using the 12-lead ECGs, the Holter rhythm recordings, and serial vital signs. The FDA requested additional searches, and they included additional broader terms for AEs. For example, syncope and dizziness were added to hypotension; decreased

heart rate was added to bradycardia.

We conducted all of the FDA requested assessments, and I won't show the detailed tables. The results showed no new safety conclusions and no new SAEs for ventricular arrhythmias, bradycardias, or hypotension. Additionally, we reviewed patients who received only one dose and did not convert in order to identify any additional AEs using the expanded terms. We also compared the treatment groups using medication lists and procedures that might be associated with possible resuscitation.

Here are the adverse event rates using the sponsor's assessment for ventricular arrhythmias, bradycardias, and hypotension. In the left panel in hour 0-2, the rate of ventricular arrhythmias is higher for vernakalant, shown in blue, then higher for placebo, shown in gray for hours 2 to 24. Remember, this is a time of electrical cardioversion. The right set of bars shows the rate from 0 to 24 hours in both groups.

The FDA comparisons emphasize the event differences at 0 to 2 hours, the time of vernakalant

cardioversion; whereas our analysis -- indeed, that rhythm control has been the choice for treatment here -- also examined the overall event rates of 0 to 24 hours, to include those events associated with electric cardioversion after 2 hours.

In the middle panel are the bradycardia event rates, higher for vernakalant in hour 0 to 2, but higher for placebo in hours 2 to 24. In the right panel, this same pattern is present for hypotension AEs. This pattern of events suggests that most are associated with cardioversion.

This is a more detailed assessment of ventricular arrhythmia events, which now includes the ECG and rhythm recordings. In the left column, top row, there were three VF events in the 0 to 2-hour time period after treatment with vernakalant. Two of them occurred after severe hypotension; that's the patient with aortic stenosis and the ACT V patient. The third occurred in a phase 2 study with an unsynchronized cardioversion of AF that the investigator reported was unrelated and secondary to a loose electrode.

For ventricular tachycardia, on the lower two,

there were more events for vernakalant in hour 0 to 2, 4.3 versus 2.3 percent in placebo. But in hours 2 to 24, there were more VT events in the placebo group, 9.6 versus 6.4. In the Holter analysis, the incidence of both nonsustained polymorphic and monomorphic ventricular tachycardia was similar for both groups.

There was one single reported event of sustained VT in the vernakalant group. However, this rhythm was adjudicated as atrial fib with aberrancy by the events committee. This is the same event that's described as one of the serious cases of ventricular tachycardia as event 22 on page 59 of the FDA briefing document. There was also one instance of Torsades in a phase 2 study. It occurred at 2 to 24 hours. This patient did not convert with vernakalant, was then given ibutilide, and had a few beats of Torsades seen on Holter shortly after.

There were 4 SAEs and one drug discontinuation for vernakalant and one in the placebo group. For all of these events of interest shown above, only the three in VF patients received treatment. Thus, there was no evidence of proarrhythmia. The two VF events, which

occurred after hypotension in patients with reduced myocardial reserve, both of these should not have been enrolled in the clinical trials.

Here are the bradycardia events. There are more in the vernakalant group in our 0 to 2, 2.5 versus 0.2 -- that's the time of vernakalant cardioversion -- and more for placebo at hours 2 to 24 shown in the middle, the time of electrical cardioversion. Sinus arrest or pause, there were 8 in the vernakalant and one in the placebo group. Each one of these occurred at the time of cardioversion, six at the time of vernakalant cardioversion, shown on the left, and the two others in the middle panel, they occurred after electrical cardioversion.

There were two events of third-degree heart block, one after conversion by vernakalant and the second after electrical cardioversion in the 2-to-24 hour period. There was a 1 percent more SAEs or drug discontinuations for bradycardia after vernakalant, and that's shown in the far-right column at 24 hours, 0.4 versus 1.4 percent.

The bottom three rows show treatments for the

events above. First, most of these brady events were self-limiting. One patient got a few seconds of chest compressions and no drugs, atropine was used in two, one other received both atropine, and a pressor for persistent bradycardia. The two pacemaker uses, one was in a post-cardiac surgery patient, and the placebo patient received a permanent pacemaker for continued symptomatic bradycardia. To conclude, bradycardias that occurred with cardioversion were managed with a known sequelae.

Moving on to hypotension, significant hypotension, first, was infrequent. It was often associated with bradycardia at the time of cardioversion or occurred in patients who today would be contraindicated from receiving this drug. The hypotension events recorded from all sources -- AEs, vital signs -- as 0 to 24 hours, far-right columns, are higher for placebo than they are for vernakalant, 9.3 versus 8.1.

On row 2, to hypotension AEs at 0 to 24 hours, shown on the right, 4.3 percent for placebo versus 5.8 percent for vernakalant. Of those 60 AEs of

hypotension, almost all were either not serious, did not receive an intervention, or occurred in patients with conditions which today would be contraindicated. For SAEs and drug discontinuations 0 to 24 hours, the overall rate 0.4 percent for placebo, 1 percent for vernakalant.

Let me provide the details surrounding any patient who received a vasopressor. In the all-patient population, there were three such cases in the vernakalant group. One was a postsurgical patient with 1 minute of asymptomatic hypotension. The two others occurred in patients who would be excluded in the proposed target population. The other SAEs are drug discontinuations that were either transit, received no treatment, or managed by Trendelenburg positioning or saline. There were 27 instances of atrial flutter; three were recorded as SAEs, none in hypotension, no required immediate electric cardioversion.

Next, we looked at the baseline histories and risk factors for hypotension and brady arrhythmias. Here is the risk difference for vernakalant versus placebo for hypotension events for the clinical

baseline histories, which are all listed on the left. There were two factors with a significantly added risk, the history of heart failure on row 2 and the history of structural heart disease on the second to the bottom row. Most of that was driven by heart failure. Although beta blockers appear to be a risk factor, it was not a significant treatment interaction.

These findings are consistent with the nonclinical mechanistic studies, where hypotension was only demonstrated when LV function was severely impaired and the clinical trial observations, in which the few cases of serious hypotension occurred in subjects with either symptomatic or marked reductions in myocardial reserve.

Here are the risk factors for bradycardia. The only variable that stands out on row 3 is valvular heart disease, but again, there was no independent significant treatment interaction. The totality of these analyses was instrumental in identifying a target population for vernakalant. The drug may decrease cardiac output, but there is no hypotension unless there is a marked reduction in myocardial reserve,

preventing a compensatory increase in output.

Hypotension is often related to bradycardias at the time of cardioversion. Serious hypotension can occur without bradycardia in the setting of moderate or severe reductions in myocardial reserve. Therefore, the target population is more restrictive than it was then, and now includes patients with these conditions.

The target population is a subset of the all-patient data, which excludes subjects with those proposed label contraindications. We conducted a post hoc analysis first to determine the events of these three events of interest.

Given the caveats of this analysis and the limitation that the specific variables of moderate and severe left ventricular function were not collected in the clinical trials, we found the following: the target population analysis showed a reduction in events, particularly in those requiring an intervention for hypotension.

Here are the SAEs and drug discontinuations for the three time periods. In the 0 to 2 hours on the left, hypotension occurred in just 6 patients, or 0.9

percent, and the number of receiving an intervention for hypotension is even fewer. The two uses of pressor in this example were the asymptomatic postsurgical patient who received a pressor at the time of cardioversion, and the second was the ACT V patient. All others were managed with typically used interventions, atropine, fluids, and Trendelenburg positioning.

To summarize the findings in the clinical trials, the events of concern have been carefully studied and characterized. Most were self-limiting and happened at the time of cardioversion. There was no evidence of proarrhythmia, bradycardias occurred with cardioversion.

Hypotension, SAEs, and drug discontinuations were associated with identifiable risk factors. Most important, the findings identified a target population with a positive benefit-risk profile. The EU post-approval safety study prospectively tested this target population, and I'll now share those results.

In addition to the SPECTRUM findings, I'll provide an overview of the literature and PV reports

since the drug was approved nine years ago. The primary objective of this safety study called SPECTRUM was to estimate the incidence of clinically significant adverse events, so-called health outcomes of interest, which simply put are SAEs that might require an intervention.

The four HOIs were defined as follows: hypotension requiring a vasopressor; ventricular arrhythmias; sustained VT, Torsades, VF; bradyarrhythmias requiring temporary pacing or any bradycardia SAE; and 1-to-1 atrial flutter. The study also measured the effectiveness of risk minimization activities.

The study was designed to limit bias and provide a reliable estimate of clinically serious events. It included all patients who the treating investigator determined was appropriate for vernakalant, guided by the appropriate label, and the European safety management plan, which included the use of a physician education card and a preinfusion checklist of contraindications. There was extensive site monitoring. Data was captured on electronic CRFs

and was reconciled against hospital records by the site monitors.

Reporting of all SATs was mandatory. Serious adverse events were adjudicated, and to be conservative, both the investigator-reported event as well as the adjudicated event are included in the tables you'll see. The sample size was set at 2000 episodes to provide an upper bound of the 95 percent confidence limit of 1 percent for each of the events of interest.

The study includes a prospective cohort accounting for 79 percent of the episodes, and I'll put most of my emphasis there, and there was a retrospective cohort determined through chart review. The study was conducted with rigorous effort to capture all the outcomes of interest.

The baseline characteristics reflect a much narrower population that was defined by the EU label than that enrolled in the earlier clinical trials. Let's go over the medical history. The average age, 61.9; 3.7 percent with a history of heart failure much lower than the 18 percent in the earlier trials;

structural heart disease in 11.7 percent compared to 40 percent in the earlier studies.

The medium duration of AF was also shorter. Over 40 percent were described as having lone AF, and about 24 percent had first onset AF. About 4 percent were immediate postoperative patients. Beta blockers are the most commonly used rate control medications. Class 1 and class 3 meds had been received in about 5 percent of patients as opposed to 16 percent in the earlier trials.

Now for the events of interest; the all-patient data is shown on the left, and the prospective patients is shown on the right. There were no deaths nor any serious sequelae in any of these 2009 patient treatment episodes. The drug is safe when it is used in the target population.

On the top row, there are 17 patients with 19 HOIs of any kind; overall rate, 0.8 percent; 18 HOIs in the prospective cohort. Two patients had both a bradycardia and a hypotension health outcome of interest. There was a single investigator report of sustained ventricular tachycardia, which the events

committee adjudicated not as VT, but instead as atrial flutter with 1-to-1 conduction.

Next, there were 14 bradycardia events reported in the prospective group. Four of those 14 received atropine. The three pacemaker uses were temporary pacing in two to post-cardiac surgery patients, and the third was a permanent place maker implant a day after treatment in a patient with presumed sick sinus syndrome.

There are only two instances, or 0.1 percent, 1 in 1,000 incidents, of hypotension. Both of those occurred in the setting of bradycardia and are listed as two of the bradycardia events above. Both resolved following atropine treatment. None of them required a pressor. There were two events of atrial flutter with 1-to-1 conduction. One was symptomatic and electrically cardioverted; the second converted quickly to 2-to-1 conduction and was asymptomatic.

The important finding here is that when the drug was used in the target population, there was no serious hypotension, except in association from bradycardia at the time of conversion, and the

management was even not required or was typical of that would be seen in any form of cardioversion.

Next, some additional study findings. The drug was used for approved indications in 99 percent of episodes. Approximately 96 percent of patients had documentation of vital sign measures and rhythm monitoring for 2 hours or more; 69 percent had documented use of the preinfusion checklist. In summary, the EU safety management plan led to use in an inappropriate patient population.

In summary, physicians used the drug in compliance with the labeled target population and selected those patients with a positive benefit-risk profile. They achieved this in a typical practice setting. Serious clinical events were uncommon. Only two had serious hypotension, both with bradycardia and resolved with atropine. There was no Torsades, no cases of ventricular fibrillation. Importantly, all patients with a significant event of interest or SAE recovered, and there were no deaths.

The experience of SPECTRUM is reflected in other postmarketing data. Vernakalant is now marketed

in 25 countries. It's a class 1A recommended treatment for recent onset AF in patients without heart failure in the European guidelines. Independent investigator initiated studies and postmarketing safety now include 12 reported cases of 1-to-1 atrial flutter.

There is no apparent relationship for the number of doses. Half of these patients were symptomatic and were converted with electrical cardioversion. The others reverted spontaneously or were cardioverted later. There have been 199 adverse drug reactions reported, and they're summarized in the briefing document. In the nine years, there have been 6 deaths reported in over 58,000 uses of the drug, each of which occurred in patients with complicated or serious conditions, but I'd like to provide a summary of these for you.

The first patient was a 73-year-old man with a history of coronary surgery and a failed PCI of a vein graft. He was admitted with chest pain and AF. His admissions troponin was 26 and then rose to 400. He received vernakalant on day 2 and converted. He developed hypotension after treatment with his blood

pressure in the 80's, but he didn't receive any treatment at that time. An hour and a half later, he was reevaluated, and again no treatment was given. About 5 hours later, he was treated with diuretics for rales in the chest and shortness of breath, and then the record shows he continued to deteriorate and died 14 hours after cardioversion.

The other five patients are shown here. They all had very complicated conditions, sepsis in three with multiorgan failure, cancer; an open-abdomen patient post Whipple surgery; aortic rupture; stroke. Given these conditions, and the limited reporting, and the timing of the deaths, it's not possible to assign any causality.

In conclusion, safety has been carefully studied and the events thoroughly characterized by multiple assessments. We have identified a target population with a positive benefit-risk profile. It's been tested both retrospectively in the clinical trials and prospectively in the safety study. The post-approval study supports the effectiveness of the risk mitigation measures, and the safety profile of

vernakalant when the drug is used in a typical practice setting.

Thank you for your attention, and I'd now like to introduce Dr. Peter Kowey to speak to the benefit-risk of vernakalant.

Applicant Presentation - Peter Kowey

DR. KOWEY: Thank you, Dr. Weaver.

Peter Kowey again. I just want to spend a very few minutes summarizing many of the points you've already heard and to put them in a clinical perspective from the point of view of somebody who takes care of a lot of patients with atrial arrhythmias, and has been an investigator in this field for quite some time.

I think it's fairly clear from the data that you've seen today, and reviewed in the sponsor's briefing document, that vernakalant administered parenterally has therapeutic advantages. It is clearly effective for the prompt termination of atrial fibrillation, which in turn is associated with relief of symptoms in patients with AF, and as such facilitates subsequent care.

What usually happens today in patients who

come to our emergency departments in the United States and other acute care settings is that they receive drugs administered parenterally and orally to slow the heart rate and to anticoagulate with the need for extensive follow-up.

The strategy that's being put forward today doesn't preclude those strategies or subsequent electrical cardioversion. What prompt parenteral pharmacological conversion provides clinicians in several healthcare settings is another important option to efficiently manage patients who have AF of recent onset. Colleagues around the world have this option available for their patients. We're simply asking you today to recommend to the FDA that American patients have the same advantage.

The clinical trial data that was presented to this committee in 2007 and data that had been accumulated more recently have established that vernakalant has clinically meaningful efficacy for the indication of terminating AF of relatively recent onset, including patients who have postoperative atrial fibrillation. I would emphasize that post-op AF is a

significant problem, where, again, options for prompt reversion are very limited.

As you've seen in the sponsor's presentation and in the FDA briefing document, vernakalant works rapidly in the vicinity of 8 to 14 minutes after administration, and the effect is durable. Sinus rhythm is maintained in over 90 percent of patients at 7 days. The data from SPECTRUM and postmarketing investigator studies are wholly consistent with placebo subtracted rates from the randomized clinical trials.

It's also important to consider vernakalant's performance in the context of what we currently do for our patients. Vernakalant provides an easier and faster alternative when we do choose to convert patients pharmacologically compared to drugs we have available now, including off-label oral class 1C drugs and intravenous amiodarone.

Oral drugs have a clear disadvantage in the emergent setting with delayed time to onset, and as we saw in the AVRO trial, amiodarone may be effective, but the time determination is much longer and less reliable than with vernakalant, and is therefore not practical

in the emergency department or other acute care settings.

One drug, ibutilide, has been approved for this indication of conversion of recent onset atrial fibrillation to sinus rhythm by the FDA. Ibutilide is an IV drug that gained approval despite modest efficacy at a high rate of ventricular proarrhythmia, as well as the need for prolonged and intensive monitoring, 4 hours after dosing, all of which seriously limits its use in the United States. Keep in mind that oral dofetilide is also approved for AF conversion but is not used in the acute care setting.

How does vernakalant fit in with electrical conversion, the most popular way of terminating atrial fibrillation in the United States? Electrical conversion is very effective when carried out by experienced operators in appropriate settings. We expect immediate conversion rates in excess of 70 to 80 percent when properly performed. It is a terrific procedure, but electrical conversion has issues, as I've listed on this slide.

First of all, as the FDA briefing document

points out, there is a significant incidence of pulmonary edema, hypotension, ventricular fibrillation, asytole and bradycardia after electrical conversion. Electrical conversion can't be applied for many logistical reasons, including the need for anesthesia.

It is expensive, and many patients are anxious about having their heart shocked with paddles, as well they should be, since inexperienced operators may not provide adequate anesthesia or may not prepare the electrodes properly, which causes skin burns. And I see patients in consultation who flatly refuse to have another cardioversion because of trauma with electrical cardioversion that they suffered elsewhere.

One of its most frustrating limitations, both for doctors and hospitals, is the relatively high rate of immediate or early recurrence of atrial fibrillation, especially when patients haven't been treated with an antiarrhythmic drug like vernakalant prior to cardioversion.

But the most critical issue for the committee today is not efficacy. The FDA agrees that vernakalant is effective. It was safety concerns that led to the

non-approval of the drug in 2008, and a reasonable recommendation from the FDA for a larger data set. The sponsor's accumulated more data in SPECTRUM and other sources that are highly consistent with what was seen in the original experience.

More importantly, as Dr. Weaver has said repetitively, we have learned that patient selection is by far the most important issue in preserving patient safety. The FDA has criticized SPECTRUM because of a patient selection bias. Patients were selected carefully for IV vernakalant administration in SPECTRUM, and we believe that's the reason for the good safety profile.

I would also point out that this drug will be administered in hospital areas, where careful patient monitoring is routine and highly effective. A comprehensive educational program for healthcare providers, who either administer the drug or monitor the patients after the drug has been infused, will be critically important, and the message will be familiar to physicians. Safety is the principle that guides the selection and use of every single antiarrhythmic drug

in clinical practice. Vernakalant will be absolutely no different.

As I said, the FDA has criticized SPECTRUM and these safety data obtained in the real-world clinical practice settings, but they're highly consistent to what they observed in the clinical trial database. Here, I've listed those four adverse events of special interest that you heard about: ventricular arrhythmia, bradycardia, hypotension, and atrial flutter. And as you can see, in each of these categories, the incidence in SPECTRUM was replicative, and because of the larger number of patient studied, and the confidence intervals, thus, the reliability of these observations has improved.

After carefully considering the efficacy and safety of vernakalant across several studies, I think we can come to a reliable benefit-risk calculus. Efficacy is consistent and assured, and with careful patient selection, we can limit the chances of important cardiac adverse events.

After a painstaking review of individual cases, as you heard from Dr. Weaver, we can state with

confidence that dire outcomes and deaths seen in the early clinical trial program after IV vernakalant administration occurred in patients, who with proposed labeling will not receive the drug today, I believe we can protect patients with appropriate labeling and tools for the physician, such as checklists and education to ensure appropriate use of this new antiarrhythmic agent in a variety of acute care settings.

I hope the committee will agree that we have on the table today an opportunity to provide U.S. patients with an established, safe, and highly effective method for stopping AF of recent onset. Thank you for your time. I'll now turn the podium over to Dr. Mark Corrigan, who will conclude our presentation.

Applicant Presentation - Mark Corrigan

DR. CORRIGAN: As we come to the end of our presentation, I'd like to provide a short summary. Atrial fibrillation is a common and increasingly prevalent problem, which has a significant impact on patient health, quality of life, and is a significant

drain on healthcare resources in our country. Pharmacologic conversion is an important and recommended treatment option in the appropriate clinical situation.

There are patients who cannot tolerate or would like an alternative choice to ECV, and there is a medical need for another treatment option. Vernakalant offers that choice. In clinical studies, the efficacy has been clearly and consistently demonstrated. The safety profile has been thoroughly characterized in real-world patient population. This is a well-defined, appropriate population with a favorable benefit-risk profile.

We've developed appropriate guidance for the use of vernakalant in a controlled medical environment. We've taken the FDA discussions and input from our clinical advisors to heart. We're committed to the robust risk mitigation measures beyond labeled indication and checklists. We'll work with the agency to include education programs and risk management elements that will be useful to U.S. physicians in order to ensure vernakalant is used in the right

patients. We look forward to your thoughtful discussion here today. Thank you.

Clarifying Questions

DR. LEWIS: That concludes the sponsor's presentation. We will now begin clarifying questions.

Are there any clarifying questions for Correvio International Sarl? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. Also, please indicate to Yinghua or myself that you want to ask a question, and we will acknowledge you in the order that we see you indicate it.

I'm going to use the chair's privilege to ask two quick questions that I think you might need to get data for.

Dr. Tershakovec, several times in Dr. Kowey's presentation, there was an implication that the long-term 7-day efficacy of sinus rhythm with vernakalant was outstanding and that ECV didn't always have sustained sinus rhythm. I think the appropriate comparison would be the placebo ECV group who conversed to sinus rhythm, and what happens to them at 7 days,

versus the vernakalant group that converted to sinus rhythm in 7 days, rather than the general population ECV data.

My second question, which I think goes to Dr. Corrigan, 58,000 people since 2010 have received this drug. Again, the presenters have implied that ibutilide has been used sparingly in the United States, with the implication that that suggests a physician's sense of comfort or benefit-risk, perhaps hypothetically, with the drug.

Do you have any information on the population of patients over these last nine years that could have received vernakalant in the approved countries versus the 58,000 patients who did?

Thank you. Then we're open for questions from the -- I don't know if you have the answers to those or you're going to need to --

DR. TERSHAKOVEC: I can tell you in the patients who converted in the primary endpoint period, in the placebo group, most of those were still in sinus rhythm out to 7 days. There is a compounding of the people who were in the placebo group that then got

other therapies and those who didn't convert. But I can work on getting that information for you. I think that's the second question that you wanted.

Dr. Corrigan, if you'd answer.

DR. CORRIGAN: Thank you. I'm going to have to ask you if you could clarify that question. I'm not quite sure I got it, on the number of patients who could have been treated with ibutilide; is that --

DR. LEWIS: No, no, no. I'm sorry. Since 2010, you've been approved, and 58,000 people have received it, roughly.

DR. CORRIGAN: Right.

DR. LEWIS: Do you have any concept of how many patients, in that time period, in the approved countries, could have received vernakalant; like they would have met the criteria, but the physicians did or didn't use it? Like, I don't know if 58,000 is they're using it in 90 percent of the indicated population or 10 percent of the indicated population.

DR. CORRIGAN: I'm not sure that we have that data, but if you give us a little time, we'll see if we can find something.

DR. LEWIS: Thank you.

DR. TERSHAKOVEC: Actually, I'll ask Dr. Camm to come up, who can maybe describe kind of the treatment paradigms in the EU and the choices that physicians are making.

DR. CAMM: Good morning. My name is John Camm, and I'm a cardiologist and cardiac rhythm doctor in London, in the United Kingdom. Today, I'm working as a paid consultant for Correvio.

In the United Kingdom and in Europe as a whole, we have a wide choice of agents available for pharmacological cardioversion of atrial fibrillation. Some of these are applied intravenously; for example, we have IV flecainide, IV propafenone, and in some countries IV sotalol, IV amiodarone, IV ibutilide, and IV vernakalant. In addition, of course, we can use oral application of drugs for pharmacological cardioversion.

I suspect that the 58,000 patients that received vernakalant was a relatively small proportion of patients who theoretically might have been able to take this drug, but I think it's the calculation, which

is very difficult to make.

DR. LEWIS: Fair enough. Thank you very much, Dr. Camm.

Dr. Alexander?

DR. ALEXANDER: Yes. Thank you. John Alexander from Duke. I have a couple questions -- maybe the first is for Dr. Kowey -- about post-cardiac surgery patients and their atrial fibrillation. Maybe you could talk a little bit about how much of that resolves spontaneously. How much of it is treated and actually has implications on their length of stay?

DR. KOWEY: Peter Kowey again. Great question. You know, Dr. Alexander, you see these patients all the time on the clinical wards, kind of the bane of our existence. Many of these patients have spontaneous reversion. As you saw, as a signal of that, the placebo group the ACT II study actually had a higher placebo conversion rate than any of the other studies that we did. IT was 14 or 15 percent, which is exactly what you're saying.

A lot of the AF is very short duration. So

obviously, they weren't candidates for this study if they didn't have atrial fibrillation at least of a couple of hours duration, because a lot of those people spontaneous -- you can't even get them signed up for the study.

The patients that we're concerned about are the patients who go on longer. And as you also know, telling a surgeon that you're going to come in and do an electrical conversion on one of their fresh post-op patients makes their hair stand on end, so we're always looking for alternatives. And frankly, the alternative in our hospital is IV amio; I mean, that's the default that patients get in the hospital when they have AF that they can't stop any other way. This, again, would just supply us with another way of doing it.

I want to get back to your question, Dr. Lewis, about what happened to patients who got electrically converted. There actually was a higher recurrence rate in that population -- and we can get the numbers for you -- than there were in the vernakalant group. But remember, if you got vernakalant and you converted, you weren't allowed to

get anything else for that time period, until the end of their observation period at 24 hours. If you got electrically converted and reverted, you could get another electrical conversion or you could get antiarrhythmic drugs.

So the population was contaminated. It's very hard to make the direct comparison between the two groups, but we might be able to get the numbers for you at the break.

DR. ALEXANDER: I just had one other question -- again, John Alexander from Duke -- and this is really about the trial populations. It looked to me -- the age looks to me young for AFib, and I presume that's because most of this is new AFib. And I had a question about how anticoagulation and transesophogeal echocardiography was handled in patients who had some of those longer durations of AFib before they were enrolled in the trial.

Obviously, part of the benefits that you've laid out require assuming that you don't have to do any of those other things in somebody you convert with vernakalant.

DR. TERSHAKOVEC: I can ask Dr. Weaver to address the use of some of that ancillary assessment in the trials and in the eventual use of vernakalant.

DR. WEAVER: Your first assumption is the right one in that the population of patients with persistent and permanent, they're not in these trials. That's part of the reason the age is so much younger than what you and I might see in our clinics. The use of transesophogeal echocardiography wasn't recorded in the trials, but many of these were done even before that became a focus, I think.

I don't know the distribution overall, how many were admitted within 48 hours versus 7 days. I do know that the majority of them were admitted in the first half of that 7-day period, but the data, that we have lumped them from a statistical analysis to show that there was benefit up to 7 days.

DR. LEWIS: Dr. Packer?

DR. PACKER: Could I ask the sponsor for two slides, if I could? Could you put up your proposed checklist? Then while we're discussing it, could you prepare the slide of your figure 4 in your briefing

document? It is on page 66.

DR. TERSHAKOVEC: Slide up. This is the checklist that was used to support the study and modify it for draft for the U U.S..

DR. PACKER: Sure. Can I just ask a couple questions from a heart failure point of view? It says, "Does the patient have severe heart failure?" Is that different than moderate heart failure? Is that different than mild heart failure?

DR. TERSHAKOVEC: Well, you can see in parentheses it's giving some explanatory to define. I mean, obviously, there's a judgment that the physician --

DR. PACKER: So a class 2 heart failure would be okay?

DR. TERSHAKOVEC: As per this definition, yes, but it was also broadened. The addition of the known moderate or severe left ventricular dysfunction has been brought in because of the potential that the New York Association classes may not always identify subjects with --

DR. PACKER: Class 2 heart failure with a 40

percent ejection fraction would be okay?

DR. TERSHAKOVEC: I'll ask Dr. Weaver to come up. If you want to ask specific questions about those, there's not an ejection fraction for specific criteria.

DR. PACKER: I'm asking you because this is your checklist.

DR. TERSHAKOVEC: I understand, and I'll ask Dr. Weaver to come up and address your questions.

DR. WEAVER: In the earlier clinical trials, the exclusion criteria were just class 3, class 4, or uncompensated heart failure. In the European study, post-approval study, they were class 3, class 4 heart failure or uncompensated. We've suggested in the U.S. that this be broadened, so that if a physician had any concern about the underlying left ventricular function in these patients, and had evidence or wanted to obtain evidence, that those patients would also be excluded that have significant reductions in LP function.

DR. PACKER: I just wanted to know, class 2 ejection fraction 40 percent, does it make this checklist?

DR. WEAVER: I would say class 2 LV 40

percent, the patient would likely be treated.

DR. PACKER: Then can you put up your slide for figure 4, for page 66.

DR. TERSHAKOVEC: Slide up.

DR. PACKER: This is interesting because you display these data in your briefing document. These are the pooled data from ACT I, II, and III. There are two baseline variables that are interesting because this is not a plot of safety; this is a plot of efficacy. The two that are interesting, one is age; elderly patients didn't respond as well. But the other one that's sort of interesting is history of heart failure, which did not respond as well.

When you did this analysis, did you include all people with heart failure?

DR. TERSHAKOVEC: These are thoughtful analyses from those pooled pivotal data, ACT I and ACT III>

DR. PACKER: Did you include everyone with heart failure?

DR. TERSHAKOVEC: Yes, they were full data. There were no exclusions. This is the ACT I and

ACT III pooled data.

DR. PACKER: You included class 2 patients?

DR. TERSHAKOVEC: Yes.

DR. PACKER: Okay, the patients with ejection fractions of 40 percent?

DR. TERSHAKOVEC: We did not have full ejection fraction information for all the subjects. These are the ACT I and ACT III pooled data.

DR. PACKER: I guess what I'm trying to -- could you maybe put up your slide CS-20. This is exactly the same kind of data -- it's sort of not exactly the same. This is all phase 3, but this is safety, not efficacy. The point that's of interest is heart failure. There's a striking difference in risk of hypotension if you have heart failure or not.

When you put heart failure into this analysis was class 2 included in the heart failure?

DR. TERSHAKOVEC: Dr. Weaver?

DR. WEAVER: No. This was either -- they had to have class 3 or class 4 heart failure, or an ejection fraction in the record of less than 40 percent.

DR. PACKER: No, no, no. That can't be that. That can't be, Doug, because you have a patient from ACT V, which is patient 25811197, who had no history of heart failure and had an ejection fraction of 44 percent, who had profound hypotension --

DR. WEAVER: Right.

DR. PACKER: -- and died.

DR. WEAVER: He would not be in that heart failure group.

DR. PACKER: He would not be in that heart failure group.

DR. WEAVER: Not, because we retrospectively put it there.

DR. PACKER: The point, that patient would be listed here as no heart failure?

DR. WEAVER: He did not meet the criteria of having, in his medical record, class 3, class 4, or an EF of less than 40 percent.

DR. PACKER: Can you make sure that that's right because your point estimate for heart failure here, for a risk ratio, is 10, and your hypotensive episodes, in all of the phase 3 trials, you had like

6-7 hypotensive episodes. If you had one patient with hypotension who died, you included that patient in the no heart failure group?

DR. WEAVER: That's correct. Do I agree with that? I would like to have him in there, but we couldn't do it.

DR. PACKER: I was sure hoping that you were going to say you included them because now you have a patient who has hypotension, who had an ejection fraction of 44, which subsequently was 25, who didn't have a history of heart failure but actually did have heart failure --

DR. WEAVER: Correct.

DR. PACKER: -- and your checklist wouldn't have worked.

DR. WEAVER: The checklist, because he did have moderate systolic dysfunction described by the investigator, he would be picked up today.

DR. PACKER: No. His ejection fraction was 44 percent. Does that count or it doesn't? Because I asked you whether 40 percent was in or out.

DR. WEAVER: Different. So for the checklist,

it does not specify at a specific ejection fraction. It only specifies uncompensated, or class 3 or 4 heart failure, or evidence of moderate systolic dysfunction.

DR. PACKER: So your checklist doesn't work?

DR. WEAVER: It would work. It would work.

DR. PACKER: Would that patient have received the drug according to your checklist?

DR. WEAVER: Not today.

DR. PACKER: In what way would that patient have violated your checklist?

DR. WEAVER: Because the physician did have evidence that he did have moderate systolic function.

DR. PACKER: I know; 44 percent, Doug. You said 40 percent was okay.

DR. WEAVER: So different. This patient had atrial fibrillation at a rate of 150 beats per minute. Most of us would have difficulty in assigning an exact percent of ejection fraction, and therefore, in order to narrow that population further, we included terms like "any evidence," looking at that overall echocardiogram and there was moderate or severe systolic dysfunction, they should not be included.

DR. PACKER: Let me try -- would it be fair to say that you would exclude this patient if there were any evidence of heart failure or any evidence of left ventricular systolic function?

DR. WEAVER: Yes, I would because --

DR. PACKER: But that's not what your checklist says.

DR. WEAVER: But this patient was misclassified as well by that treating physician. He had dyspnea, orthopnea. He was limited. He did have heart failure. And why he was included is totally unclear to me. Why he was not thought to be drug related is unclear to me.

DR. TERSHAKOVEC: Dr. Packer, if I could just say that any patient that presents with A fibrillation, the treating physician should do a full assessment. And if there are concerns, based upon their history or physical, about heart failure or any of the contraindications, then they should be further assessed.

DR. PACKER: Okay. That sounds like a wonderful thing that all physicians -- you're telling

me that all physicians should be good physicians. I agree with you. I just want to understand whether your checklist matches your data, and how your checklist gets operationalized in the real world. In SPECTRUM, you excluded people -- 5 percent of your people in SPECTRUM had heart failure.

DR. TERSHAKOVEC: The SPECTRUM data reflect the patients that were enrolled based upon guidance from the label and use of the checklist. If there are suggestions --

DR. PACKER: I'm just going to ask one last question. The European guidance that you say provides a 1A recommendation, do they exclude all heart failure or heart failure according to your checklist?

DR. TERSHAKOVEC: I can ask Dr. Camm to talk about the European guidance.

DR. CAMM: The European Society of Cardiology guidelines specifically says, with regard to the 1A recommendation, that patients have no or minimal heart disease. And for patients who have heart failure with a reduced ejection fraction or preserved ejection fraction, it's specified as class 3 or class 4 heart

failure, and the recommendation there is to 2B.

DR. PACKER: I'm sorry, John. I just wanted to clarify it's okay for a patient with an ejection fraction of 40 percent and class 2 symptoms to receive this drug as a 1A?

DR. CAMM: There's no specification related to ejection fraction in the ESC guideline.

DR. LEWIS: Thank you, Dr. Camm.

Dr. Ridker? And I want to remind the committee these are clarifying questions.

DR. RIDKER: Yes. I'm going to try to get a clarification on SPECTRUM, but it comes back to the issue of your checklist, actually. I'm an echocardiographer. That may be a problem for you today because I'm struggling here. I accept the biology here that the drug's fundamental way of causing the hypotension bradycardia is reduced cardiac output. So the clarifying question is simply, wasn't echo required in SPECTRUM? That's the question, and then can we go back to the checklist after that?

DR. TERSHAKOVEC: No, an echo was not required for SPECTRUM.

DR. RIDKER: Okay. So if we can go to the checklist for a second.

DR. TERSHAKOVEC: Slide up.

DR. RIDKER: Dr. Packer has already asked questions about the severity of heart failure. I'd like to go to severity of -- what is clinically significant aortic stenosis?

DR. TERSHAKOVEC: I can ask Dr. Weaver, again, to describe those.

DR. WEAVER: It was by the physician's note, Dr. Ridker. It was not specifying any particular gradient in these patients,

DR. RIDKER: But a patient has died on the drug who had critical AS, and I have to assume the doctor either knew it or didn't know. It's hard to know.

DR. WEAVER: No, he did know. He did know.

DR. RIDKER: And many patients presenting with AFib may well have underlying structural heart disease. So will you as a physician recommend they all get an echo before they get this drug?

DR. WEAVER: The data that we have does not

suggest that that it's necessary. And I say that -- first of all, only 15 percent of those patients in that post-approval study had echocardiographic findings. So by history, by clinical presentation, and by known past medical histories in these patients, we found that those physicians chose a target population with a very low risk of any severe event.

DR. RIDKER: Yes. But Dr. Weaver, that's part of my problem. So can we go to CS-28, then, which is I think what you just described, which was the baseline characteristics suspected.

Can I keep this clarifying? We're going to have a robust discussion later, I'm sure, about SPECTRUM, in general, after the FDA presentation. But 28, without echos, how do I know that only 15 percent have valvular heart disease and only 11 percent have structural heart disease without an echo? That's just a clinical guess; is that the point?

DR. WEAVER: It would be clinical history, so it could be underlying ischemic heart disease, and the physician said the patient has structural heart disease. It could be valvular heart disease. Any kind

of valvular heart disease, they were put in that category. I suspect many patients with heart failure were put into that category, but it was the physician's determination.

DR. RIDKER: Last, let me just ask it clinically, then. Would you want to get an echo before you gave this drug, from a clinical perspective?

DR. WEAVER: From the data that I see, no. When I see that 2,000 patients were selected without that, using the medical history and using symptoms and signs, I couldn't find evidence that it would be necessary. I would use your judgment, though. I think the physician should use judgment; any questions, no prior clinical history, then I'm not sure it's necessary in all patients.

DR. LEWIS: Thank you, Dr. Weaver.

Dr. Moliterno?

DR. MOLITERNO: Thank you. David Moliterno. Some of this may be on the briefing material, and I missed it. Could you briefly say what the demographics were in SPECTRUM? I think on your clinical trials, you had 3 percent were non-Caucasian. As you know in the

United States, we have about 5-fold or more non-Caucasians. So can you tell us the racial breakdown? Do you have data on people of African or Asian ancestry descent?

DR. TERSHAKOVEC: These are the demographics for SPECTRUM. Slide up. It is a predominantly white population, yes.

DR. MOLITERNO: So 97 percent. Could you continue with SPECTRUM and tell us how many received 1 dose versus 2 doses of the drug?

DR. TERSHAKOVEC: I know in the clinical trials, it's about 40 percent.

DR. MOLITERNO: And my recollection is one of the biggest reasons not to get a second dose was because for hypotension or concern for impending hypotension. So I think it would be important to know what percentage of patients only received one dose in SPECTRUM.

DR. TERSHAKOVEC: We will get that information for you. I can tell you, actually, the primary reason for getting only one dose is conversion. It's about 90 percent of the subjects.

DR. MOLITERNO: Maybe the last question for me. Just to clarify, I think there was mention of no deaths, Dr. Weaver, among 2,000 patients. What was the duration or what was the time of follow-up? I'm extremely impressed that 2,000 cardiac patients, nobody died.

DR. TERSHAKOVEC: The follow-up was 24 hours or at the time of discharge, and any other events would have been reporting by postmarketing assessments. There were two events that reported in that system, but no deaths that were reported.

DR. LEWIS: Thank you. Dr. Gibson?

DR, GIBSON: Great. Thank you. I think you've shown some compelling efficacy data. Obviously, when you have that kind of efficacy data, you don't need a very large study to demonstrate that you have efficacy. They're very well powered. But this is a group of agents in a setting where there are some very real safety concerns.

So my question for you is what were the considerations in planning the initial studies with respect to statistical power? Which is, by the way, a

prospective construct. We can't look retrospectively. So how well powered were you to identify some of these fatal or catastrophic events in the initial studies, and then knowing some of these issues, when you went to do SPECTRUM -- which really isn't a trial.

But do you have any information about your ability to make inferences about safety based upon prospective assessments of statistical power, looking at these fatal catastrophic events?

DR. TERSHAKOVEC: Yes, I can ask Dr. Rajicic to address your power questions.

DR. RAJICIC: Good morning. Natasha Rajicic, biostatistician, paid consultant to Correvio. I hold no financial interest in the outcome of this meeting.

As you said, in the clinical trials, they were powered primarily for the primary endpoint of the efficacy, and for most studies, consider about 25 percent difference between placebo and vernakalant for the efficacy endpoint.

The SPECTRUM, the large --

DR. GIBSON: But was there consideration of safety endpoints, and was there any estimation of event

rates, and was there any power calculation to exclude harm or to protect yourself against potential type 1 error. So what were the considerations with respect to safety?

DR. RAJICIC: Not in clinical trials, but there was in SPECTRUM. The SPECTRUM was designed around those considerations

Slide up. The sample size for SPECTRUM -- the consideration for sample size in SPECTRUM were around the expected proportion of these events, and then a range of sample sizes were considered with the evaluation of potential precision around those point estimates. The point estimates that were considered in the first column were based on HOI incidence in the pooled phase 2 clinical trials, and you can see the range is there in the first column.

DR. GIBSON: And what did you expect in terms of expected probability and the actual observed probability? Was it much lower than that, which then eroded your power?

DR. RAJICIC: To clearly specify that it was not in terms of power, but it was in terms of the

expected precision around the point estimates; so the width of the confidence interval. The protocol states that, for example, for the expected proportional 0.6, so 0.006 there, with the planned sample size of 2,000, the upper confidence bound would be 1 percent.

DR. GIBSON: I didn't see on slide 20-21, any p for the interaction testing. It would be helpful for us to put some of those findings in context if there were some interaction p-values.

DR. RAJICIC: Oh, in the slide with the forest plot?

DR. GIBSON: The forest plots.

DR. RAJICIC: Yes. Dr. Weaver did point out, but we can also put the actual numbers, yes.

DR. GIBSON: Great. And the final question, the checklist was used in only 69 percent of patients; is that correct?

DR. TERSHAKOVEC: Yes, with 60 something percent in the treatment episodes, yes.

DR. GIBSON: How successful do you think that is? Why was it only used in that many patients? That seems quite low.

DR. TERSHAKOVEC: I can ask Dr. Ritz to come up and talk about the experience with the checklist.

DR. RITZ: I am Beate Ritz, medical information at Correvio. The checklist was used in 68 percent of patients, and essentially, the label broke down in an accessible format to have a practical tool for the patients and physicians. It was used specifically in the settings where the physician had a more -- in the emergency department where the constraints of treatment are more difficult.

So there, 90 percent of patients got the checklist used. We do see also in smaller hospitals more use than in large hospitals, which have better treatment protocols. We do see also, over the conduct of the study, that when these additional risk mitigation measures were introduced, the incidence of severe events went down.

DR. GIBSON: So the events went down if the checklist was used; is that what I'm hearing?

DR. RITZ: Yes.

DR. GIBSON: But it was only used in 69 percent of patients. Okay. Thanks.

DR. LEWIS: I think we'll take time for one more question. Dr. Floyd?

DR. FLOYD: I have several. Should I wait till after the break?

DR. LEWIS: I think that's a good plan.

We will take just a 10-minute break instead of a 15. It's 10:10. We'll be back here at 10:20. Thank you.

(Whereupon, at 10:10 a.m., a recess was taken.)

DR. LEWIS: I think that we're going to proceed with the FDA presentation. Then some of our clarifying questions, we have kept the list of those of you who we didn't get to and may be addressed by the FDA presentation, or we'll ask those questions to the sponsor during the clarifying questions for the FDA. We will now proceed with the FDA presentation.

FDA Presentation - Preston Dunnmon

DR. DUNNMON: Thank you very much, Dr. Lewis, committee members and guests, ladies and gentlemen. I'm Preston Dunnmon from the Division of Cardiovascular and Renal Products and the clinical reviewer for this

resubmission of NDA 22034.

For this presentation, I will take you through a brief overview of the long regulatory history of this drug. We will then examine the question, what is vernakalant, based on its channel-blocking profile, its in vivo effects on left ventricular function, and its effects on the QRS duration in human studies.

I'll then show you the elements of the safety data from the clinical trials that continue to be concerning to the review division and address whether the single-arm observational SPECTRUM safety registry ameliorates these concerns.

We will examine the preinfusion checklist to determine if it can reliably identify subjects at risk for cardiovascular serious outcome events, focusing particularly on vernakalant-induced severe hypotension and cardiogenic shock, and then separately consider whether this infusion checklist can realistically be operationalized.

Next, our colleagues from the Office of Surveillance and Epidemiology will present data on the safety profiles of alternatives for the rapid

conversion of atrial fibrillation. And finally, I will conclude with our overall assessment regarding the safety profile of vernakalant.

In 2006, the original NDA 22034 was submitted based on 375 treated subjects. Among them, 8 serious adverse events related to hypotension, arrhythmias, and sinus pauses occurred within 2 hours of vernakalant infusion. One of these 8 subjects died. While accepting the efficacy of vernakalant for the rapid conversion of atrial fibrillation to sinus rhythm, questions about vernakalant's safety profile resulted in the agency issuing an approvable letter in 2008.

In that 2008 approvable letter, FDA stated that the serious cardiovascular adverse events suggest a level of risk of vernakalant use that seems excessive in light of its benefits compared to no treatment or electrical cardioversion.

So we requested an additional, larger, randomized, double-blind study in atrial fibrillation patients with entry criteria that would lead to a less than 1 percent cumulative risk of all serious cardiovascular adverse events within the first 2 hours

following the initiation of treatment.

It was and remains our opinion that the rapid conversion of atrial fibrillation to sinus rhythm in the sponsor's target patient population should not result in non-embolic death. And I'd like to clarify that we're interested in the period of 0 to 2 hours because after that time period, other drugs could have been administered, and the safety does not specifically reflect vernakalant's safety profile.

In 2009, ACT V was initiated to address our request for more data. The planned enrollment was 474 patients enrolled with 2-to-1 randomization. However, in 2010, enrollment in ACT V was halted prematurely after 217 patients were enrolled because of several episodes of hypotension requiring CPR after vernakalant administration.

In the last of these cases, cardiogenic shock occurred in the absence of bradycardia, and indeed pulseless electrical activity was confirmed, both by bedside EKG and echocardiography done simultaneously during the drug-induced arrest. This patient never regained consciousness and subsequently died.

Consequently, the IND for IV vernakalant was placed on full clinical hold in 2010 for unreasonable and significant risk of illness or injury to human subjects. In the 2014 to 2016 time frame, the sponsor's attempts to change the dose and speed of vernakalant administration in canine studies that we requested failed to identify a new dosing strategy that would be effective without causing negative inotropic effects.

NDA 22034 is now resubmitted with additional safety information, including some additional clinical trial data that were collected after the original 2008 submission, and SPECTRUM, a large single-arm, uncontrolled, postmarket safety study performed following vernakalant's approval in Europe.

So let's begin with the all important question. What is for vernakalant? Here on this slide, you can see the applicant's perspective on this question from statements taken from various documents supporting this NDA submission. Vernakalant IV, an atrial selective ion channel blocker, has a differing mechanism of action that mitigates some of the main

safety concerns of other antiarrhythmic treatments.

Vernakalant is a multichannel blocker of certain potassium channels and a typical class 3 antiarrhythmic. Brinavess is an antiarrhythmic drug that acts preferentially in the atria by prolonging atrial refractoriness and slowing impulse conduction in a rate-dependent fashion. Because of its atrial preferential actions, vernakalant does not readily fit in the Vaughan-Williams antiarrhythmic drug classification, which is based on ventricular activity.

To evaluate these claims, FDA began our task of comprehensively reviewing vernakalant safety profile with a contemporary evaluation of the ion channels that vernakalant actually blocks. What you see here are the IC50 values for vernakalant's blocking activity of multiple channel currents expressed in micromolar values. The information on this table was extracted from the sponsor's voltage clamping study results, showing me the lowest IC50 value for each current.

There are several things we would like you to notice on this slide. First, all of the listed currents care blocked at therapeutic vernakalant

concentrations. Second, IC50 values that are not different from each other by 3 to 5 fold are generally considered to be not different in these kinds of studies. Therefore, all of the listed channels you see here are blocked, but with indistinguishable potency by vernakalant.

Third, the channels rendered here in blue are all expressed in the ventricles, as well as the atria. The two channels rendered in black to your right are expressed only in the atrium.

Finally, it is important for you to see and for you to understand specifically that vernakalant blocks the peak sodium current, here circled in red, to an equal degree that it blocks the channels that are atrial specific, IKur and IKAch. So from our perspective and from a safety evaluation perspective, vernakalant is in fact a potent sodium channel blocker, making it a Vaughan-Williams class 1 antiarrhythmic drug.

To further assess vernakalant's channel current blocking profile, we compared its ion channel blocking characteristics with flecainide, which is a

known potent Vaughan-Williams class 1C sodium channel blocker. The checks here on the top row, the top being vernakalant, represent the data that I showed you on the previous IC50 slide, that vernakalant has an inhibitory effect, activity, on all of the listed channels.

For comparison, we then extracted IC50 data for flecainide's channel-blocking profile from the listed literature sources that you see at the bottom of the slide, and found that flecainide, indeed, blocks all of these same channels with similar potency as vernakalant, including the atrial channels IKur and IKAch.

By their nature, ventricular sodium channel blockers, all Vaughn-Williams class 1 drugs can prolong the QRS, and they can be important negative inotropes. In addition, class 1 antiarrhythmic drugs can be divided into three subclasses, depending on the rapidity with which they dissociate from the sodium channel.

Class 1A drugs like procainamide demonstrate intermediate dissociation kinetics with dissociation

constants of 1 to 10 seconds. Vaughan-Williams class 1B drugs like mexiletine demonstrate fast kinetics with a dissociation constant less than 1 second. At the other extreme, 1C drugs like flecainide demonstrate slow dissociation kinetics from the sodium channel, with dissociation constance exceeding 10 seconds.

To determine which class 1 subclass vernakalant belongs in, the applicant calculated sodium channel dissociation constants for a mixture of vernakalant and its diastereomers using several methodologies. All of these diastereomers demonstrated similar binding potency to the sodium channel, and this diastereomeric mixture demonstrated first-order dissociation kinetics, supporting the idea that all of the diastereomers were dissociating in the same manner.

Indeed, using the methodology that FDA thinks was the most accurate, the dissociation constant for vernakalant and its diastereomers was calculated to be 49.4, strongly suggesting that vernakalant, like flecainide, is a Vaughn-Williams class 1C antiarrhythmic drug.

The sponsor subsequently undertook two studies

at our division's request to shed light on vernakalant's affects on left ventricular systolic function and electrophysiology in an animal model. The figure you see on this slide are the results of a ventricular contractility study in normal dogs. Contractility was assessed as dp/dt, which measures how fast the ventricle can generate pressure as it contracts.

This is expressed here in change from baseline. On the Y-axis, dp/dt worsens as you descend from the zero marker at the top of the Y-axis until you get to the bottom of the Y-axis, where it meets the X-axis at the minus 35 percent marker. In this figure, vernakalant depicted by the solid blue line causes a decrease in contractility in the these animals that is equal in magnitude to the negative change caused by IV flecainide, depicted here in the broken orange line. However, two additional concerning observations were made from this study.

First, vernakalant's negative effect on dp/dt did not recover during the 90-minute post-infusion observation period, whereas the effect of flecainide

recovered to nearly baseline. Second, from the table at the bottom of this slide, circled in red, notice that the mean vernakalant concentration in these dogs was 1800 nanograms per mL. This is less than half the peak vernakalant therapeutic concentration of 4300 nanograms per mL that is noted in human subjects.

Furthermore, during the two dog studies that assessed vernakalant's effects on ventricular performance, two out of the 19 dogs included in these studies died. In the first death case, 1 of 6 dogs administered vernakalant, after at least 3 weeks of rapid ventricular pacing, died on study.

This dog's QRS widen significantly, and the infusion was stopped due to animal distress. Within one minute, the animal's blood pressure, pulse, and cardiac output dropped rapidly and became unstable. After another drop in blood pressure and pulse, the animal could not be recovered and died. A detailed review of the EKGs during this study revealed that no atrial or ventricular arrhythmias proceeded the first drop in blood pressure and heart rate in this animal.

In the second fatal case that occurred, in the

dog contractility study that I just showed you on the prior slide, the sponsor had planned to assess the inotropic effects of vernakalant versus flecainide in the dp/dt stud in dogs, following 1 week of rapid atrial pacing, to simulate the human circumstance of atrial fibrillation with a rapid ventricular response of 1 week's duration. However, the only dog that received IV vernakalant after 1 week of rapid atrial pacing was found dead in its cage within 2 hours of vernakalant administration. The sponsor therefore abandoned the 1-week period of rapid atrial pacing, completing this dp/dt study in healthy young dogs in sinus rhythm.

Finally, to further confirm vernakalant's sodium channel blocking activity in human ventricles, FDA examined the QRS duration changes from baseline by cumulative distribution function analysis from the integrated clinical trial ECG data. In this figure that you see, the changes from baseline QRS duration for placebo subjects is represented in the dark blue line all the way to the left, that is just right around zero for most of its heighth.

Changes from QRS baseline for vernakalant-treated subjects are stratified by the number of doses they received and whether they converted or did not convert in the curves to the right of that placebo curve. Note that vernakalant prolonged the QRS duration relative to placebo in all its strata. The red stratum that shifts dramatically represents a group of patients, their experience, longer QRS durations, and a higher rate of serious adverse events in general.

I will more completely describe the findings in this group in a future slide, but I wanted you to notice that given the 50 millisecond increments that you see on the X-axis of this figure, some of the QRS prolongations in this group are large and some of them were very large.

It also is important to know that what you're looking at here does not include the P wave on the EKG, so it is not caused by any atrial specific effect. And likewise, this display does not include the ST segment, which is prolonged by things like IKr blockers. What you are looking at here is the consequence of

ventricular sodium channel blockade.

In summary, vernakalant is a Vaughn-Williams class 1C antiarrhythmic drug that is a potent negative inotrope and markedly prolongs the QRS duration in some subjects. It is not atrial selective, particularly with respect to safety. Because the same sodium channels exist in the ventricles as exists in the atria, vernakalant has an overall channel current blocking profile that is similar to flecainide's.

In accordance with its pharmacologic properties, we would expect vernakalant to cause serious cardiovascular adverse events such as hypotension, bradycardia, ventricular arrhythmias, atrial flutter, and conduction system disturbances, and possibly fatalities secondary to these events.

Understanding vernakalant is, let's look at the relevant summaries of the vernakalant safety versus placebo data from the reintegrated clinical trial database to see what actually happened.

We were not interested in looking just at all adverse events. We really wanted to focus on what was serious, understanding that if you get serious

bradycardia and that's your only problem, we understand you can pace that. What we are specifically continuing to worry about with this is this serious hypotension that you can't pace because it's not associated with bradycardia.

What you see here in this slide is that it represents a pooled analysis of the cardiovascular adverse events occurring within 2 hours of vernakalant administration. As would be anticipated from the safety profile of flecainide, the administration of vernakalant does in fact demonstrate multiple serious adverse cardiovascular events of hypotension, arrhythmia, atrial flutter, bradycardia, ventricular arrhythmia, conduction system disturbances, and death, all of which occurred in vernakalant-treated subjects, none of which occurred in placebo-treated subjects.

Please note that the death row is rendered in blue as one of these events experienced serious hypotension without bradycardia, and I wanted to clarify that. This person experienced this hypotension within 2 hours of vernakalant administration, but did not die until 4 weeks later due to the complication of

his 40-minute pulseless resuscitation effort necessitated by vernakalant-induced cardiogenic shock.

Unlike what you heard this morning as far as this patient being described, I will be happy to talk about this and show you the data. This person was listed as not having had heart failure in the sponsor's database. This person was not shown to have heart failure from what they submitted to me in the MedWatch reports on physical exam. And this person had an EF of 44 percent that the reader felt was only mildly depressed because his resting heart rate was 156 when they did the echo, and echos tend to underestimate EF when people were going that fast. The reader of the echo specifically noted that there were no segmental wall motion abnormalities present.

In an attempt to identify prospectively patients who might be at risk for serious cardiovascular adverse events, we focused on this subset of 43 patients with exaggerated QRS prolongation that I showed you in the prior slide, who received only one dose of vernakalant, did not convert to sinus rhythm, but did not get a second infusion because the

investigator was worried about what was going on clinically and aborted the infusion protocol.

So these patients only got one dose of drug and did not convert, and stayed in sinus rhythm. This subset had worse outcomes than the rest. Twenty-six percent of these subjects experienced serious cardiovascular adverse events within the 2 hours of initiating vernakalant therapy. The mean placebo adjusted increase in the QRS interval was approximately 20 milliseconds, on average, and the mean placebo adjusted increase in the QTc greater than 30 milliseconds.

This subset experienced significantly more hypotension, as you see on this slide. Unfortunately, analyses of the medical histories and demographics of this subgroup, which we tried to do, failed to identify characteristics, which would have prospectively identified most of these subjects.

In summary, from the clinical safety data set analysis, vernakalant prolongs the QRS interval in clinical trials. Vernakalant causes adverse events consistent with its Vaughn-Williams class 1C sodium

channel blockade, and most patients who will do poorly with vernakalant cannot be prospectively identified, and therefore the harm cannot be predicted.

Reliable risk mitigation for serious cardiovascular events could not be achieved on the basis of demographic characteristics, therefore, we did not see a way that the harm could be prevented through risk mitigation. Finally, in ACT V, serious hypotension occurred without bradycardia and was unresponsive to pressors for 40 minutes. From that, we determined that when the harm does occur, at least in some cases, it is not treatable.

Let's turn our attention to SPECTRUM. SPECTRUM was an observational registry for patients who received IV vernakalant in six Western European countries following its approval in Europe. It is the predominant safety data source on which this NDA resubmission is based.

SPECTRUM enrolled 1,778 patients who underwent 2009 vernakalant treatment episodes. Seventy-nine percent of these subjects were prospectively enrolled. The 21 percent of them were retrospectively enrolled.

The data were largely collected through medical chart abstraction.

Comparing the incidence rates of the serious cardiovascular adverse events of interest within 2 hours of vernakalant administration in SPECTRUM versus the controlled clinical trials, which you see here compared in these two columns, you can see that most all of the serious cardiovascular event types, including serious hypotension, were reported in SPECTRUM but occurred at lower rates than were captured in the clinical trials.

FDA is not reassured by the SPECTRUM results because of its multiple sources of bias, particularly relating to who might not have been enrolled in the registry and how this might have affected the demonstrated safety profile. These include potential selection bias due to physician-selected patients; lack of clarity as to whether all vernakalant eligible subjects at a given site underwent screening for enrollment; non-consecutive enrollment, 21 percent of screened patients did not get enrolled in SPECTRUM; and finally, the retrospective enrollment of 21 percent of

enrolled subjects, representing a group that had to survive to give retrospective consent for their chart data to be abstracted.

In addition, the pattern of occurrence of serious cardiovascular events was consistent with the clinical studies as far as these events being reported, albeit at a much reduced frequency then was captured in the clinical trials. Whether the frequency of the adverse events in SPECTRUM was related to biased enrollment or adverse event underreporting is unknown.

The sponsor has proposed to you the use of a preinfusion checklist as a risk mitigation tool for use with vernakalant. We have concerns about the adequacy of this tool for identifying patients who might experience serious cardiovascular adverse events after the vernakalant infusion.

The items rendered in blue on this slide are the yes and no questions from the preinfusion checklist that addresses the proposed label's contraindications for vernakalant therapy. We find these items problematic in that subjects who did not demonstrate low baseline blood pressures, severe bradycardias, QRS

or QT prolongations, heart failure, or valvular heart disease, went on to experience these events in the controlled clinical trials in SPECTRUM and in the postmarket setting. We've seen reports of these events in all these places.

The last two items on this list, rendered in black, are meant to avoid dosing of subjects with vernakalant who may require a class 3 antiarrhythmic drug within 4 hours prior to or 4 hours after vernakalant administration, or beta blockers 2 hours before or 2 hours after vernakalant administration.

Regarding the other antiarrhythmic drugs, it is noted that during the attempted resuscitation of the patient who died in ACT V from cardiogenic shock, the patient received IV amiodarone and electrical cardioversion after the vernakalant administration in an attempt to achieve rhythm and hemodynamic stability.

Thus, we question whether this exclusionary statement can be realistically operationalized in that it will not be possible to prospectively identify who may need amiodarone therapy 4 hours following vernakalant administration, either in an arrest

scenario or for vernakalant-induced arrhythmias.

Likewise, the checklist states the use of IV beta blockers is not recommended within 2 hours of vernakalant administration or 2 hours after. However, most subjects who received IV beta blockers within 2 hours of vernakalant administration received them for acute rate control of rapid atrial fibrillation or atrial flutter. In our assessment, it is not possible to prospectively identify who may need these therapies after the vernakalant has been administered.

I finish this presentation where I started by sharing with you that FDA's ongoing and overarching concern is that the proposed preinfusion checklist will not reliably predict which subjects will experience serious and potentially fatal cardiovascular events caused by IV vernakalant administration.

At this time, I'd like to introduce you to Dr. Daniel Woronow from FDA's Office of Surveillance and Epidemiology, who will summarize for you his division's review of the world's literature regarding the safety of alternatives for the rapid conversion of atrial fibrillation, and specifically pharmacologic

cardioversion with ibutilide, which is approved for this indication, as well as electrical cardioversion.

Dr. Woronow?

FDA Presentation - Daniel Woronow

DR. WORONOW: Thank you, Dr. Dunnmon.

I'm Dr. Daniel Woronow of the FDA Division of Pharmacovigilance, Office of Surveillance and Epidemiology. I will be presenting safety information FDA reviewed for ibutilide pharmacological cardioversion and electrical cardioversion in patients with atrial fibrillation or atrial flutter.

This presentation is the review of information to determine if there is a substantial risk of death or severe hypotension with ibutilide pharmacological cardioversion or electrical cardioversion. Additional information related to ibutilide pharmacological cardioversion and electrical cardioversion can be found in the appendix of the FDA briefing document.

Ibutilide is presently the only FDA-approved drug with the same indication being sought by vernakalant, which is for the rapid conversion of recent onset atrial fibrillation to sinus rhythm.

Ibutilide is also approved for rapid conversion of atrial flutter.

Based on review of available evidence per medical literature and postmarketing case reports, there is no conclusive evidence of electrical cardioversion or ibutilide pharmacological cardioversion causing non-embolic fatalities or severe hypotension in patients meeting the ACT V study enrollment criteria such as absence of history of heart failure, significant valvular stenosis, acute coronary syndrome within the preceding 30 days, or clinically significant illness. Heart failure, valvular heart disease, and acute coronary syndrome are also warnings and precautions or contraindications in the proposed vernakalant label.

We compared ibutilide and electrical cardioversion safety to the ACT V study because ACT V was initiated by the sponsor to address FDA's concerns regarding the safety of IV vernakalant with respect to serious drug-induced hypotension, bradycardia, and arrhythmias. The primary objective of ACT V was to evaluate the safety of vernakalant injection in

subjects with atrial fibrillation and no evidence or history of heart failure. The history of heart failure exclusion criteria and other exclusion criteria make ACT V a more restrictive study in terms of severity of patient comorbidities than that typically applied to ibutilide or electrical cardioversion evidence that we will present.

American College of Cardiology and American Heart Association guidelines for the management of atrial fibrillation state that electrical cardioversion is preferred over pharmacological cardioversion in patients with decompensated heart failure, ongoing myocardial ischemia, or hypotension. These electrical cardioversion patient populations all have more severe cardiovascular comorbidities than patients eligible for enrollment in ACT V, and these are also contraindications listed in the proposed vernakalant label.

ACC and AHA guidelines state electrical cardioversion has a class 1 recommendation to restore sinus rhythm in patients with atrial fibrillation or atrial flutter. There are no patients subgroups for

whom pharmacological cardioversion is preferred over electrical cardioversion within these guidelines, although electrical cardioversion should not be performed in patients with evidence of digoxin toxicity.

A survey of the University of Michigan healthcare system cardiologists, emergency room physicians, and hospitalists showed electrical cardioversion is used more commonly than pharmacological cardioversion. Phase 2 and phase 3 clinical trials demonstrated that ibutilide injection was generally well tolerated. Of the 586 patients with atrial fibrillation or atrial flutter who received ibutilide, arrhythmias that required cardioversion occurred in 1.7 percent of ibutilide-treated patients, and these were all treated successfully.

It is of note that ibutilide registration trials included patients with more severe baseline cardiovascular comorbidities than allowed for in the ACTV study. About two thirds of patients in registration trials had cardiovascular symptoms, and the majority of patients had left atrial enlargement,

decreased left ventricular function, or a history of valvular heart disease. Importantly, there were no deaths in these phase 2 and phase 3 clinical trials among patients who received ibutilide. Instances of sustained polymorphic ventricular tachycardia were all treated successfully.

The postmarketing randomized-controlled trials also provide safety information for ibutilide in the three trials. There was only one ventricular arrhythmia requiring intervention, and this was polymorphic ventricular tachycardia, which was successfully treated with electrical cardioversion.

The investigators reported that the patient was in violation of the protocol because the patient's pre-dose serum potassium and magnesium levels were below the accepted parameters. As reported in these clinical trials, no ibutilide patients experienced hypotension, and there were no ibutilide events leading to death.

To determine if there were any fatal cases in patients who had used ibutilide, we searched the FDA adverse events reporting system, or FAERS database, for

all reports of ibutilide and outcome of death since U.S. market approval 24 years ago through September of this year.

This resulted in 14 reports after excluding two reports because of insufficient information to determine a causal association. The 14 reports were heavily confounded and included patients with do not resuscitate orders or patients meeting ACT V exclusion criteria. Additional details about the FAERS search results can be found in the FDA briefing documents.

The literature search identified 4 prospective randomized-controlled trials evaluating electrical cardioversion of atrial fibrillation to sinus rhythm. Among patients who underwent electrical cardioversion as the initial cardioversion strategy, there were no instances of patients requiring intervention for potentially fatal ventricular arrhythmia, hypotension, or need for mechanical respiratory assistance. There were no deaths in these randomized-controlled trials.

As stated on the previous slide, there were no respiratory or pulmonary edema adverse events reported, requiring mechanical assistance in these

randomized-controlled trials. However, respiratory or pulmonary edema adverse events requiring mechanical assistance were rarely reported in these retrospective observational studies that included electrical cardioversion patients with moderate or severe cardiovascular comorbidities.

Of note, prior to electrical cardioversion, almost half the patients reported by Davarashvili and colleagues had moderate or severe aortic stenosis at baseline, and 13 percent were described as having moderate or severe left ventricular dysfunction at baseline.

Therefore, it is not surprising that aortic stenosis and left ventricular dysfunction patients would be at risk for pulmonary edema or other complications. Patients with these comorbidities would have been excluded from ACT V, and they would not be eligible for vernakalant based on proposed label contraindications.

We were unable to find any conclusive evidence that electrical cardioversion is causally related to non-embolic death among over 33,000 electrical

cardioversion procedures performed for the rapid conversion of atrial fibrillation to sinus rhythm. This includes patients summarized in the previous electrical cardioversion slides and all other studies reviewed. Results reported by the Euro Heart Survey Registry was also included in this total.

Periprocedural characteristics of this study lists 2 non-sudden sudden cardiac deaths, although the study does not report sufficient information to determine a causal association between electrical cardioversion and death. Age, time to onset, comorbidities, concomitant medications, and hypothesized mechanism of death are not reported for these two patients.

Therefore, our summary impressions are the literature search did not identify any instances of ibutilide-related death during index hospital stay among patients who otherwise could have been enrolled in ACT V.

Electrical cardioversion is generally successful in rapidly converting atrial fibrillation to sinus rhythm. Electrical cardioversion literature did

not identify any non-embolic deaths causally related to electrical cardioversion despite most of these studies, including patients with more severe baseline comorbidities than in ACT V.

Electrical cardioversion related serious adverse events that are non-transient and not self-limited occur uncommonly or rarely despite most of these electrical cardioversion studies, including patients with more severe baseline comorbidities than in the ACT V study. The reference we used today can be found in the FDA briefing documents.

Thank you for your attention, and I now return the podium to Dr. Dunnmon for concluding remarks.

FDA Presentation - Preston Dunnmon

DR. DUNNMON: Thank you, Dr. Woronow.

In concluding, our assessment from our comprehensive review of vernakalant safety is as follows. Vernakalant is a Vaughan-Williams class 1C antiarrhythmic. It is not atrial specific. It affects both the ventricles and the atria, and that is particularly true with respect to safety. Vernakalant prolongs the QRS markedly so in some subjects, and it

is a potent negative ionotrope in dogs and in humans, and has caused deaths in dogs and in humans.

Vernakalant is similar to flecainide. In dogs, vernakalant's negative inotropic effect is as large as that observed with IV flecainide but does not recover during 90 minutes of post-dosing observation. In humans, adverse events are similar with hypotension, bradycardia, ventricular arrhythmias, atrial flutter, conduction distant system disturbances, and deaths observed with both drugs.

The proposed preinfusion checklist will not reliably predict which subjects will experience cardiovascular serious adverse events with vernakalant, and SPECTRUM results are not reassuring regarding vernakalant's cardiovascular safety for the reasons that I shared with you.

Vernakalant has induced harm that cannot be reliably predicted, prevented, or in some cases treated. In contrast to vernakalant, electrical cardioversion and ibutilide pharmacologic cardioversion can cause adverse events, but these are transient and treatable. We believe that the benefit-risk profile of

vernakalant is unfavorable for the proposed indication. Thank you.

Clarifying Questions

DR. LEWIS: Thank you.

We'll begin with the clarifying questions for the FDA, and then I think we'll have time for clarifying questions for the sponsor as well, if some were unasked. Please remember, once again, to state your name for the record before you speak, and if you can, please direct questions to a specific presenter.

Dr. Dunnmon, my understanding of a clinical hold is that the position of the FDA is that you would not approve a patient entry in a clinical trial and receive this drug, vernakalant. Is that correct?

DR. DUNNMON: That that is why the IND remains on full clinical safety hold, yes.

DR. LEWIS: Thank you. I think Dr. Ridker, you were first.

DR. RIDKER: Sure, two brief clarifying questions. Paul Ridker from the Brigham. The first is, on slide 24, you laid out -- and I think correctly, epidemiologically -- that it's very difficult to

address survival bias in the retrospective cohort because, obviously, the patients had to be alive to consent to be in it.

I wonder if you'd address the survival bias that you might be concerned about in the prospective cohort. We heard earlier -- I think Dr. Moliterno raised it -- that the follow-up was rather short. How would you like us to think about survival bias there? Then I have a second very brief question.

DR. DUNNMON: It's not clear to us that everybody who could have been enrolled in SPECTRUM was screened sequentially to do so. We know that 21 percent of people who were screened did not get entered into the trial. What we don't know on top of that is how many people didn't get screened. What was their medical condition that caused them not to get screened; not to get entered; not to get dosed? We just don't know.

DR. RIDKER: Okay. And the second clarifying question actually comes very close to what Chairman Lewis already asked. What are the formal criterion to reverse a clinical hold?

DR. DUNNMON: We work with sponsors very closely, as we have for the last nine years here with this program, to alleviate the concern that has caused our safety worries, whatever they are. In this situation, what became clear to us after the dog dp/dt study, confirming the important negative inotropic effects of this drug.

We worked with the sponsor very closely for several years to try to identify a dosing algorithm that would separate the negative inotropic window from the efficacy window. In this case, that's what we needed to do, and that attempt failed.

DR. RIDKER: And just to be crystal clear to me, then, a decision to undo a clinical hold is to allow for more clinical research to move forward.

DR. DUNNMON: Correct.

DR. RIDKER: Thank you.

DR. LEWIS: Dr. Packer?

DR. PACKER: I just have a question. One thing that I'm trying to figure out is your conclusion that there is no patient population that you are comfortable having identified where either approval

would be indicated or even additional clinical studies could move forward. I just want to make sure -- I understand your concerns about heart failure -- by the way, when I say heart failure, mild, moderate, severe, LV dysfunction, any LV dysfunction.

In your slides, you had a reference on slide 5 -- there's no reason to put it up there -- that there was a patient in 2010 with pulseless electrical activity, where the patient had hypertension and left ventricular hypertrophy, and developed pulseless electrical activity. That patient had structural heart disease.

If I remember correctly, when flecainide was approved by FDA, which is an analogous 1C drug, it was and currently has an indication for use in patients without structural heart disease. without structural heart disease, I mean it's not just no heart failure; it's no LVH, no -- essentially no structural heart disease.

Is your sense that if the sponsor wanted to do clinical trials in patients without structural heart disease, and that would be confirmed by an echo or

however one would go about doing it, in order to study a patient population similar to the patient population for which flecainide is approved, what would be your view?

DR. DUNNMON: Two things I think we need to clarify. Flecainide is approved for maintenance of sinus rhythm.

DR. PACKARD: Yes.

DR. DUNNMON: This is being used for acute conversion, number one. Number two, that's a very interesting question because the only data I have to go on is what I'm sharing with you from these trials.

Could I bring up FDA backup slide number 52, please? The thing that I think would have to be disclosed, if the sponsor was going to go forward to say, okay, we're going to echo everybody, and only people with normal LV function, that would be a pretty stringently defined group to say if you're going 160 beats per minute with no loss signal or wall motion abnormalities, 44 percent is moderately to severely depressed, I don't think anybody would go for that.

The reason I bring this up, this is a case

from the postmarket experience. This was not a clinical trial. And the person who wrote this specifically wrote that this patient B had no cardiovascular disease at all and was dosed with vernakalant for AFib.

This prodrome that I keep seeing over and over again, with the itchy, clammy, diaphoresis stuff, starting usually with a metallic taste in their mouth, got started at about minute 10. At minute 12, they're bolusing with saline for hypotension. At minutes 15 to 25, they're bolusing more saline because of more hypotension. At minute 25, they're having tonic-clonic seizures, loss of consciousness, no carotid pulse, with the cardiac arrest being called and compressions initiated.

Then this person slowly recovers after about 27 minutes, remembering that unlike flecainide, where in the post 90-minute observation period, after that IV infusion in the dogs, it recovered. This drug's negative dp/dt did not.

So this person who wrote this got very vocal about his best echocardiographer being in the room and

taking these three sequential echos, where this person had low normal ejection fraction early on at 30 minutes. It went down to less than 20 percent, and then at minute 300, which was in 5 hours with negative troponins, was back up to normal again.

I suspect if you echo all these people, a lot of people are doing this, and some are more symptomatic with it than others. I think this information would have to be disclosed if a trial like that was going to be run because at this point, I'm seeing this happening in somebody where the investigator is telling me they had nothing.

DR. LEWIS: Dr. Davis?

DR. DAVIS: Barry Davis, University of Texas. This is for Dr. Dunnmon. I'm looking at slide 18, and it speaks back to slide 17 and slide 19, and it was sort of related to a question I had for the sponsor earlier. On slide 18, you say there's no demographic or disease-specific characteristics, which would be found to prospectively identify most of the subjects.

DR. DUNNMON: Right.

DR. DAVIS: The question is being raised by

the sponsor and you, too, about this evidence of heart failure and structural heart disease. The question is, was there any evidence for differences in heart failure or structural heart disease prevalence in these two groups, or there's just nothing there?

DR. DUNNMON: We found nothing. Now, there are a couple of glaring exceptions here. The first person who died with this infusion from the earlier ACT experience, that had aortic stenosis that you heard about this morning, that's why we let ACT V go forward, because we were thinking the same thing everybody else was. Well, they gave a vasodilator to somebody with critical aortic stenosis and loss them.

But then this fellow in ACT V that we put it on hold for, which was the second CPR case within 2 weeks in that study, had none of that. And he died without aortic stenosis, with the record showing no heart failure, no segmental wall motion abnormalities, an EF of 44 percent at a heart rate of 156 during the study, which the echocardiographer read is mildly depressed LV function. This person would not have been capped out.

By the way, Dr. Packer, to address something you asked this morning, I've got the exclusion criteria pulled up here for ACT V, which this person was not a protocol violation for, and it was pretty stringent. Let me read you what they could not have.

To get into ACT V, exclusion number 1, any patient who would be excluded from the study with any of the following criteria being met; number 1: had a history of heart failure or documented left ventricular dysfunction evidenced by any of the following: a history of heart failure defined as physician documentation or report; or any of the following symptoms of heart failure before the current care encounter, described as dyspnea, fluid retention, and/or low cardiac output secondary to cardiac dysfunction, or the depiction of rales, jugular venous distention, or pulmonary edema. Previous hospital admission with a diagnosis of heart failure was considered a heart failure history.

There could not be objective evidence of heart failure at the encounter for getting into this study, including rales, jugular venous distension, or

pulmonary edema. There could not be left ventricular dysfunction defined as an ejection fraction less than 40 percent. They tightened up on this to do what exactly we had asked them to do to give us less than 1 percent of these events. But even with this, they ended up with cardiogenic shock in somebody with LVH.

So when you ask me is there a way to identify these people, that stringent list I just read you failed to do so. Furthermore, there's another exclusion in his trial that reads that you're excluded if you have any significant organ dysfunction at all. So your lungs have to be working right; your liver's got to be working right; your kidneys have to be working right; and your heart has to meet all of that. And they still had this happen.

DR. DAVIS: I had one slight follow up question on slide 19 --

DR. LEWIS: Can I just make one quick comment? Those criteria are on page 64 of the FDA briefing book, if you want to review them in detail.

DR. DUNNMON: One last thing I have to note. I think there is a factual inaccuracy of the

description of this case in the sponsor's briefing document because there was a discussion about this person having an alcoholic cardiomyopathy. We dissected this case over the last 10 years.

When you actually go back to the original source documentation, which I did, and read the Spanish history, which I did, there's a question there that says "Bebes alcohol?" And the answer to that was no. So I don't think there's strong support for that. There was not laboratory support for it, and he was not smelling of alcohol, intoxicated, or any of that other stuff when he came in. It was also noted that that person had an ejection fraction of 25 percent on day 3, with severe MR. So his real problem was his alcoholic cardiomyopathy, his dilated LV, and severe MR, and then he happened to die when he got vernakalant.

That sequence of events was not correct. When you look at the echos that were actually done, he came in with that first EF of 44 percent with good segmental wall motion. Then following his EF going down to zero in echo documented PEA, that 25 percent was documented that same night after he got amiodarone, after he got

electrically cardioverted, and that was his first recovery study.

The next morning his EF was back up to 40. It went up to 49 a couple of days later. In all of these echos, his MR was only mild. He didn't start dilating and get bad MR until on the fourth week, during which he died, after which his kidneys had gone completely out. He was dialysis dependent. He had shock GI tract proven by colonoscopy and was hemorrhaging from his gut, and had gotten like 30 units of blood products, and was now dilating with MR. That MR was not chronic.

So I think that description in that briefing package that this was alcoholic cardiomyopathy was not correct.

DR. DAVIS: The only other question I had was on slide 19, and actually it's alluded to in other places. You use this phrase, "Harm caused cannot be reliably predicted." Is there some quantitative standard for that? What do you mean by reliably?

DR. DUNNMON: That's also a good question, and I'm certainly not an expert in defining what will happen in the future. In this scenario, when things

are happening, every list we have to check off a check box, or whatever, still allows it to keep happening.

DR. DAVIS: Well, you can't get the risk to zero.

DR. DUNNMON: You can't get the risk to zero, but these are not the only cases that it's happening in. If you look at your briefing package, I had every single serious adverse event that occurred in this program back there, and they're multiple. It's not just happening in one location, or in one, period.

DR. DAVIS: No, I understand that. I just wondered whether there was some quantitative level.

DR. DUNNMON: We tried actually to help in that regard, because what we tried to do with that group, where the investigator aborted the infusion in those 43 people that had those high adverse events rates -- what I was really hoping is that we could dissect the demographics and say, okay, if you just exclude these people over here, then you're okay. That's what we were really trying to do, but we were not successful at doing that. We could not find something to say that's who they're going to be.

DR. LEWIS: Dr. Alexander?

DR. ALEXANDER: I have a question for Dr. Woronow. On slide 38, you talk about electrical cardioversion. I actually looked up yesterday how many I've done in the last three years, and I've done about a hundred a year, and I've had at least a couple of deaths, and those are often sicker patients. I'm not sure they're the lone, low-risk AFib patients that we're talking about.

But it's almost impossible to tease apart what's the risk from cardioversion, versus what's the risk from the transesophogeal echo we often do along with it, versus what's the risk from the sedation. But it's a little implausible. Don't you think it's a little implausible that there are no deaths with electrical cardioversion in 30,000 patients?

DR. WORONOW: First of all, to go back to that slide, we're talking about clearly causally related, non-embolic deaths. But just to address your question, let's go to backup slide 73. These are deaths that were mentioned, and some of those 58 studies, 33,000 patients. This fits with what a lot of clinicians have

told me about atrial fibrillation and electrical cardioversion.

Let's look at El-Am study at the bottom. One death, patient with cardiac amyloidosis developed left hemiplegia, probably embolic, same night following successful electrical cardioversion, died 5 days later.

Let's go up to the top, Guédon-Moreau, again, a small percentage of deaths, 0.4 percent; lethal brain hemorrhage in a patient on dual anticoagulants; also an 86-year-old patient with hypertrophic cardiomyopathy died of heart failure one day after electrical cardioversion; a 78-year-old patient with valvular cardiomyopathy who died 1 month after electrical cardioversion.

I think this reflects that, overall, these can be very sick patient subsets, and atrial fibrillation is not the only problem that patients have among these patients who are dying with electrical cardioversion.

Let's go to the next slide, slide 74. Even though none of these deaths, in my opinion, are causally related to electrical cardioversion, let's count them anyhow; 43 deaths out of over 33,000

patients. That gives a death rate of 0.13 percent, about 1 per 1,000.

Let's go to the next slide. Let's throw this up against vernakalant deaths; 8 vernakalant deaths in the clinical studies. Regardless of whether you think they're causally related or not. we're going to do the same analysis with electrical cardioversion, causally related or not; 0.7 percent for vernakalant, 0.13 percent for electrical cardioversion.

DR. LEWIS: If the committee is agreeable to cut our lunch to 45 minutes instead of an hour, we can proceed with some more questions.

(Affirmative gestures.)

DR. LEWIS: Okay. Our next question for the FDA is Dr. Packer.

DR. PACKER: I just want to ask one follow-up question, and forgive me if I'm trying to find some path forward, but I'm trying to get my arms around the way that you are thinking about this and how the interactions with the sponsor have taken place. One thing that seems striking is that without invasive measurements, purely by echocardiography, there seems

to be some people who have a profound fall in ejection fraction with this drug. It is possible that maybe a lot of people have a decrease in ejection fraction, and it's not measured.

Just suppose this sponsor were to come to you and say we would like to do a study in the United States, and we would like to take 30 people, of a broad range of age, and all of them are totally healthy. They have no heart disease whatsoever. They will not be in atrial fibrillation; they will be in sinus rhythm.

Let us make sure that, just for purposes of discussion, they have the best imaging imaginable, 3-D echo, magnetic resonance imaging, it's the state of the art. They can detect the change in ejection fraction, and all they want to do is take 30 people and measure the delta ejection fraction before and after the administration of the drug. Would you approve such a study?

DR. DUNNMON: Let me back up to the consent phase because the people signing up for that will have to understand it would have to be disclosed that,

apparently, normal people have gotten this, and ended up needing CPR, and that it doesn't happen with the second or the third dose, like your platelets slowly dropping where you can say, "Okay, I've seen enough." You get the first dose, bombs away; hold on.

As long as they understand that and would be willing to sign on the dotted line, I'd have to defer to my division director about what he'd think about that. But I suspect the patients probably would have some reservations about it.

DR. LEWIS: We could probably discuss that further in the discussion section.

Dr. Davis, do you have another clarifying question with the FDA?

(Dr. Davis gestures no.)

DR. LEWIS: We have some clarifying questions left for the sponsor. I'd like to turn to those now. Dr. Floyd?

DR. FLOYD: Alright. Great. I think I have three sets of questions. Some of this has been addressed. I want to go back to SPECTRUM, and I don't want to beat a dead horse too much.

I understand this was not an interventional study. No biospecimens were collected. This was simply data collection of information that is readily available in the chart or for monitoring. So why was informed consent required to include patients in this study? I'm kind of puzzled by that.

DR. TERSHAKOVEC: I can ask Dr. Ritz to describe the SPECTRUM data. But this was prospective collection of data as it happened, so it was not anything like a chart review. This is implemented with site training. Investigators were trained in the procedures of the study to collect the appropriate information: SAEs, HOIs, or mandatory reporting. There was site monitoring. There was source document verification.

So a lot of the same procedures you would use with a clinical trial were implemented to make sure that their data were collected appropriately. I think FDA raised questions about underreporting. We are confident that there was not underreporting with the SPECTRUM data.

DR. RITZ: As a requirement of informed

consent, this is due to the European data protection laws. You cannot do any source of verification if you don't have an informed consent.

DR. FLOYD: I think of the epidemiologic studies that I do, and we often collect these types of information with a waiver of consent. But it seems like there are some protections required in Europe, and I accept that.

The second question is I understand that 20 percent of the people who were screened were not enrolled in the studies because they didn't give consent. Are we confident that everybody who is screened -- the people who were screened include every person who got a drug at all of the registry sites? Do we know that?

DR. TERSHAKOVEC: There were other treatment place -- so if there was an emergency room and that was the treatment site, but the cardiology department was not in a site, then there may have been subjects that were not treated in that setting, yes.

DR. FLOYD: If you could bring up slide CE-17?

DR. TERSHAKOVEC: Slide up.

DR. FLOYD: When I look at this, I see that the conversion rates are consistent across every randomized controlled trial, 50 percent, but there's 70 percent in this registry analysis. And this seems pretty clear evidence of selection bias in that because informed consent was required, anyone who had early treatment-related adverse effects, rendering them incapable or lacking the desire to participate, they would be excluded, especially if they died.

Do you have any other explanation for why the conversion rates might be so high in this slide, other than that selection bias?

DR. TERSHAKOVEC: There are three reasons that we feel that the SPECTRUM results are consistent with what we have in the clinical trial database. Number one, these are uncontrolled data, so if you subtract -- so the placebo rate, that that's part of the issue; the patient population, especially the duration of atrial fibrillation, the shorter duration of atrial fibrillation in the SPECTRUM data compared to the median in the clinical trials database, and that's consistent with a higher conversion rate. If you also

look at the postmarketing literature, you generally do see higher conversion rates more consistent with the SPECTRUM.

DR. FLOYD: My second set of questions are along the lines of what Dr. Packer was getting at, trying to think of a way forward. Are there specific populations you could identify where the risk of harm can be mitigated? There might be benefits that are worthwhile.

I'm thinking about pharmacokinetics and pharmacogenomics, specifically about the 2D6 pathway. We don't really have readily available point-of-care genetic testing, but in the future, this may be widely available. You can identify which patients are on 2D6 inhibitors.

I did read the materials in the sponsor packet about serum rates not being substantially elevated amongst poor metabolizers, but still, I'm wondering if there are genetic or drug interaction data amongst the people enrolled in the trials, and if anyone has tried to look at that if they exist.

DR. TERSHAKOVEC: I can ask Dr. Leonowens to

address your question.

DR. LEONOWENS: Cathrine Leonowens, clinical pharmacologist, and I'm a paid consultant for Correvio. Although in our popPK analysis, we did find that there was about 50 percent lower clearance for poor metabolizers versus extensive metabolizers, when we used the population PK model to run a sensitivity analysis, the differences in Cmax and AUC were minimal, and they were deemed not clinically important. So because of this, no dose adjustment is necessary for poor metabolizers.

DR. FLOYD: That wasn't my question. I understand the in vivo modeling that was done, but this is not entirely predictive of clinical adverse effects. My question was -- probably the answer's no, but were any genotypic information collected on the trial participants?

Do you have genotypes that tell you if they were poor metabolizers, fast metabolizers? Did you collect information on inhibitors of CYP2D6, of UGTs, things that are involved in glucuronidation, things like that?

DR. LEONOWENS: Not for glucuronidation specifically, but for CYP2d6 inhibitors, we did collect that information, and they didn't come up as statistically significant in the popPK analysis.

DR. FLOYD: Then the last question, this is going way back I think to the things that Dr. Alexander was asking about with the post-op cardiac surgery patients. In contrast with the general population where patients are presenting with symptoms -- and that's the benefit. It's not converting to sinus, it's that these patients are having symptoms related to AFib, presumably, with RVR. So converting to sinus, which is a biomarker, is translating to some clinical benefit.

For the cardiac surgery patients, that's not clear to me. So I'd like to know if in ACT II, how much of the AFib was simply detected on routine cardiac monitoring, while they were hospitalized, during clinic visits, versus they presented with symptoms and were found to be in AFib? I think that's a critical distinction.

DR. TERSHAKOVEC: I can ask Dr. Weaver to

address that question and also the general management in the postoperative setting.

DR. WEAVER: Sorry. I had to check that. This is Doug Weaver. The post-op patients had both. Those were symptoms and some were detected because they were being monitored.

DR. FLOYD: Do you have any slides or data like you do for ACT I and ACT III?

DR. WEAVER: Not handy, anyway. I could look and see if we have some.

DR. FLOYD: I'm looking specifically at slide CE-19. You actually showed changes in symptoms for patients who presented symptomatically in ACT I and III. If there's something similar for ACT II patients, that would be helpful. Otherwise, I would kind of presume that most of these patients simply were found to be in AFib because of routine monitoring, and it would be hard to infer that they have direct tangible benefits in terms of symptom reduction.

DR. TERSHAKOVEC: So in ACT II, the patients who had any AF symptoms were very high. Slide up, there. This is the overall population.

DR. FLOYD: Excluding ACT II.

DR. LEWIS: Excuse me. This actually appears to exclude ACT II. Perhaps you guys can come back to us after lunch.

Do you want to come back after lunch with the answer?

DR. TERSHAKOVEC: I can tell you that it was over 80 percent that had any symptom of AF in ACT II.

DR. LEWIS: Dr. Floyd, do you want the specific numbers? Is over 80 percent an answer?

DR. FLOYD: Yes. I think to draw any conclusions, I need similar systematic data like this, if they're available.

DR. TERSHAKOVEC: Okay.

DR. FLOYD: Yes, if they have the data.

DR. LEWIS: So after lunch, if you guys actually have the specific data, that would be great.

Dr. Needleman?

DR. NEEDLEMAN: Matt Needleman. One question. There's really two different groups of patients. There's the healthy heart, AFib patients, who have AFib less than 7 days duration, and then the CT surgery

patients, which was only 5 percent of the SPECTRUM database.

If you apply that checklist to see post-cardiac surgery patients, what percentage of patients do you think would not have structural heart disease and be good candidates for the medication?

DR. TERSHAKOVEC: The numbers are small to apply that, I think. I know Dr. Ritz has the application of the checklist to the postoperative population. That's something we can look at to do, but the numbers are small, so it would be difficult to really have too much inference from that.

DR. LEWIS: So are you guys going to look for that and come back after lunch?

(Dr. Tershakovec gestures yes.)

DR. LEWIS: Thank you.

The last question, Dr. Mandrola?

DR. MANDROLA: This clarifying question goes to the rhythm control strategy. Over the last 10 years, my impression of the rhythm control strategy -- and this goes to unmet need -- is that rhythm control, cardioversion being a rhythm control

strategy, doesn't really look that good. The drug studies haven't been good. CABANA didn't reduce outcomes.

I would be interested specifically in the sponsor's comments to the Dutch study published in New England, in the spring, which showed that delayed approach to cardioversion was just as good as the immediate approach; furthermore, the Gillinov post-cardiac surgery patient, which showed no advantage to rhythm control strategies.

I'm, as a clinician taking care of patients, just very concerned that maybe there isn't that much of an unmet need for this abrupt rhythm control.

DR. TERSHAKOVEC: I'd ask Dr. Kowey to address that question.

DR. KOWEY: Peter Kowey. Yes, you're absolutely correct. If you look at long-term management of patients with atrial fibrillation, there's no premium in restoring sinus rhythm for a large percentage of the patients that we see in terms of hard outcomes, which is what the studies you're quoting reference.

The question being asked here, however, is a little bit different in that we're dealing with patients who are highly symptomatic. They come into the emergency department. We really don't know what to do with these people a lot of the times. We try to give them some AV nodal blocking drugs. They sort of guess at the drug, guess at the dose, try to anticoagulate them, and then reference them on to chronic management.

The question that's being asked here is, is there a benefit in restoring sinus rhythm in those patients to reduce their symptoms at the time that they present? It does not necessarily commit you to a rhythm control strategy over the long term. If these patients have recurrences and you can control their heart rate and anticoagulate them, their chronic management might be exactly as you stated.

DR. MANDROLA: I know it's a select group, the Dutch study. They did screen a lot to get these patients, but two-thirds were in sinus rhythm the next day, I think, or in 48 hours. That's pretty impressive.

DR. KOWEY: Yes. The study that you're quoting has a fairly select patient population who were not terribly symptomatic at the time that they presented. They responded very rapidly to AV nodal blocking drugs, and they were left in atrial fibrillation to be observed to see how many would revert. By the way, the majority of those patients had previously been seen in emergency departments; they were not necessarily new onset AF patients.

I agree completely that in patients that you know that have come in before, and that you can rate control them and anticoagulate them, I think it's a perfectly reasonable strategy to leave those people alone. Again, the question is, phrased for the patient who is highly symptomatic in an emergency room setting, is there a premium to restore sinus rhythm? And I think you see from symptom reduction that there may be.

DR. LEWIS: I would like to take a moment to recap
the questions. Dr. Needleman has an outstanding question for the sponsor, I believe, about how the checklist was applied to the post-op patients.

Dr. Floyd has a question about the symptoms of AFib in the ACT II study. Dr. Packer, I believe, had a question about one versus two doses in SPECTRUM.

Oh, you did? Sorry.

DR. MOLITERNO: Yes, and the reason, they only received one. Did they convert or did they have some sort of untowards sequelae that they didn't give a second dose?

DR. LEWIS: Is that clear? Then I had the two questions about the penetration and comparing sustained sinus rhythm in 7 days, placebo ECV versus vernakalant.

Dr. Gibson, did you have an unanswered question?

(Dr. Gibson gestures no.

DR. LEWIS: We will meet at 12:30. The open public session has to start at exactly 12:30, so we will meet.

We will now break for lunch. We will reconvene in this room at 12:30. Please take any personal belongings you may have with you at this time. Committee members, please remember that there should be no discussion of the meeting, none, during lunch

amongst yourselves, with the press, or with any member of the audience. Thank you.

(Whereupon, at 11:46 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:32 p.m.)

Open Public Hearing

DR. LEWIS: I think we're going to go ahead and begin our 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 speakers, 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, it's 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 this meeting.

Likewise, FDA encourages you at the beginning

of your statement to advise the committee if you do not have any such financial 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 the committee place great importance in the open public hearing process. The insights and comments provided could help the agency and the 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 the 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, please only speak when recognized by myself, the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. ZELDES: Good afternoon. My name is Nina Zeldes, and I'm here as a senior fellow to speak on

behalf of the National Center for Health Research. Our center analyzes scientific and medical data to provide objective health information to patients, providers, and policymakers. We do not accept funding from drug and medical device companies, so I have no conflicts of interest.

Although there are several treatments for patients with atrial fibrillation, new options that are effective with fewer safety concerns would greatly benefit patients. However, it is not clear that this drug fulfills those goals. We strongly agree with the FDA assessment that the new postmarket study data that were provided to alleviate the agency's safety concerns have not adequately addressed those concerns.

We also agree with the FDA analysis that the benefit this drug might possibly provide to a subset of patients does not outweigh the serious risks associated with it. This is especially worrisome since the subset of patients most likely to benefit hasn't been clearly defined and because there are other safer treatment alternatives available to patients.

The new safety data come mainly from one

study, SPECTRUM. There are several serious concerns with the study design, which may have contributed to selective enrollment and the underreporting of adverse events. As a postmarket observational study with no control, this is of particular concern.

For example, there were large differences in the rates of serious adverse events reported in prospectively and retrospectively controlled patient groups. These large differences seem to be an indication of selection bias and the fact that patients who had serious adverse events may have been like less likely to be included in the retrospective study.

Additionally, the study was not conducted in the United States. It was conducted in Europe, so the patients could differ greatly in terms of BMI, health habits, and access to healthcare. There was also a lack of diversity; 96 percent of the patients enrolled in the SPECTRUM study were white. It is, therefore, not clear how applicable the data are for the U.S. population, which are the patients that are the most important to the FDA.

Given the risks and the unknowns, there's no

urgency to approve this drug, especially since there are treatment alternatives available. As advisers to the FDA, it is essential that you speak on behalf of patient safety as you carefully consider the data available for how this drug could help or harm patients.

We, therefore, do not support approval. However, if the majority of you recommend approval, we respectfully urge you to limit the indication to narrow the group of patients for whom the benefit is most likely to outweigh the risks. Thank you for your time.

DR. LEWIS: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. MILLER: Hello. I'm Sue Miller. I don't have any conflicts of interest to report, however, my transportation --

DR. LEWIS: Yes, it's on. We hear you.

MS. MILLER: Okay. Well, I had slides, but that's okay.

DR. LEWIS: The slides are on.

MS. MILLER: But how can I make them go forward?

DR. LEWIS: There will be someone to show you in a moment.

MS. MILLER: Okay. Thank you.

Well anyway, I don't have any conflicts of interest to report, however, my transportation to attend this meeting was paid for by the sponsor.

In February 2012, I was diagnosed with atrial flutter, and two weeks later with paroxysmal atrial fibrillation. In August of 2018, I was diagnosed with early-stage breast cancer after a routine mammogram. After a year of treatment that included lumpectomy, chemotherapy, and radiation, I am now cancer free.

I've always considered good health important, but now more than ever. I adhere to a mostly healthy diet and make time for regular exercise. My Fitbit is a favorite accessory. I appreciate the excellent medical care I've received in recent years, but my goal is to become a boring patient with no difficult medical problems.

Almost eight years ago, I went to the

emergency room with a rapid heart rate. My heart had been racing for several days. Once there, my ventricular heart rate climbed to 300 beats per minute. I remember staff wheeling in the crash cart and preparing an amiodarone drip. Before they could administer either, I reverted back to my presenting rhythm, atrial flatter.

I was admitted to the hospital, where I was put on metoprolol and Pradaxa. I also had blood work, including a D-dimer test for the presence of current or recent blood clots. My results were sky high, although further tests revealed no existing clots. I went home two days later on Pradaxa and metoprolol.

Several weeks later, I went into atrial fibrillation at a high rate during a treadmill stress test. My cardiologist sent me to the ER. When diltiazem infusions didn't lead to sinus rhythm, I was again admitted to the hospital.

There, I was put on Multaq and magnesium, and scheduled for an electric cardioversion. Several days later, two attempts at cardioversion failed, but that evening I converted to normal rhythm. If this episode

happened now, my treatment options would be the same as they were eight years ago.

After five days in the hospital, I was discharged on Multaq in addition to metoprolol and Pradaxa. I was rattled by my diagnosis, but gradually learned to cope. My cardiologist told me, "I want you to live your normal life." That became my goal, and it took several months or more to reach.

While I was rocked by my diagnosis, I was also intensely curious about it. I searched the internet for information about AFib and flutter. I was interested in credible information, which can be hard to find, especially when you don't have a medical background. I came across a straightforward website, stopafib.org, that was filled with what seemed like reliable information on every aspect of the condition. I started to work my way through a huge amount of material.

Soon I came across Stop AFib's discussion forum. I read through many pages of patient comments. After a while, I started posting. I'm still active on the site and now help moderate it. My participation on

the Stop AFib site is what brought me here today. While I can only speak from my own experience, I know from years of online chatting that my situation is not unique. We're all scared in the beginning, and sometimes beyond. For many of us, AFib episodes are unnerving.

Initially, I did well on my prescribed drugs. While I had occasional AFib episodes, they were easily resolved with extra doses of metoprolol or tricks that seemed to help, such as taking long walks, sipping ice water, or eating electrolyte-rich foods. Soon I began to have longer and more frequent breakthroughs.

Twice in a month, I ended up back in the hospital. During the second stay, my cardiologist took me off Multaq in favor of dofetilide. Unfortunately, I did not meet the protocol for the drug. Instead, I was loaded on amiodarone. As my doctor explained at the time, he didn't think too mild or antiarrhythmics, flecainide or propafenone, would be strong enough for me. Despite what he called its nasty side effects, amiodarone was my only drug choice.

I took to the drug immediately, although it

took months to become fully effective. Once it did, I was in normal rhythm for long periods of time. I also met with an electrophysiologist that my cardiologist recommended for a second opinion. I started seeing her as a regular patient. I did well on amiodarone, but I really worried about long-term side effects. Although I was monitored regularly for potential problems, I was still concerned. After several years on the drug, my EP suggested I cut my dose in half.

After five months on the lower dose, I began to have episodes of AFib and tachycardia approximately every 10 days. Sometimes my episodes lasted 2 or 3 hours, but mostly they were much longer. I was willing to tolerate frequent episodes if I could stay on the lower dose of amiodarone, which was 100 milligrams per day. However, my EP said amiodarone was too dangerous to take without perfect control. She put me back on 200 milligrams daily while I considered next steps.

I regularly expressed my concerns about the drug's toxicity to my cardiologist. He listened to me and I listened to him, but I was wary. I didn't want to head into old age with drug-induced problems added

to whatever health issues might come with age. To my surprise, my doctor said I should start to think about catheter ablation. My EP concurred.

In December, 2015, I had a cryoablation for a AFib and radio frequency ablation for standard or typical AFlutter. Four years later, I'm still in normal rhythm. I take Pradaxa, an anticoagulant, but no other AFib medications. With hindsight, I'm grateful that my cardiologist put me on a potent drug that kept me in normal rhythm most of the time. My AFib burden, the percentage of time I was in AFib, was about 5 percent, a relatively low burden.

In addition to my EP's remarkable skill, I think my ablation was successful partly because my heart was in good shape at the time of the procedure. I had some, but not much, scarring or remodeling of my heart. Without effective rhythm control, my situation might have been quite different.

During this journey, I've learned that AFib patients are similar but not the same. One size does not fit all, which makes treatment challenging. We have several options: a short list of medications,

various ablation techniques, and several surgical options that may or may not work. While patients have better treatments now than we did 5 or 10 years ago, no new antiarrhythmic drugs have been approved since Multaq in 2009, at least in the United States.

It's encouraging that a new antiarrhythmic drug, vernakalant, may be in the works. I may never need it, but others will. From my perspective as a long time patient, the need for safe and effective AFib medication is critical. Thank you for listening.

Clarifying Questions (continued)

DR. LEWIS: Thank you.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will allow the sponsor to now answer the questions they were asked before our break.

DR. TERSHAKOVEC: I'll start off with the question about the checklist being used in the

postoperative patients. About three-quarters of the subjects came from -- and again, these are relatively small numbers for surgical patients in SPECTRUM. About three-quarters of the subjects came from one site that actually had their own internal protocol for use of the drug, so they did not use the checklist. So that left limited numbers, but in the remaining sites, the checklist was used in 55 percent of subjects.

Regarding symptoms, in ACT II, which is the post-surgery patients, 91.6 percent of subjects had symptoms at baseline, any AF-related symptom.

The next question was on --

DR. LEWIS: The dose --

DR. TERSHAKOVEC: -- the subjects, SPECTRUM, who got one dose. Slide up. I would look at the center column as the prospective subjects, and you can see that about 60 percent got one dose; over 90 percent had converted; and about 7 percent had an adverse event or other. Serious adverse events in others were very light, small, and were reported by Dr. Weaver in his presentation. And we are working on the 7-day endpoint -- or the sinus rhythm in the placebo group.

DR. LEWIS: Did you have any estimate of eligible patients that could have received the drug other than Dr. Camm's comment, which was quite helpful?

DR. TERSHAKOVEC: For SPECTRUM?

DR. LEWIS: For Europe?

DR. TERSHAKOVEC: For Europe.

DR. LEWIS: The 58,000, does that represent widespread use of the drug in this setting or more limited use?

DR. TERSHAKOVEC: We don't have a denominator that we can get from that, no.

DR. LEWIS: Thank you.

Dr. Stockbridge will now provide us with the charge to the committee.

Charge to the Committee - Norman Stockbridge

DR. STOCKBRIDGE: Well, I can tell from the kinds of questions that you've been asking, that you perfectly well understand what our issue with this application has been, so I think we're probably ready to get started.

I will mention one thing because it's been four years since I've had a chance to do this. I care

a whole lot more about why you think the way you do than I do about how you vote. You will get asked to vote at some point here, but it's important that you articulate your thought process around the things that you vote on. Thank you.

Questions to the Committee and Discussion

DR. LEWIS: I'll add we're hoping that all members of the committee will share with us their thoughts.

The first question I will read. We will not proceed with the questions to the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at this specific request of the panel.

The first question I'll read. Please discuss whether the safety profile of vernakalant, for rapid conversion of recent onset atrial fibrillation, has been adequately characterized. If so, please comment on the sources upon which you relied: randomized studies, SPECTRUM, others.

Are there any questions or clarifications

about the questions?

(No response.)

DR. LEWIS: Then discussion is open.

Dr. Needleman?

DR. NEEDLEMAN: As the sponsor has mentioned, performing a cardioversion on somebody, it has a lot of limitations. You have to get anesthesia there. Many times with the sedation and just the cardioversion, there is hypotension; and a lot of times as an electrophysiologist, I don't deal with that because the anesthesiologist deals with that kind of in the acute time frame. But it's something we deal with all the time.

I think there is a role for pharmacologic cardioversion in healthy patients, whereas it may be limited in patients with structural heart disease. You talk about selection bias in SPECTRUM. It was actually, in my opinion, a good thing. You selected patients who were low risk, and those patients seemed to do well with the medications; realizing that it's not perfect.

If you look at other medications that we have

for atrial fibrillation, I know that it's not FDA approved, but we frequently do use flec -- there's that New England Journal paper, the pill-in-the-pocket flecainide, where we'll give people 300 milligrams of flecainide. We know flecainide works very well in patients without structural heart disease. We use it, and it works great. But it's not for everybody, and we've learned from the CAST trial, we don't give it to patients with ventricular arrhythmias; they'll have increased mortality.

Multaq, or dronedarone, is another perfect example of a medication that we learned a lot about, after the fact, with the PALLAS trial. It also probably decreases ejection fraction and increases mortality in patients with heart failure.

So I think structural heart disease is a significant problem with some of our antiarrhythmic medications, but in that subset of patients who don't have structural heart disease, there is potentially a role for a pharmacologic cardioversion.

DR. LEWIS: Dr. Needleman, are you summarizing that the SPECTRUM data in the low-risk patients, you

found reassuring in terms of safety? Do you want to comment further on whether the safety profile, you think, has been adequately characterized for vernakalant specifically?

DR. NEEDLEMAN: Yes. I think that's a -- yes. I think it was very reassuring that it was safe in those groups. I guess my question earlier was a little bit -- it was two groups. I think there's the healthy person, AFib, 40-year-old endurance athlete, who comes in with AFib, who has a normal EF and no other comorbidities. That patient may do very well with vernakalant; whereas your patient with severe heart failure may not.

You have that healthy person AFib, and then you have the post-op AFib, and those patients are very different, the post-cardiac surgery patient. Most of the people who are going for cardiac surgery have structural heart disease. They have valvular heart disease. They have coronary artery disease. They could have just had an MI, and that's a different kind of AFib.

I think you get that inflammation from post-op

pericarditis and may not respond quite as typical medications. A lot of those patients have reduced ejection fractions post-op. I'd be much more concerned about giving a cardiac depressant to those patients.

DR. LEWIS: Dr. Alexander?

DR. ALEXANDER: I'm going to try to limit my comments to safety here because I think that's where the question's focused. I'm going to try to answer the question of whether the safety profile has been adequately characterized. From what I've heard, I would take away that there's a clear risk that vernakalant's a potent negative inotrope. In my looking at the totality of the evidence as has been presented, there are some patients who tolerate that okay, for a brief period, and some patients who clearly don't tolerate that okay.

I agree with what's been said. I find the SPECTRUM results reassuring that there is a population where vernakalant is reasonably safe in that selected population. I would answer this question, focusing on the word "characterized" here. My question is can we identify this low-risk population?

I think SPECTRUM, to a large extent, successfully did that in Europe. I'm not sure the checklist or what we know can completely get us there. I have concerns about post-CT surgery. I've concerns about the elderly. I have concerns about heart failure, which is hard to diagnose, particularly in the setting of rapid AFib. I have concerns about EF, which changes and is hard to assess in these settings; and about duration of atrial fibrillation and whether -- certainly people with atrial fibrillation, for a while with high heart rates, are at higher risk for having LV dysfunction and reduced cardiac output.

So I'm less confident that I can say with certainty that we've characterized what these high- and low-risk groups are, and that we can define them, and identify them, and help physicians and patients do that.

DR. LEWIS: Thank you. Ms. Hazlett?

MS. HAZLETT: So I'm looking at this from a slightly different perspective as the patient representative here, and I'm also a clinician. As the administrator for the atrial fibrillation support

forum, every day what I hear from patients is how they would be thrilled to have something that would help them to convert this quickly.

But the thing I think that has not been addressed is our average age on the forum is 40. That means we have so many people in their 20's and in their 30's. Let's just say they present in the ED an acute episode of atrial fibrillation, and vernakalant is offered to them, and the checklist has been gone through. I like the checklist. I love checklist. I like things that make things clear. However, these patients may not have been worked up. They may never have had an echo. They may not have had their stress test. They may not have had anything to say we've got no defects here.

So that concerns me, that they would very much say, "Sign me up. I'll take it." Their understanding of the risks versus benefits may be different, and they would just say yes. And I'm just concerned that there would be a problem because they may have things that are not handled already. This is a very anxious population. They're anxious for a new drug, but

they're also -- say amiodarone to any of them, and there's a big stress level going on there.

My concern is that if this drug is given, the risks of the unknown outweigh the benefits in a younger population. For the older population, I think the checklist seems appropriate. I think it seems, for most people, we do have the ejection fraction. We have the history. We have their workups, and that that would be a good choice.

DR. LEWIS: Thank you. Dr. Floyd?

DR. FLOYD: This is relevant to question 1 about whether the safety profile is adequately characterize, and I would say no. I want to focus on this issue of selection bias in SPECTRUM.

In contrast to a randomized comparison, where you take healthier people and you're looking at a treatment effect across two treatment groups, I would say, yes, that would be great; reassuring if the event rates were quite low. But this is a single-arm observational analysis, and, in fact, people could not enroll and could not be observed unless they survived treatment, and were recruited, and provided informed

consent.

So I'm pretty well convinced, along the lines of the FDA analysis, that we did not observe deaths, serious events like that hypotension that incapacitated people because the study design fundamentally did not allow this. So I don't find the event rates credible, when the thing we're really concerned about is something that happens right when you get the treatment.

This is a basic problem with the study design, and regardless of what the numerical estimates are, I don't think it's possible to conclude reassuringly that this drug doesn't cause serious hypotension, cardiogenic shock, based on the results from that study.

DR. LEWIS: Dr. Moliterno?

DR. MOLITERNO: The specific question is safety and adequate characterization. Back to my earlier question, I would say no; it hasn't been adequately characterized if, again, we believe that 97 percent of the patients were white. We know that a much higher proportion of patients in the United

States, in the Americas at least, are non-white. So I would like to know if that belongs on a checklist or not.

I can say as a busy practitioner, there are many patients whom I see in the emergency room with atrial fibrillation, who when asking them if they have any cardiac history, they say no, but once we start doing an evaluation, we find that they do have either structural heart disease or other problems that otherwise would have been unbeknownst to us, and they could be potentially at increased risk in receiving this drug.

With regard to SPECTRUM, I think that the data show it's probably safe, but without a control group, I'm hard-pressed to say if it's adequately safe. I think that they saw no death among 2,000 patients is reassuring, but there are few patient groups of 2,000 cardiac patients that we don't see at least one death. So it makes me wonder how representative the sample is of, in fact, 2,000 patients with important heart disease.

DR. LEWIS: Thank you.

DR. STOCKBRIDGE: Can I get some clarity on one aspect of that?

DR. LEWIS: Yes, you may.

DR. STOCKBRIDGE: Thank you. Can you say why you're concerned about the racial distribution here? Is there an expectation that AF is different in other racial groups or the response to the drug might be different?

DR. MOLITERNO: Yes, yes, and yes. I think that, gosh, you've been doing this for longer than I have, and you've seen curve balls when you didn't understand maybe if there are in fact off-target effects. We heard from the investigators that there weren't off-target effects. I'd be surprised. Maybe there is not, but we're talking about sodium channels, potassium channels. Obviously, they exist in most cells, let alone myocytes, whether they're in the atrium or ventricle.

But sure; beyond the things that Dr. Ridker studied with lipid profiles and the differences among the races, we can look at predisposition to hypertension, to ventricular hypertrophy, and

structural heart disease. That's just on the biologic side.

Now, if we go on the socioeconomic or medical socioeconomic side, we know that we have a higher proportion of our population that do not have universal health care like you'd see in Europe, where they may have a diagnosis established there but not here. So I think there are biologic and social reasons to believe that there are differences between and among races.

DR. LEWIS: Dr. Stockbridge?

DR. STOCKBRIDGE: That's fine. Thank you.

DR. LEWIS: Ms. Alikhaani?

MS. ALIKHAANI: Yes. As a heart patient, volunteer advocate, and family member, and caregiver, I'm really very concerned about a number of issues with this trial that have been -- the clinical trials that have been discussed here today about this particular drug.

I'm also very concerned -- the number of adverse affects that happened during the trial are of great concern to me, that there were so many patient deaths. Also, in cases where animal subjects were

used, some of the dogs died also. In fact, I remember seeing something about one of the primary dogs in the trial had died.

I think that patients like myself, and other healthcare consumers across the country, really, it's very important to me that patients be able to get the kind of treatments they need to address their healthcare problems and also the disparities in care they may be experiencing. But at the same time, I think it's really important that patients be assured that their treatments are as safe and effective as possible.

With all the questions and discrepancies surrounding vernakalant, I just don't feel comfortable with it. There are a lot of unanswered questions, and I just don't feel like all the evidence is available that needs to be available to assure patients that they're getting a very, very safe and effective treatment. I just don't want patients to be misled, expecting one thing and getting another. I think it's really, really critical. We just need to have better evidence.

I'm concerned about, also, given the fact that in the United States, African Americans and other communities of color, and traditionally underserved communities, have the highest level of disparities in care for heart disease, yet this category of patients is not really representative in the trials, how could you have the best evidence if they're not really fully represented? I saw just a couple of patients.

So there doesn't seem to be the right kind of demographics there to produce the kind of evidence that we need to serve a really diverse community in the United States. So how do we know, if such a drug is approved, that maybe it can have some, really, much more dire effects on a segment of the community that was not really present in the collection of the evidence? It just seems to me it's not there.

So I would be really concerned about doing harm to more patients. Even if someone might say, oh, only a few patients died, those are lives. Those are people. It really matters to me, and that really matters to me about the animals that died, too. And some of those, they died after the first dose. They

didn't even get to the second dose.

So that's a concern to me. I also believe that we just need to have better evidence because patients need to be able to make informed decisions, not guesswork.

Also, the issue about the questionnaire and the selection of the patients, there seems to me there are significant discrepancies with the questionnaire that don't appear to have been addressed in a way that it needs to be in order to have patients feel more assured. Patients, healthcare consumers, in general, and family members, and caregivers are relying on us to make the best decision possible, and I think we have a duty to do that.

So I don't think the safety profile of vernakalant is really well characterized here.

DR. LEWIS: Thank you. Ms. Merandi?

DR. MERANDI: Yes. Hi. Jenna Merandi from Nationwide Children's Hospital. I also agree with many of the others that the safety profile has not been adequately characterized. Coming from someone who

operationalizes a lot of things like this checklist and other means of risk mitigation and evaluation strategies on drugs that are of high risk, I think it's very important that we are very crystal clear on exactly what we are trying to predict and prevent.

I know it was stated, one of the conclusions by the FDA, that vernakalant has reduced harm that can't be reliably predicted and prevented. So when thinking about how would we put in place some type of risk mitigation strategy for a drug like this if we don't know those particular answers to those questions, I don't think that we would be able to do this in the safest way possible to prevent harm to our patients.

DR. LEWIS: Do any other members of the committee have a comment on this question? Dr. Alexander?

DR. ALEXANDER: I have one clarifying question about SPECTRUM for the sponsor. My understanding is that the prospective patients enrolled in SPECTRUM were identified prior to getting vernakalant, enrolled in the trial -- enrolled in the registry, and then followed prospectively, so that patients who had

serious events or died would be in at least the prospective part.

That's not the case for the retrospective patients, where patients would have to be alive to give consent for the retrospective. Is that correct?

DR. TERSHAKOVEC: Yes, that is correct.

DR. ALEXANDER: Thanks.

DR. LEWIS: Okay. To summarize, I think several of our advisory committee members felt some reassurance from the results of SPECTRUM. However, there are concerns expressed that they were very low-risk patients and that they might be difficult to identify, particularly difficult to identify perhaps in our healthcare system where we don't have universal records or with young patients who may not have had any evaluation previously. Also, there is an underrepresentation in SPECTRUM and in the clinical trials of important populations from the United States.

Dr. Stockbridge, do you have any other specific questions to this question?

DR. STOCKBRIDGE: No, I think we're good to go.

DR. LEWIS: Okay. I'm going to read the second question. Please discuss whether the efficacy and safety profiles of alternate approaches to cardioversion are relevant to assessment of vernakalant's benefit-risk assessment. If so, given the indirect comparisons, how do vernakalant and alternatives compare for A, effectiveness, and B, for safety?

Are there any questions about the clarity of the question for the FDA?

(No response.)

DR. LEWIS: The question is now open for discussion. Dr. Ridker?

DR. RIDKER: Sure. I think this is actually a terribly important part of the question and as a clinician who has the advantage of having lots of EP colleagues nearby, but has to make real-world decisions. I think half of this is we do recognize there's a significant clinical need here. I think that's real for me. There are many patients where recurrent atrial fibrillation is a big issue. I do have some very high-risk patients.

Electric cardioversion works great -- no doubt about that -- but there are some circumstances where it is difficult, and I do have sympathy for that. I also have sympathy, as Professor Camm pointed out, that our European and Canadian colleagues do have access to far more drugs than we do, and I'm sure that changes the nature of practice in a pretty fundamental way.

I think the difficulty for me here today is I found the post-authorization safety study pretty marginal, and I thought that SPECTRUM didn't provide to me what I was hoping for. Then that leads to the fundamental issue with this question, which when I came here, part of me was wondering, in the complexity of being asked to approve a drug in a clinical hold, how you work that through.

Early on I asked Dr. Weaver, actually, whether or not having an echo would help, and the response was, "Not really." And I can understand that response, but also, I suspect that means a REMS that would be echo oriented probably wouldn't fit the bill either, which sort of leaves me with this fundamental question, which is what's being asked here in question 2, which is how

do you feel as a clinician versus cardioversion and versus, I guess, ibutilide? Those are my options.

I suppose the difficulty of today is I walk away feeling like, well, maybe our goal as a clinician -- because I think these meetings are ultimately about what's the net upside, and is this a substantial advance? That's sort of how I look at these things. And I'm afraid I'm sitting here saying to myself, maybe what we really need to do is just improve access to electrical cardioversion and make it really, really easy.

Then B, I was very impressed with something that Professor Kowey said, which was that ibutilide just isn't used very much, but I didn't hear why it wasn't used more. And if there is this need for this, and we have an approved drug -- I mean, I recognize it's not exactly the same, but it seems to me that those would be more straightforward things to do.

So for me, yes, I think that it does matter that we have these alternatives out there, and I think what I'm struggling with is what's a substantial advance for patient care versus what's another option,

and right now, I'm not convinced it's a substantial advance.

DR. STOCKBRIDGE: Can I just point out to you that it's not the standard for approval that it be an advance.

DR. RIDKER: Okay.

(Laughter.)

DR. LEWIS: Dr. Mandrola?

DR. MANDROLA: I kind of want to echo what Sue said about patients wanting safe drugs that are available. Atrial fibrillation is different. Atrial fibrillation, much of cardiology is heart attack and heart block. Patients need care. They're dying, and if they don't get it, they're going to die.

Atrial fibrillation is a different condition. It's what I take care of, and almost every day, what guides me is harm reduction and harm avoidance. Antiarrhythmic drugs can create harm; AF ablation does. It's these tail events. You don't need many events. It doesn't have to be a high percentage; it just has to be bad events that can get your attention, and you're taking care of these patients every day.

So the sponsor has rightly said, we need to select patients who are better for this drug, so we're going to exclude patients with hypotension, with LV dysfunction, and with all of these bad problems, and that then leaves us with this relatively healthy population.

For home, I'm not sure that the small number of events is a fair trade for the convenience of cardioversion. I think ibutilide has a pretty good safety -- we've seen ibutilide. We've seen the safety of electrical cardioversion, but we also have the watchful waiting approach. These alternative approaches are favorable because they avoid harm.

I was struck by the FDA presentation, where if you don't convert with this drug, it's really bad because now you're looking at a high rate, potentially low blood pressure, and negative inotropy. Okay, 50 percent convert, but 50 percent don't. So I'm concerned about not a high percentage of harm, but a high consequence of the harm.

DR. LEWIS: Dr. Needleman?

DR. NEEDLEMAN: Matt Needleman again. What

are other options? We talked about -- I'll kind of go backwards, pharmacologic cardioversion agents. We have flecainide, 300 milligrams a day. I think that's maybe 30 percent effective, so that's much less effective than this potential medication.

I was really excited when ranolazine was approved because I thought that may work. That's probably less than 5 percent effective, 2 grams, it doesn't work. Dofetilide, maybe 40-50 percent effective, also less effective than this. But in a real-world trial, 30 percent of people weren't able to tolerate that medication because of QT prolongation.

Ibutilide, also is probably in that less than 30 percent effective regimen, much less effective than that. And having caused Torsades in patients who shouldn't have been risk factors for Torsades, I have a healthy respect for it. I won't give it without preloading magnesium now and all these things that I've kind of learned.

Cardioversion is probably our most effective treatment, but it's a significant limitation with the sedation. There are patients who do very well with

cardioversion. But when you cardiovert and sedate somebody -- like that patient, the 77-year-old gentleman who passed away in that first trial, I guarantee, if somebody came in with dyspnea and a heart rate of 174 as an initial thing, I was going to sedate and cardiovert him, he would have been hypotensive before I even got to push the button on the cardioversion.

Something else was going on with him. I think he was sick from some other metabolic or process. Something else was causing him to be sick, and I think he would have had a bad outcome no matter what. Unfortunately -- Dr. Alexander brought it up earlier. But I think we underreport the serious events with cardioversion.

It's not necessarily the electrical part, it's the sedation and -- I think the reason we get away with it a lot is because we have an anesthesiologist there, most of the time when I do it, micromanaging the blood pressure and giving all sorts of different little doses of medications to kind of get you through it. Cardiac outputs, heart rates, and stroke volume, if you changed

the heart rate very suddenly, the cardiac output is going to decrease very suddenly, and the body's got to compensate for that. And during those few minutes after cardioversion, it's a dangerous time, I think, no matter how you get there.

So I think we just really need to realize that our current treatments are very imperfect.

DR. LEWIS: Dr. Alexander?

DR. ALEXANDER: I think that certainly to do justice to an evaluation of the effectiveness and safety of vernakalant clinically, one has to compare it to alternatives. That's largely because the benefits of it are largely avoiding the alternatives, maybe, which is having to be hospitalized, stay longer, get anticoagulated, maybe or maybe not, and get sedated, and have electrical cardioversion.

Actually, what's missing under A and B down there is a process of care. In my mind, really, the biggest benefit of vernakalant that I've heard is that it would allow people to be quickly cardioverted in the ER. That has all kinds of health economic, and avoids a hospitalization for a patient, which likely has risks

in and of itself. So I do think that it's relevant to compare vernakalant to the available alternatives.

We've talked a lot about cardioversion, and I think that cardioversion with sedation, with the delays that are necessary because of the need for sedation, has I think some risks that are not always appreciated. Others have brought up do we really need to cardiovert all these people? Could we just watch and wait? Most of them would end up back in sinus rhythm anyway. Then the safety, also, I think is relevant to think about what the alternatives are, watch and wait, the risks of electrical cardioversion with associated sedation.

Again, I go back to this idea of can we identify the right patients? I think there probably is a patient cohort in whom vernakalant is an attractive alternative. I'm just not sure we can identify it, and I think we'll get to that later.

DR. LEWIS: Dr. Packer?

DR. PACKER: Julia, could I ask the sponsor a question, especially the electrophysiologist? I just want to be able to understand the world, and the issues that you face, and the patients you see, because I want

to make sure that I understand this.

Let me just try to explain my thinking while I wait. For patients who are elderly and patients who have LV dysfunction and who have heart failure, my sense is these people are off the table for this drug. The efficacy is markedly diminished. The risks are markedly increased. The risk-to-benefit relationship in that population is really demonstrably unfavorable. As John had said, if you give the drug and they don't convert, then you're in many ways worst off than you did, and those are the patients who don't convert, the elderly patients and the patients with heart failure.

So let's just take them off the table. If I could ask Peter and John, forget about the checklist that the sponsor has put forward, just take it off the table, could you tell us what your personal checklist would be, and based on the totality of your experience, what other options you have?

We rarely give the consultants or the sponsor a chance to talk during this session. I guess you can talk only if you're invited, so I'd like to invite you.

(Laughter.)

DR. PACKER: Forget about anything that was presented today. If you had your own personal checklist, and you had to develop it right now, what would it be?

DR. TERSHAKOVEC: I'll ask Dr. Camm to start because he has access to the drug in the EU, and then Dr. Kowey after that.

DR. CAMM: I think the first thing that I would do on seeing a patient in the emergency room is ask a simple question of how well this patient was. I don't mean whether they have symptoms or not, but just how well is he from the hemodynamic perspective, and, of course, would make the relevant measurements to ascertain that.

The majority of patients that I would consider for pharmacological cardioversion would have to be symptomatic and would have to be well. When I went to into it, I would want to have a fairly negative medical history for most serious conditions, most serious cardiac conditions, for example, because by definition, that patient is going to need a much more significant workup before I consider doing anything such as giving

pharmacological cardioversion, and to some extent before considering electrical cardioversion.

So I think the major issue is, first of all, significant medical history; secondly, extent of symptoms; and thirdly, what underlying cardiovascular disease they have. And if they're relatively hemodynamically stable and they have no significant past medical history, and they're symptomatic, and I can cardiovert that patient, and have done with that particular medical problem for that occasion, I would then proceed to cardiovert that patient, and pharmacological cardioversion would be a quite reasonable approach.

Obviously, we'd have to match drug and patient, and there are specific reasons why I might not use a particular drug in a particular patient.

DR. LEWIS: Dr. Camm, before you sit down, may I ask you a question since we've opened it?

DR. CAMM: Of course.

DR. LEWIS: To the point of operationalizing this, no significant medical history is a pretty broad comment.

DR. CAMM: Yes, of course it is.

DR. LEWIS: I think our point about some of these people being very young, and this is their first episode, perhaps, and not having had a lot of health care, how would you operationalize no significant medical history?

DR. CAMM: Well, I think it is difficult just with my saying any significant medical history, and, of course, there's a whole list of things that one could put on any checklist. But personally, I don't have a definitive list of issues that I go through. I see the patient, I hear what they've got, and I decide from that whether or not I might proceed. But I definitely don't have a mental checklist with dozens of conditions in it.

DR. LEWIS: Thank you.

DR. PACKER: Peter?

DR. KOWEY: Milton?

(Laughter.)

DR. KOWEY: Thank you for this opportunity. And you're right, we don't usually get a chance to do this. First of all, what John said is absolutely

correct. The initial evaluation of patient in the emergency department history, I know this is going to sound like an anathema, but a physical examination, a global assessment of the patient in the emergency room, background therapy, previous history of presentation, all that stuff obviously comes into play.

I'm going to be perfectly honest with you, Milton. I think it would be highly unlikely that I would give this drug to somebody without an echo, within the last few months, perhaps. It doesn't necessarily have to be right this minute., but knowing what I know about this drug and all the other options that I might have -- even an electrical cardioversion, I would be very reluctant to electrically cardiovert a patient without having a fairly good idea, with all the limitations of doing echos in people who were in atrial fibrillation, granted. I think I'd like to have that information before I cardioverted a person, either pharmacologically or electrically.

What's been missing is exactly what you've brought up, exactly what you brought up, which is we depend on our clinicians to make an adequate assessment

of the patient, and to make a risk-benefit assessment of the patient at the time. You can't globalize that. You can't generalize that. That's what John was saying. You have to individualize it. But I think that, knowing what I know about the drug and the clinical situation, that I can make that decision. As a doctor, I can make that decision, and I can preserve patient's safety adequately doing it that way.

DR. PACKER: Peter, if I could, just ask one brief follow-up on. From a committee and from an FDA point of view, the question isn't whether we trust you, because we do; it's whether we trust all the physicians out there to do this, so that's a problem.

But let me, if I could, just ask a very specific question. I'm going to make this as clean as I possibly can. A young person without any known structural heart disease, comes in with 2 hours of palpitations, racing heart rate, whatever symptoms you want to give them, is found to be in rapid atrial fib, and make that person 30 years old.

I'm going to put two options on the table, and I just want to make sure that I understand how you

would choose. The patient is symptomatic. You can say -- and I'm going to ask you not to do the following. John has brought up a very good point; just send them home and say come back when you've converted yourself.

MALE VOICE: That's not what he said.

DR. MANDROLA: Not just that.

(Laughter.)

DR. PACKER: I'm joking. Why don't you electrically cardiovert that person right then? Why does this recommendation exist that prior to electrical cardioversion, you have to anticoagulate, but prior to pharmacological cardioversion, you don't? That makes no sense.

DR. KOWEY: Oh no; that's a misunderstanding. The same rules apply for anticoagulation in either kinds of conversion.

DR. PACKER: Why not just electrically cardiovert that patient immediately?

DR. KOWEY: Totally reasonable to do that. By the way, let me just back up for a minute and tell you that when a 30-year-old comes into my emergency room

with atrial fibrillation, I'm even more worried about why, and should I maybe even be more likely to get an echo on that person than I would in an older person that it's a known flyer with atrial fibrillation.

That aside, absolutely, positively, if your hospital is geared up to have somebody come down and do adequate anesthesia for that patient, and put them to sleep, and cardiovert them, absolutely, and some of the guys in my department do that. I personally believe that in most emergency departments that don't have big electrophysiology sections and a lot of fellows running around, which is what we use, that having something available to cardiovert that patient, again, in the setting of what John and I have very clearly outlined, would be a tremendous advantage for some patients, but it's just something that you need to individualize.

I think this issue of characterizing the patient before you give the drug, everybody around the table said the same thing, listening to the responses. I think that that is absolutely paramount, but it is what we would hope to be able to educate. This really gets down to something that hasn't come up, which is

education here of the practicing physicians is going to be of paramount importance.

What usually happens in this situation is the EPS are the first people who adopt this stuff, and then it sort of gets down to the cardiologists, and then back down into the emergency department. That's what happened with adenosine; remember? It's the same thing that's happened with a lot of drugs that we use in emergent settings.

So the process I think is in place. It's a question of educating doctors appropriately.

DR. LEWIS: I think if we could direct ourselves back to the question about comparing vernakalant to ECF and ibutilide. Dr. Davis?

DR. DAVIS: Barry Davis, University of Texas. I think one should look at the things that are relevant. Unfortunately, indirect comparisons are really not that great all the time, unless you can make them as much alike as possible. It seems to me, here listening to the whole discussion today, that there's a lot of information all over the place. Obviously, it would be nice if there was a head-to-head comparison of

these things. I don't think that's going to take place.

It seems to me that everybody thinks that it's effective, and a lot of the data looks like it really is effective. But there are these safety concerns. The biggest problem in my mind, the thing that was brought before us today, was that the SPECTRUM would allay these concerns, and for me that really doesn't.

SPECTRUM just has a lot of problems. It's combined this combined prospective and retrospective. It's selection bias. It's a mix of the kind of patients that got in there, so I'm not sure. There were some serious problems before this, and I'm not sure that this solved it.

DR. LEWIS: Do any of the committee members want to comment on their comfort with vernakalant's safety versus ibutilide, or ECF?

DR. RIDKER: Just a clarification from Dr. Kowey. Now, I got a little confused. How long can a patient, in your mind, have AFib and get a pharmacologic cardioversion before you want to anticoagulate them? I'm just a little bit -- can we

clarify that?

DR. KOWEY: This is Peter Kowey again. The conventional wisdom has -- I don't know if you remember the paper in the animals several years ago said 48 hours was this magical time period. Well, we've learned that's probably a little long, because if you look at transesophogeal data, for example, left atrial clot tends to form a lot faster than 48 hours. So we don't give people 48 hours anymore. We give people several hours, a few hours.

The problem is -- and I don't know who said this. Maybe it was Dr. Needleman -- trying to time when somebody goes in -- maybe it was Dr. Mandrola -- trying to time when somebody goes into AF. When they say they did is not always that reliable, and a lot of times, people get it wrong. They think they were in AF earlier than they were and vice versa.

So my inclination in this situation is, unless I'm very sure, and it's within, say, 6 to 12 hours, then anticoagulation is on the table. If you can't, acutely anticoagulate within that time frame of

transesophageal echo before conversion.

DR. RIDKER: Right. That's why I want to get to here. I'm often asked to do a TEE on very short notice because we want to electrically cardiovert, and I can't remember being asked to do a TEE because we wanted to give ibutilide. I'm trying to understand why that is.

DR. KOWEY: That's exactly the point. is that you can get ibutilide into somebody a lot faster than you can make the arrangements to electrically convert somebody. So the hope is that if you had a drug in the emergency department, they wouldn't have to go through the rigmarole of getting the anesthesia people and everything, and use up a lot of time, but the rules are the same.

DR. RIDKER: Are you willing to do it without the TEE.

DR. KOWEY: The rules are the same.

DR. RIDKER: But that's why I'm stuck because it sounds like -- you've said you would like an echo, and you might even prefer a TEE if you could get it quick. But I'm not hearing that in the whole

discussion today about how this drug would get -- I mean, a REMS that said you must have a TEE might change my whole attitude towards this, I suppose, but that's not what I'm hearing, even remotely.

DR. KOWEY: Paul, I tend to agree with you about the echo. I already said it, okay? And I know the sponsor hasn't necessarily gone there, so maybe I'm going a little off the reservation. But my opinion is that any question whatsoever -- Milton used the 30 year old. Thirty year olds in AF, by the way, scare the hell out of me. I mean, they really do because I don't know why they're in AF, so I have a pretty low threshold.

You know, as well as I do, the handheld echo things in the ER now, you can hook up to your smartphone. I mean, what are we talking about here? Why not? If you really want to assure yourself that you're in good territory, why not? And I agree with you also. If you're not sure about the anticoagulation issue, the best thing to do is just do the TEE, which is low risk.

DR. LEWIS: Thank you. I think we are a

little bit off at least this question's topic, and I do think that we need to separate that thought of wouldn't it be great not to have to wait for an electric cardioversion, and organizing it in our hospital and just get a shot and run versus is this the drive we want to do that with.

Dr. Unger has the next question.

DR. UNGER: Ellis Unger. I just wanted to make a point or two, and then there's another point I think I want to make when we discuss number 4. Dr. Stockbridge pointed out that the approval standard is not better than a comparator. But I will say that in the approval standard is safe and effective, and you saw this converts about half the people.

So the number needed to treat is about 2, and about 1 percent of people have misadventures, so the number needed to harm is about 100; and compared to most drugs we approve, that's pretty good.

But when we do our little risk-benefit calculation at the FDA, there's a section on other therapies. So that's how we kind of massage this and say, well, we don't like this compared to other

therapies. I just wanted to clarify that because it's an unusual situation.

The other thing I wanted to do, I've written two notes to Dr. Stockbridge during the meeting, the possibility of no echo, no drug. And I would like to hear -- and maybe not until question 4 -- a robust discussion of why that would or would not mitigate the risk, at some point. I don't know when we should discuss that, but I want to make sure that we have that discussion, because we're hearing it now from a number of people.

DR. LEWIS: Can I pause for a moment because I was hoping that before we got to the voting question, this subject of echo would come up. The sponsor would like to discuss the echo report, if I've got that correctly, and then I want to give Dr. Dunnmon an opportunity to respond to what they say.

DR. TERSHAKOVEC: So there were some questions about the echo report and the different interpretations, and I want to ask Dr. Weaver to come up and show the echo report and the translation. This is for the ACT V patient that we discussed.

DR. WEAVER: Thank you. I appreciate the opportunity because I know a lot of this has been driven by these deaths in these early studies, these two deaths. I have to say that when I started to work with the sponsor, when I saw this first patient, who died, I wondered why. Why should this fellow, when I know the mechanism and everything else, have died? Then, why should he have not been resuscitated even after he had his cardiac arrest?

So I went to the source records. Being an investigator, I didn't stop with the monitored records; I wanted to see what was in the source.

Can we pull up the echogram? Slide up, please.

For those of you who can read Spanish, it's on the left side here. When I saw this, compared to what was in the medical monitor's report, I didn't have to have it translated to say, "Sistolica moderadamente reducida por hipocinesia, difusa hipocinesia." That's moderate systolic dysfunction. That's not minor. It's moderate, and the translation's over here on the right side.

So not only did this guy have symptoms and signs, he actually had an abnormal echo at the time of this. So in my mind, he should have never been enrolled in this study. He shouldn't have been enrolled because of anticoagulation as well, but he did have a cause, and that's why we have looked for what are those things, signals that come up?

As Dr. Packer pointed out, heart failure looks pretty powerful on those things. Structural heart disease looks powerful. I didn't show you, but we've done some pharmacovigilance studies. Heart failure comes up in that as a significant risk factor for developing a hypotensive event.

So I think we can't get confused that the early sponsors did trials with almost a wide open population of atrial fibrillation, and wide open was a big mistake because you're going to have errors. You're going to get burned, just like what happened here. And that's why we've looked so hard for a target population and tested it retrospectively, and then prospectively tested it forward.

Paul, when you asked me that question about

would I do an echo, well, based on what I saw for clinical events in SPECTRUM, I wouldn't. But like Dr. Camm, when I look at a patient, if I have any questions, I'm going to do something to understand this person's physiology because I think I do understand who's going to have this problem, and I think I can obviate giving this to the wrong patient.

DR. LEWIS: Dr. Packer?

DR. PACKER: Doesn't this report scare you to death?

DR. WEAVER: Yeah.

(Laughter.)

DR. WEAVER: It does.

DR. PACKER: Does it scare you the same way it scares me?

DR. WEAVER: Absolutely.

DR. PACKER: Let's make sure; okay? Here's a patient who got this drug, who after getting this drug had an ejection fraction of 20-25 percent, and severely so. This is the screening echo, which is not terribly -- depending on how you look at it, 44 percent ejection fraction LV is not dilated -- not dilated --

DR. GIBSON: And this is 44 percent at a rate of 156, so I don't know what to make of that. And then when he recovers and has a normal heart rate, his ejection fraction is normal, right, If this is patient B.

DR. WEAVER: Later on, yes.

DR. GIBSON: But that's what's most frightening to me, is this patient had a normal ejection fraction, eventually, had a normal heart rate, and having a normal ejection fraction and a normal heart rate would not have identified this patient as being someone at risk. And that's what I find most --

DR. PACKER: That's what scares me as well. What terrifies me is exactly what Michael said. The whole point of this is this is a patient -- this is not a patient who had a big dilated heart with an ejection fraction to 20 percent who fell apart. This is a patient who didn't have a dilated heart, ejection fraction of 44 percent; I understand, atrial fib, but later --

DR. GIBSON: Normal.

DR. PACKER: -- normal, and who had this

profound drop in ejection fraction even though this echo is not terribly impressive. Therefore someone could have gotten this echo and said, "This is good enough. We'll give the drug."

DR. LEWIS: I'm going to give Dr. Dunnmon a chance to see if he wants to add any comments.

DR. DUNNMON: Could you please bring up FDA backup slide 50? Thank you.

I've seen multiple different translations of mild or moderate. The thing that concerned us was the fact that this was a not bad ejection fraction for going 156. In their system, in multiple places, they documented this person was not in symptomatic heart failure. It's in the database. It's in the MedWatch reports. And he was closely supervised while this was going on. It wasn't like this snuck up on anybody, and he was kind of away for a while from treatment. They were right there on -- he had an electrophysiologist in attendance. I mean, it was closely monitored, and they could not stop this while this was going on.

The thing that I had described to you before in this sequence of echos, it went 44 percent, 0 during

the CPR because the man was described as having no contractile activity at all, with an AFib rate of 110 on the ECG that was done at the same time. He started after 40 minutes of resuscitation with high doses of pressors that he was not responsive to, started sleeping this off.

You remember the dp/dt study I showed you in the dogs, where this was still going after 90 minutes. After about 45, he started coming around. That EF at 25 percent was after they loaded him with amiodarone and shocked him, trying to get hemodynamic and rhythm stability, and then the next day, he was 49. And then you can see there, what I described to you earlier, his MR assessments were mild until the week he died, and he'd gotten a lot of fluid, and got dilated, and start leaking.

The other patient that I showed you -- and by the way, on this person's echo report, the abnormality that was present was they said that he had LVH, and every reader remarked on that, and he had a left atrium about 50 millimeters. So it looked pretty classic, really, like hypertensive heart with normal right-sided

chamber sizes and dimensions, normal pericardium, thickish heart, kind of wound up in a ball going 156, with no reported symptoms, at least to the system as it reported this.

But then I showed you that patient B, where that person was not in the clinical trials. That was just a spontaneous case, where they happened to have an echocardiographer in the room.

By the way, you can stop there. This is what I told you before that was in your -- the applicant had written on the left, where they were saying that this was really an alcoholic cardiomyopathy with EF at 25 percent, LV dysfunction, and MR.

We did not have that assessment. Our assessment was that this patient's recovery of his function, following that 40-minute pulseless arrest, does not support the implicit or explicit thought that somehow there's a safety advantage here when you've got a sodium channel blocker doing what we know it does to the ventricle from the dog studies.

Now, could you please go to FDA backup slide 52? This is that patient B, where the attending

physician remarks specifically that this person had no history of cardiac disease, and I didn't see other structural abnormalities documented in anything that got sent to us at all. This started in the same sequence.

These are not unique to these two people. When you read the other adverse reports that are in your appendix --

DR. GIBSON: But the thing about both of them is they ended up with a normal LV function.

DR. DUNNMON Oh, yeah, and this one was remarkable --

DR. GIBSON: So they not have benefited from --

DR. DUNNMON: -- and it happened quickly.

DR. GIBSON: an --

DR. DUNNMON: Absolutely. So if you look at that series of events, at some point he didn't have enough of an ejection fraction to stop CPR from being started, so I think that 20 was probably not his nadir. But you look at that sequence of low normal, less than 20 percent, back up to normal at 5 hours with normal

troponins, with no echocardiographic abnormality here, this is what we started thinking about, writing that in a consent form that what is the predictor here that you're going to have a poor outcome?

DR. LEWIS: Thank you Dr. Dunnmon and Dr. Weaver.

Dr. Alexander?

DR. ALEXANDER: Yes. I was going to ask you -- and you don't have to answer because it's sort of a rhetorical question of how old this patient was; because I think we're overplaying the importance of ejection fraction in two ways.

One, it's one marker of cardiac function, and there are lots of ways people can have low cardiac reserve with a normal ejection fraction. I mean, severe LVH, a 78 year old, you wouldn't expect them to have any cardiac reserve in there. They could have totally normal systolic function and tolerate a negative inotrope like this really badly.

Then the other challenge I think with an echo is that without vernakalant in these patients, their EFs change. You make someone's heart rate go from 80

to 150, their EF changes. You change their pre- and afterload, their EF changes. So what you really want on all these patients is their EF when they were in sinus rhythm before they got any of this. And I don't know how long before. I mean, that's the other challenge. If you want an echo before you give vernakalant, I don't know whether that's in sinus rhythm, right before they go into AF. I mean, that's what you'd really like, and that's unlikely to be available.

DR. LEWIS: Thank you, Dr. Alexander.

I'll make one quick comment that it is concerning that two investigators, at least, enrolled patients that arguably were, according to the sponsor, misenrolled, who probably got a lot more background on who to enroll and not enroll than our average ER doctor might get; so I think we have to be very cautious. I think I would trust Dr. Camm's judgment in any situation, but we have to think about the wide use in our healthcare system.

I'm going to summarize question 2, and then I think we'll take a -- do I have more people that have

comments for question 2?

Dr. Needleman, did you have -- no, no. I'm happy to do more comments.

DR. GIBSON: I'll just do one comment, which is you focused a lot on HFrEF as a risk factor, but perhaps there's something going on with HFpEF. For instance, amyloid, if you give digoxin, will concentrate the drug, and you have some toxicity. So is there something here that is allowing that kind of toxicity that's not obvious in terms of left ventricular ejection fraction reduction?

DR. LEWIS: Dr. Needleman -- [inaudible - off mic].

DR. NEEDLEMAN: Just to follow up on that one patient. He was 77, and his presenting heart rate was 174. To me, that's an emergency situation. A 77 year old shouldn't have a heart rate of 170. That's really outside the normal. Does anybody think -- that's a dangerous situation.

DR. PACKER: It sounds like a great case for electrical cardioversion.

(Laughter.)

DR. LEWIS: Dr. Packer, I thought you didn't have another comment?

(Laughter.)

DR. LEWIS: Dr. Needleman, are you done?

(Dr. Needleman gestures yes.)

DR. LEWIS: Dr. Ridker, I believe you have one short comment.

DR. RIDKER: Yes. This is just to return to Dr. Unger's question to us a minute ago about the echo issue, and Dr. Alexander I think got halfway there.

We're going to go to the real questions in a second, and this is an entree to that, that I think it's important. I must say I came here today wondering something related to this, which is would the FDA lift the clinical hold and have the sponsor do the proper study, where you got a baseline echo in lots of people at high risk for recurrent AFib, so you knew the echo at baseline, and you did something?

Is that within the realm of what you're asking us or is that just off the table for this kind of discussion? Because you were asking about what the echo issues might be here.

DR. STOCKBRIDGE: If we thought there was a reasonable study to be done, a theory for how to manage this risk, and we wanted it studied, then we'd lift the hold. There's no question we'd do that.

DR. LEWIS: Okay. I'm going to make a stab at summarizing our wide-ranging discussion on question 2. I think that in terms of comparing it to the other alternative, we have heard, again, a little bit of a mixture of points of view that ECF works great. It's really just a management or a healthcare issue of getting the anesthesiologist and mobilizing the resources, and an inconvenience to the patient to have to stay longer for all that to happen, and that harm reduction should be our focus.

On the other hand, we've heard that ECF is not necessarily as safe as we think it is, that there is much underreporting of negative effects of it, as well as ibutilide. Other drugs are thought to be less effective, so there are not other drugs that are as effective to help patients convert pharmacologically.

Is the risk of the drug worth getting out of the ER more quickly? Then I think we did focus a

little bit on a discussion that will come more to our fourth question, which is could we identify a population for which the safety compared to the alternatives would be acceptable? We've heard about selecting people with no significant past medical history that is relevant; nothing can beat the physical exam. I think that summarizes it.

Dr. Unger or Dr. Stockbridge, do you have any other comments or questions for this one?

DR. STOCKBRIDGE: I think we're good.

DR. LEWIS: Okay. We will take a break. We will take a 10-minute break. Panel members, please remember there should be no discussion of the meeting topic during break amongst yourselves or with any member of the audience, and we will resume at 2:10-ish.

DR. RIDKER: Julia, would there be a possibility of skipping the break, by chance?

DR. LEWIS: I'll give you a little bit longer. You want a 15-minute break.

DR. RIDKER: No, no. I was actually wondering if we could skip the break because --

DR. LEWIS: Excuse me?

DR. UNGER: Our recorder would like a break.

DR. LEWIS: You want a break? Okay. Our recorder needs a break. We'll compromise. We'll do a 10-minute break.

(Whereupon, at 2:01 p.m., a recess was taken.)

DR. LEWIS: Thank you for all taking that short break. If there's no further discussion on this question, we will now begin the next question, which is the voting question.

We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO 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. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed.

I'll read our voting question. Do you recommend approval a vernakalant for the rapid conversion of recent onset atrial fibrillation? Does anyone need a clarification of the question?

(No response.)

DR. LEWIS: Okay, then we are ready to vote. Oh, I'm sorry.

DR. ALEXANDER: Does this include necessarily both the postoperative patients and presenting in the emergency room patients?

DR. STOCKBRIDGE: I think if you can name a circumstance under which you're ready to approve it, you should vote yes.

DR. LEWIS: We'll proceed with voting.

(Voting.)

DR. LEWIS: Please press the button on your microphone that corresponds to your vote. You will

have approximately 20 seconds to vote. Please press the button firmly. It looks like we've succeeded in our vote.

DR. WANG: For the record, we have 2 yeses, 11 nos, and zero abstain.

DR. LEWIS: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. Dr. Ridker?

DR. RIDKER: Yes. Paul Ridker. I voted no. I don't think it's worth going through a lot of the details of why; we've talked about it a lot. I would say one thing, though, which is that I don't want this vote to imply that we should shut down pharmacologic cardioversion in general as an approach, nor that this drug as an approach should necessarily be abandoned.

I would like to say, for the record, I probably would encourage the FDA to consider lifting the clinical hold and allowing the sponsor to maybe figure out some study designs that would answer some of these critical questions, so that we could come back

here with more data on benefit-to-risk ratio, because I suspect there are patients this is a good idea for; I just haven't been convinced today of who they are. And that would require a lift of the clinical hold to allow them to do that.

DR. GIBSON: Yes, I agree with Dr. Ridker it would be great to see more data, the drug evaluated further. Dr. Gibson. Sorry. As an interventional cardiologist, we're always weighing risk and benefit. In order to take a risk, there has to be a very clear benefit. For instance, we do things like put stents in that have a 0.5 percent risk of stent thrombosis, which carries a substantial risk of harm, and we weigh the risk of bleeding in that context.

Here, there is a risk of a very infrequent, potentially catastrophic fatal event, but I'm looking for what's the advantage, and I'm not seeing -- it's convenience. But when I look at our hospital, we have a room full of 10 to 15 people getting cardioverted all day. Getting them out quicker I'm not sure is necessarily an advantage to the health status of an individual patient.

I was struck by some of the basic animal lab data, the fact that the negative inotropic could not be separated from the antiarrhythmic effect. Mostly, I was concerned and struck by the persistent inhibition of dp/dt, all the way through 90 minutes, and I never saw that come back up. I was left wondering when does the LV function return?

I was also very worried about the two patient narratives. Both seemed to have normal LV function at the end of the day, and when I looked through their histories and began to apply the checklist, I don't know that the checklist would have identified those two patients as having been people at risk.

If you're going to take a risk, you have to say, well, are there other alternatives? There did appear to be other alternatives that have treatable side effects. The SPECTRUM data was submitted. I just think it's hard to believe the mortality rate was that low. Obviously, you had to be alive to consent, so I think that's a big limitation; that we did not adequately capture what may have been some events.

I do a lot of adjudication of events, and

people may not die within 24 hours. They may have begun the spiral down at 24 hours, and they may die at day 31, not within 30 days. They may have died from pneumonia, or sepsis, or something, a complication, and they may die somewhere else. You may not have the medical records to review right at your hospital. If you only complete 68 percent of the checklist, I wondered about your ability to collect data about those adverse outcomes.

So at the end of the day, I just didn't feel, at this point, in this development, of this drug, there was an unpredictable risk. We take risks, but here the risk was unpredictable. And when you have an unpredictable risk, I think it really makes it much more concerning as a healthcare provider, and then you have a side effect that did not appear to be easily treatable. So in my mind, the benefits did not outweigh the risks at this point in time in this development plan, but hopefully the sponsor can make some changes to change that.

Dr. Gibson. I voted no.

DR. LEWIS: Dr. Packer?

DR. PACKER: Milton Packer. I voted no. I will not repeat what Michael said, and I would agree with what he said and the way he said it. This is a drug, in large part, of convenience, which is not counterbalanced by a harm that's unpredictable, but serious. I really tried very, very hard to find some patient population, some low-risk patient population that could be identified, even after the fact, that would allow for a risk to benefit that would favor using the drug in someone, and I couldn't find it.

DR. DAVIS: This is Barry Davis. I voted no. I think Dr. Gibson summarized it excellently. It's a benefit-risk calculation. It clearly has benefit, but it does have risks. If this was the only drug around or the only treatment around, yes, but there are other options. And from what I've heard today, even though I commented upon how you could reliably predict, I don't think that there's any sort of way of getting a handle on this just yet. I would think they could go back to the drawing board and maybe design something that might better say that there's a certain population that would benefit.

DR. MANDROLA: John Mandrola. I voted no for the same reasons that have already been stated. It's just not a favorable benefit-risk ratio. I don't think I need to reiterate what others have said.

DR. LEWIS: Julia Lewis. I voted no. I thought the totality of evidence supported the hypothesis that this drug has a potential for a fatal side effect in a disease that you can live with potentially, although I respect Sue's comments and how difficult it can be, and that there are other treatments for.

DR. ALEXANDER: This is John Alexander. I voted yes, and my rationale is actually not that different than what some of the other people have said. I think the benefit is that the drug clearly converts atrial fibrillation, although it's only a transient conversion of atrial fibrillation; it does nothing to prevent long-term atrial fibrillation. There's clearly a serious safety signal in some populations of patients.

However, I was more reassured by the SPECTRUM data, and I think there is a low-risk population, where

the convenience factor of this drug, that would provide an important option for providers and patients, outweighs the relatively low risk of serious complications. Patient selection is key, and I think more work needs to be done on identifying the patient population that has a favorable risk-benefit profile.

I think there's a pretty clear really low-risk population, I think there's a pretty clear really high-risk population, and I think there's this huge gray zone, which is a big problem. So more work needs to be done to clarify who are the low-risk patients where it would be favorable.

DR. MOLITERNO: David Moliterno. I also voted no, and I don't think I need to repeat what others have said. But distilling it down, I would say it's the net benefit, meaning benefit minus potential harm versus other available options. So for me, it was a relatively easy decision.

MS. ALIKHAANI: My name is Jacqueline Alikhaani, and I voted no, primarily because I'm very concerned about the seriousness of the adverse side effects and the lack of diversity in the clinical

trials.

MS. HAZLETT: My name is Nedra Hazlett, and I voted no for the safety concerns. The potential risks were too great compared to the benefits, which seemed no better than things that exists that are safer.

DR. FLOYD: James Floyd. I voted no. I think this drug clearly has efficacy, but I think it also clearly has dose-dependent effects, negative inotropic effects, that can lead to death. For me, the issue is effect modification. I think that we were shown evidence that clinical heart failure, LV dysfunction, structural heart disease, that these account for a lot of the serious safety issues, and also account for reduced efficacy. So that's clearly a population where you would not want to use this drug, and then we're left with the really healthy patients.

Even there, we heard a number needed to treat of 2 and a number needed to harm of maybe 100; maybe it's 500. But given the asymmetry of the benefit outcome and the harm, that still is not acceptable to me. There could still be opportunities for further clinical development, and I would like to give advice

along those lines.

If you can identify the population where you think the efficacy is preserved, where the harms are minimized, I think the key is to do the study that's designed for that purpose and actually powered to exclude the clinically acceptable amount of harm. Often we do these studies with a few hundred patients.

We see one death, two deaths, and we have wide confidence intervals. I think if that is really the hang-up, then probably the study that's designed needs to exclude what we think is the amount of harm that's unacceptable, which of course is really hard to quantify and people might disagree what that is.

I also want to point out I was actually quite concerned that even in the ACT V study, I believe, where there were stringent exclusion criteria, there were still protocol violations. And I worry about the use of this drug once it's out in practice, where people who aren't as familiar with the benefits and harms as we are, study physicians are going to violate the protocol even more than that. So that was a major concern of mine.

DR. NEEDLEMAN: [Inaudible - off mic].

DR. LEWIS: I don't think your mic is on.

DR. NEEDLEMAN: Sorry. Matthew Needleman. I voted yes for the indication. Quality of life is an important goal, and it may be worth taking risks for. There's no perfect option for cardioversion. Every option has I think significant limitations.

The checklist also had significant limitations; I agree with Dr. Packer's concern that even in mild heart failure, we saw that there could be limitations. But as kind of a blue collar electrophysiologist taking care of a lot of AFib patients, it's nice to have options to treat people.

We've all known patients with normal ejection fractions who keep coming in with symptomatic AFib, who want to get out of it quickly and get back to their lives. So having an option like this I think would be good for a very select group of patients. I understand the concern of the committee releasing this to the wild, but I think in a very select group of patients, this has a role.

DR. MERANDI: Hi. Jenna Merandi, and I voted

no for this as well, just like many of the other reasons stated. Specifically around the risks outweighing benefits for this particularly, I think if there is further data available, it would give us the opportunity to perhaps build a robust REMS program with different elements to assure safe use, perhaps, that would allow us to better identify who should receive this therapy versus those that should not.

I think one of the comments mentioned that providers just need to be really educated on this, I think that it goes much more beyond education. A lot of the providers that are going to see these patients first might be your new learners, and residents, and fellows, and things of that nature; as already mentioned, people that might be less familiar with this therapy and the risks that are associated with it.

So I really do think before moving forward, we would need to know exactly who falls into those categories, and then have a robust program that can actually be operationalized to really capture it versus just relying on education because that doesn't always work.

DR. LEWIS: If there are no more comments on the voting question, I will read the next discussion question. If vernakalant was approved, what restrictions would you place on patients or on the conditions of use?

I think, Dr. Ridker, this could also be applied to your comment about if you were going to relieve a clinical hold and do a clinical trial in the United States, what restrictions would you put on the population entering the study.

DR. RIDKER: Right. I think a creative trial could be done here that would actually convince me this is a very good agent, and I think you'd have to sort of say -- I was thinking about this. I would take my many patients in clinic who are return AFib patients, that keep coming back with AFib, so they get cardioverted or whatever. I know who they are; they're very high-risk people if they're recurring.

Probably you have to grab their echo when they're in sinus rhythm beforehand and exclude the people that we are all concerned about risk. So now you have a randomizable cohort based on a normal echo

and all the other exclusions, like the ones that Dr. Camm laid out so nicely, and then you randomize those folks to this drug I can't pronounce -- I'm sorry -- or placebo. And I suspect you'd probably come out in good shape.

So again, I've already said I would encourage -- I do believe pharmacologic cardioversion has a role. I think there's a future in this. I just know we have to get there. Our colleagues in Europe and Canada have these options, and I'm very sympathetic to that; having multiple is generally a nice thing to have. I do think there's a clinical trial that could get done that would do this, but that requires lifting the clinical hold for this issue.

DR. LEWIS: Would you include an ECV arm?

DR. RIDKER: I guess that would be an even better study, but it raises some other issues, obviously, but it's an interesting thought.

DR. LEWIS: Dr. Alexander?

DR. ALEXANDER: As somebody who voted for thinking about approving it, I would want to restrict use to patients with no structural heart disease, and

that I mean probably more than mild. So it would require assessment of all of these things. I wouldn't just take known LV dysfunction. I would exclude everybody with LV dysfunction. I would exclude people with more than moderate aortic stenosis -- I'm sorry -- yes; more than moderate aortic stenosis, more than moderate LVH, and any recent MI, clinical diagnosis of heart failure.

Then I would want use to be in a setting that could deal -- one of the things I was struck by is, if you think vernakalant is as dangerous as it is, it needs to be used in an environment that's not that different from the environment in which we do cardioversion. It needs to be used in an environment that can use pressors, and inotropes, and intubate. So I would want to restrict use for places that can do at least some of those things, performing ACLS and care.

Paul, I think more study would be really useful. Studying people in this low-risk population to confirm safety in that low-risk population would be really useful. I think we'd want to have more discussion about what the right control group is.

What's the use of placebo? If you're trying to confirm safety, I'm not sure there's a whole lot of use of placebo. Depending on what outcome you're interested, having a cardioversion arm would be really interesting, but it would have to include process of care, length of stay, cost, things like that to be useful, I think.

DR. LEWIS: Dr. Floyd?

DR. FLOYD: I voted against approval and further study, but if this drug were approved, I do agree with the comments that it probably should only be used by the people with the most expertise in the risks and benefits; I'm thinking probably electrophysiologist but also some general cardiologists. There is a part of REMS that isn't invoked often. I think it's under elements to assure safe use, where you can require registration of physicians before they can prescribe it.

So instead of this reliance on passive education, actually have physicians take an online course, saying they understand the risks, quantify the harms, and know what can happen. You give the drug, and then you can't get them out of cardiogenic shock;

know that that's a real risk. So it doesn't have to be an EP doc, but something with more teeth than just saying we're going to educate people I would say is important.

DR. LEWIS: Dr. Moliterno?

DR. MOLITERNO: Thank you. My comments echo the prior two speakers, that if the agency did choose to approve this drug, I would probably focus more on conditions of use. Not to sound prideful, but I probably would restrict it to cardiologists initially who had a deep understanding of this drug, and then --

DR. FLOYD: I should not be allowed to use this drug.

(Laughter.)

DR. MOLITERNO: -- fair enough; come to me -- and then collect data based on that experience gained by cardiologists in the United States, and go from there.

DR. LEWIS: Dr. Needleman?

DR. NEEDLEMAN: Not to rehash what Dr. Alexander and Dr. Floyd said, I completely agree with their comments. In addition to the REMS program

and the ICU setting, I would also not use it in elderly people at all, so maybe patients less than 60.

DR. LEWIS: Dr. Gibson?

DR. GIBSON: I do think the risks of electrical cardioversion may have been underestimated. I guess that's because when I cardiovert people, they're usually in the cath lab, so maybe I have a very different view of cardioversion. But nonetheless, if there was an effort to reevaluate this, I do think electrical cardioversion would be a good comparator, and I do think you might see that the results are more durable with this agent compared to electrical cardioversion. With the sedation and everything else, you do get some hypotension with electrical cardioversion.

So rather than comparing yourself against placebo, which has no safety concerns, compare yourself to something that does have some potential safety concerns to put this in better context.

DR. LEWIS: Ms. Merandi?

MS. MERANDI: Just to add on from what Dr. Floyd said about thinking about a REMS program for

this, also thinking about the role of the patient and how they can be educated, and how they could be aware of the risks and things of that nature through mandatory patient counseling and things of that nature; also the role of the nurse and what type of mandatory education would be required upon them in terms of monitoring, how long they should be monitoring, what they could of be expecting, and things of that nature; so just making sure to include both the patient and other interdisciplinary staff when thinking about this.

DR. LEWIS: Dr. Mandrola?

DR. MANDROLA: You're going to eliminate the elderly. You're going to take away anybody with low blood pressure, anybody with mild LV dysfunction, which is, in my hospital, everybody in atrial fibrillation. And you're going to restrict it to electrophysiologists or registered docs. That leaves you with a very healthy cohort of 40- to 50-year-old people who could easily be treated with atenolol, and some peace and quiet, and sent home, and two-thirds of them will be in sinus rhythm in 24 hours. Sorry.

DR. LEWIS: Dr. Packer?

DR. PACKER: If the FDA were going to approve it, I think there is a mechanical framework for a name patient registry; is there not?

(Dr. Stockbridge nods yes.)

DR. PACKER: This goes beyond the certified physician. This is a certified physician and a named patient registry. The way that I'm thinking about this is it obviously is not going to be suitable for the vast majority of people in the world, but one could imagine that there's a patient population of patients who have just rare paroxysmal atrial fibrillation that you would not put on a long-term beta blocker even, maybe; who would come in every year or two. They could then be put into a name registry, and when they come in, they could get the drug. Because it's a name registry, you could follow them in terms of safety and in terms of how they do.

Name registries might actually provide a path forward that would provide comfort if the FDA were so inclined.

DR. LEWIS: Ms. Alikhaani?

MS. ALIKHAANI: Yes. I would like to see more

work on better identifying and categorizing the high-risk patients; also more consistency with the checklist. Also, I don't know if this is something that they did, but considering the high number of adverse side effects, I'm not sure that there was a strong patient research partner engagement team as part of the research leadership teams. So I think maybe have a consortium of patients to help advise the research effort.

DR. LEWIS: Dr. Alexander?

DR. ALEXANDER: Sorry. I didn't put my card down.

DR. LEWIS: Okay.

Are there any more comments from the panel on the last discussion question?

DR. STOCKBRIDGE: Should I take from this discussion that if we weren't to approve vernakalant at this point, that most of the committee members would sort of like to see a prospective study done to evaluate a risk mitigation plan? Is that fair?

DR. LEWIS: I think Dr. Stockbridge is asking us to clarify our comments. Are we willing to suggest

that the U.S. population should be available for a clinical trial? Does someone want to comment first? Dr. Alexander?

DR. ALEXANDER: Yes. I would say whether or not you decide to approve vernakalant, there's more work to do to characterize in whom it's appropriate and in whom it's not.

DR. GIBSON: Yes. Gibson. I agree, and again, I'd like to see some more work done in the animal studies to know when the dp/dt comes back up as well, the recovery of the LV. But I think a more appropriate comparator, as I said, would be electrical cardioversion.

DR. STOCKBRIDGE: And do you have some notion of what an acceptable performance would be? No events in 30 patients? No events in 10 patients? What are you thinking?

DR. LEWIS: We're getting close to a question here, but I think we could have a further discussion. I will comment, I actually am concerned about lifting the clinical hold only because I think that the animal data supports what was seen in, albeit, a few number of

humans, but humans, and I think it would be challenging to ask a patient to volunteer. But I think other people should comment.

Dr. Floyd?

DR. FLOYD: As I mentioned earlier, I think if a clinical hold were lifted, the trial would have to have clear objectives. I think it would be unethical to randomize, say, 30 or 40 people because the zero events doesn't tell you much compared to the information you have, and there's no point in doing that trial, except to collect physiologic information, maybe.

So I think if a trial is being done, I think a randomized design is preferable to observational, based on what we've seen. It really needs to be powered to exclude some amount of harm that some people would feel comfortable using the drug once you demonstrate that; zero events out of 100 or 200.

The rule of zero events, I think it's one over the number times 3 is the upper bound of the confidence interval. That gives you a back-of-the-envelope calculation. That may be so large a population that

the sponsor can't actually enroll that many patients because of the serious consent issues with the risk of death, and I think that gives an answer in and of itself.

DR. GIBSON: But I do think we have 58,000 patients worth of data up to now, and in kind of a Bayesian kind of way just say, well maybe we should rethink this. But again, it's hard to beat placebo in terms of safety. I do think you have to put it in the context of other therapies, and then set some noninferiority margin with respect to safety relative to electrical cardioversion.

DR. LEWIS: I think Dr. Ridker was next.

DR. RIDKER: I agree with what Dr. Floyd just laid out in terms of the big structure and probably would do it against electrical cardioversion. But I think if you were smart about this, you would also build in a second endpoint that's being monitored along the way, which is just get echo data during the actual infusion.

If you saw, we were very persuaded by these one or two cases, where it appeared that somebody

somewhere saw an echo go from functional to dysfunctional, back to functional. If you design this clinical trial, and then also were to monitor that along the way, and you saw some patients having that happen, it might change what you thought of this drug. And if it turns out that that's not happening, and this is just bad luck, anecdotal something, okay, you proceed. So that's probably how I would look at this.

DR. LEWIS: Dr. Packer?

DR. PACKER: I had previously, as a wild idea, proposed an imaging study, open label, no control, imaging study, looking at LV function during the infusion, in order to quantify exactly what's going on because we don't know.

My personal sense is if you took a group of normal people and you saw that everyone had their ejection fraction fall from 65 to 30, and then it came back after an hour, that would give you a different feel. And if you saw them go from 65 to 60, or whatever you want, you would have a better sense of how much of a negative inotrope this was, even in people with normal hearts.

That would be so informative to this sponsor as to whether they would actually want to pursue this. The problem is that, as has already been mentioned, that would be ethical only if you had adequate informed consent. I guess I would have to ask myself would I consent to that study, and I don't know.

DR. LEWIS: Dr. Davis?

DR. DAVIS: Barry Davis. I think it would be useful if he could do this study comparing to ECV, but there are so many problems. The most important one is the one that Dr. Stockbridge mentioned, which is what's your outcome there? It seems to me that you'd be talking thousands and thousands of patients if you're talking about a very low-level safety outcome.

Then the kind of patient that's going to sign up for this, they'd have to be willing to be randomized to ECV. The whole point of vernakalant was that they wouldn't get the ECV. So it would require a lot of thought as to what the appropriate endpoints are and what the sample size is. It may be prohibitive.

DR. LEWIS: Dr. Moliterno?

DR. MOLITERNO: David Moliterno. I think many

of these questions are great, and are academic, and I'd love to have the detailed information, particularly Dr. Gibson's questions about the recovery of dp/dt and when you could address it. I think Dr. Stockbridge is right and Dr. Davis, how many patients do you need, though, to find the signal beyond that.

I think the overall argument in conversation is a little bit moot since there hasn't been a clinical hold in many European countries over the last decade. So should the sponsor or academicians in Europe wanted to address this, they could have. I think three different companies have owned this drug, and they haven't.

DR. LEWIS: Dr. Alexander?

DR. ALEXANDER: Thank you. I just want to echo support for the echo or imaging study. In the way I've been thinking about this, there's a cohort of high-risk patients and a cohort of low-risk patients. But it would be very different, in my mind, if everybody's AF dropped by half, and some people had reserve to tolerate it and some people didn't.

I have sort of been working under the

hypothesis that there's a cohort that's at risk of LV dysfunction from the drug and a cohort that's not, but that may not be the case, and wouldn't take that many patients to answer that question, potentially.

DR. LEWIS: I'm going to attempt to summarize our discussion of that question. I think that the committee both looked at it as how you would restrict its use, as well as how you would lift the clinical hold. There was interest in exploring the mechanism of action of this drug, either by echo or by comparison with an active comparator, possibly placebo.

In terms of using it outside a clinical trial, I think that virtually all the committee members wanted some restrictions in its use if it was approved, either by only cardiologists or only EP people, or people that are not only both those things but also REMS certified doctors. I think it's an extremely good point that it's not just the doctors that need to be educated and certified, but also the multidisciplinary team that will be caring for this patient.

The question did come up about whether or not this would, A, be enrolled, with the big harm that you

would have to reveal to the patient the potential death, and also would you narrow the population so low, to such a small population that would potentially get this drug, that it's maybe not worth discovering a small safety signal, but a deadly one.

Do you guys have any further questions or clarifications that you want from the panel or discussion?

DR. STOCKBRIDGE: I think we're good.

DR. LEWIS: Are there any last comments you want to make?

DR. STOCKBRIDGE: Just my thanks and appreciation, and hope that you all have a safe trip home.

Adjournment

DR. LEWIS: Panel members, please take all personal belongings with you, as the room is cleaned at the end of the meeting day. All materials, however, that you leave on the table will be disposed of. Please also remember to drop off your name badge at the registration table on your way out, that they may be recycled.

We will now adjourn the meeting, and I want to thank you all for participating and for an excellent discussion.

(Whereupon, at 2:53 p.m., the meeting was adjourned.)