

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

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

1 **Meeting Roster**

2 **ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Yinghua Wang, PharmD, MPH, RAC**

4 Division of Advisory Committee and

5 Consultant Management

6 Office of Executive Programs, CDER, FDA

7
8 **CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE**

9 **MEMBERS (Voting)**

10 **John H. Alexander, MD, MHSc**

11 Professor of Medicine

12 Department of Medicine, Division of Cardiology

13 Duke University School of Medicine

14 Durham, North Carolina

15
16 **Jacqueline D. Alikhaani, BA**

17 *(Consumer Representative)*

18 Volunteer and Advocate

19 American Heart Association

20 Los Angeles, California

21

22

1 **Barry R. Davis, MD, PhD**

2 Guy S. Parcel Chair in Public Health

3 Professor, Department of Biostatistics and

4 Data Science

5 Director, Coordinating Center for Clinical Trials

6 The University of Texas School of Public Health

7 Houston, Texas

8

9 **C. Michael Gibson, MD, MS**

10 Professor of Medicine

11 Harvard Medical School

12 President

13 Combined non-profit Baim and PERFUSE

14 Research Institutes

15 Boston, Massachusetts

16

17 **Julia B. Lewis, MD**

18 *(Chairperson)*

19 Professor of Medicine

20 Division of Nephrology

21 Vanderbilt Medical Center

22 Nashville, Tennessee

1 **John M. Mandrola, MD, FACC**

2 Electrophysiologist

3 Baptist Medical Associates

4 Louisville, Kentucky

5

6 **David J. Moliterno, MD**

7 Professor and Chairman

8 Department of Internal Medicine

9 University of Kentucky Medical Center

10 Lexington, Kentucky

11

12 **Milton Packer, MD**

13 Distinguished Scholar in Cardiovascular Medicine

14 Baylor Heart and Vascular Institute

15 Baylor University Medical Center

16 Dallas, Texas

17

18

19

20

21

22

1 **Paul M. Ridker, MD MPH, FACC, FAHA**

2 Eugene Braunwald Professor of Medicine

3 Harvard Medical School

4 Director, Center for Cardiovascular Disease

5 Prevention, Division of Preventative Medicine

6 Brigham and Women's Hospital

7 Boston, Massachusetts

8
9 **David G. Soergel, MD**

10 *(Industry Representative)*

11 Global Head

12 Cardiovascular, Renal and Metabolism Development

13 Novartis Pharma

14 East Hanover, New Jersey

15
16 **TEMPORARY MEMBERS (Voting)**

17 **James Floyd, MD, MS**

18 Assistant Professor of Medicine and Epidemiology

19 Cardiovascular Health Research Unit

20 University of Washington

21 Seattle, Washington

22

1 **Nedra Hazlett, MSN, CRNP**

2 *(Patient Representative)*

3 Women's Health Nurse Practitioner

4 Administrator, Atrial Fibrillation Support Forum

5 Murrysville, Pennsylvania

6

7 **Jenna M. Merandi, PharmD, MS, CPPS**

8 Medication Safety Officer

9 Nationwide Children's Hospital

10 Columbus, Ohio

11

12 **Matthew Needleman, MD, FACC, FHRS**

13 Commander, Medical Corps, U.S. Navy

14 Program Director, Cardiovascular Diseases

15 Fellowship, National Capital Consortium

16 Director, Arrhythmia Services

17 Walter Reed National Military Medical Center

18 Associate Professor of Medicine and Pediatrics

19 Uniformed Services University of Health Sciences

20 Bethesda, Maryland

21

22

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

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

1	C O N T E N T S	
2	AGENDA ITEM	PAGE
3	Call to Order and Introduction of Committee	
4	Julia Lewis, MD	11
5	Conflict of Interest Statement	
6	Yinghua Wang, PharmD, MPH, RAC	15
7	FDA Introductory Remarks	
8	Norman Stockbridge, MD, PhD	18
9	Applicant Presentations - Correvio	
10	Introduction	
11	Mark Corrigan, MD	21
12	Recent Onset AF: High Unmet Need for an	
13	Additional Pharmaceutical Treatment	
14	Peter Kowey, MD	27
15	Nonclinical Pharmacology	
16	Peter Siegl, PhD	36
17	Clinical Efficacy	
18	Andrew Tershakovec, MD, MPH	41
19	Safety	
20	W. Douglas Weaver, MD	52
21		
22		

1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE
3	A Clinical Assessment of Benefit-Risk	
4	Peter Kowey, MD	80
5	Conclusion	
6	Mark Corrigan, MD	87
7	Clarifying Questions	89
8	FDA Presentations	
9	FDA Overview of Cardiovascular Safety	
10	Preston Dunnmon, MD	116
11	Safety of Ibutilide and Electrical	
12	Cardioversion in Patients with Atrial	
13	Fibrillation or Flutter	
14	Daniel Woronow, MD, FACC	138
15	FDA Conclusion	
16	Preston Dunnmon, MD	146
17	Clarifying Questions	148
18	Open Public Hearing	180
19	Clarifying Questions (continued)	191
20		
21		
22		

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

C O N T E N T S (continued)

AGENDA ITEM	PAGE
Charge to the Committee	
Norman Stockbridge, MD, PhD	193
Questions to the Committee and Discussion	194
Adjournment	278

1 P R O C E E D I N G S

2 (8:00 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

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

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

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

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

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

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

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

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

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

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

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

22 DR. LEWIS: Julia Lewis, nephrologist,

1 Vanderbilt.

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

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

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

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

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

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

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

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

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

6 For topics such as those being discussed at
7 today's meeting, there are often a variety of opinions,
8 some of which are quite strongly held. Our goal is
9 that today's meeting will be a fair and open forum for
10 discussion of these issues and that individuals can
11 express their views without interruption. Thus, as a
12 gentle reminder, individuals will be allowed to speak
13 into the record only if recognized by the chairperson.
14 We look forward to a productive meeting.

15 In the spirit of the Federal Advisory
16 Committee Act and the Government in the Sunshine Act,
17 we ask that the advisory committee members take care
18 that their conversations about the topic at hand take
19 place in the open forum of the meeting. We are aware
20 that members of the media are anxious to speak with the
21 FDA about these proceedings, however, the FDA will
22 refrain from discussing the details of this meeting

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

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

6 **Conflict of Interest Statement**

7 DR. WANG: The Food and Drug Administration is
8 convening today's meeting of the Cardiovascular and
9 Renal Drugs Advisory Committee under the authority of
10 the Federal Advisory Committee Act of 1972. With the
11 exception of the industry representative, all members
12 and temporary voting members of the committee are
13 special government employees or regular federal
14 employees from other agencies and are subject to
15 federal conflict of interest laws and regulations.

16 The following information on the status of
17 this committee's compliance with federal ethics and
18 conflict of interest laws, covered by but not limited
19 to those found that 18 U.S.C. Section 208, is being
20 provided to participants in today's meeting and to the
21 public.

22 FDA has determined that members and temporary

1 voting members of this committee are in compliance with
2 federal ethics and conflict of interest laws. Under 18
3 U.S.C. Section 208, Congress has authorized FDA to
4 grant waivers to special government employees and
5 regular federal employees who have potential financial
6 conflicts when it is determined that the agency's need
7 for a special government employee's services outweighs
8 his or her potential financial conflict of interest, or
9 when the interest of a regular federal employee is not
10 so substantial as to be deemed likely to affect the
11 integrity of the services which the government may
12 expect from the employee.

13 Related to the discussion of today's meeting,
14 members and temporary voting members of this committee
15 have been screened for potential financial conflicts of
16 interest of their own as well as those imputed to them,
17 including those of their spouses or minor children and,
18 for purposes of 18 U.S.C. Section 208, their employers.
19 These interests may include investments; consulting;
20 expert witness testimony; contracts, grants, CRADAs;
21 teaching, speaking, writing; patents and royalties; and
22 primary employment.

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

10 This is a particular matters meeting during
11 which specific matters related to Correvio
12 International Sarl's NDA will be discussed. Based on
13 the agenda for today's meeting and all financial
14 interests reported by the committee members and
15 temporary voting members, no conflict of interest
16 waivers have been issued in connection with this
17 meeting. To ensure transparency, we encourage all
18 standing committee members and temporary voting members
19 to disclose any public statements that they have made
20 concerning the product at issue.

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

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

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

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

19 **FDA Introductory Remarks - Norman Stockbridge**

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

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

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

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

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

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

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

7 DR. LEWIS: Thank you, Dr. Stockbridge.

8 Both the Food and Drug Administration and the
9 public believe in a transparent process for information
10 gathering and decision making. To ensure such
11 transparency at the advisory committee meeting, the FDA
12 believes that it's important to understand the context
13 of an individual's presentation.

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

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

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

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

7 **Applicant Presentation - Mark Corrigan**

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

13 Vernakalant is an atypical application for
14 this committee and the FDA to consider. The path has
15 not been straightforward. Let's set the stage. In
16 2007, the Cardiorenal Advisory Committee voted in favor
17 of approval. The two dissenting votes and the FDA
18 requested additional safety data. We now return with a
19 revised NDA.

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

1 substantial post-approval safety study in which no
2 deaths occurred, and over nine years and greater than
3 58,000 treatment episodes in the post-approval
4 experience.

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

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

22 Here is an overview of our presentation.

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

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

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

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

3 In August 2008, FDA issued an approvable
4 letter, stating vernakalant was clearly effective for
5 cardioversion of recent onset AF, and requesting
6 additional data to more fully characterize the safety
7 of vernakalant and address 8 events, adverse events, of
8 concern. The ACT V clinical trial was initiated in
9 2009, and the protocol was designed and agreed with
10 FDA.

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

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

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

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

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

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

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

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

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

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

1 management and monitoring.

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

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

14 **Applicant Presentation - Peter Kowey**

15 DR. KOWEY: Thank you, Dr. Corrigan.

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

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

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

14 Atrial fibrillation is by far the most common
15 cardiac rhythm disturbance encountered in clinical
16 practice, and its prevalence is expected to double by
17 2030. It's a complicated disease, with a myriad of
18 etiologies, and it is responsible for significant
19 morbidity and mortality in the United States.

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

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

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

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

1 the United States for several years. Pharmacologic
2 conversion is particularly useful in patients whose
3 heart rates and symptoms are difficult to control,
4 those with infrequent paroxysms of AF, for example, and
5 particularly those with new onset AF who present within
6 48 hours, where efficacy of pharmacologic cardioversion
7 is maximal.

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

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

22 Why? Currently used drugs are either not fast

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 **Applicant Presentation - Peter Siegl**

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

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

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

7 As you can see, vernakalant has
8 pharmacological activity on several cardiac ion
9 channels at therapeutically relevant concentrations.
10 This novel, multi-ion channel profile underlies the
11 efficacy and safety of vernakalant. Briefly, the
12 contributors of efficacy to vernakalant are decreased
13 excitability and slow conduction; the inhibition of the
14 peak sodium current, like flecainide and propafenone;
15 in addition to delayed repolarization in the atria by
16 inhibition of I_{Kur} and I_{KAch} , activities that are
17 unique to vernakalant; as well as inhibition of I_{Kr} ,
18 like dofetilide and ibutilide.

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

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

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

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

22 Hypotension has been observed in some

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

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

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

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

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

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

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

1 **Applicant Presentation - Andrew Tershakovec**

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

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

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

1 surgery subjects.

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

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

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

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

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

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

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

1 2 hours after study drug administration. Finally,
2 subjects had a follow-up visit as 7 days and a phone
3 follow-up at 30 days.

4 The dose used in the phase 3 studies is the
5 dose recommended in the proposed label. This is an
6 initial infusion of 3 milligrams per kilogram over
7 10 minutes, with a maximum of 339 milligrams. This is
8 based on a body mass of 113 kilograms or 250 pounds.
9 The 15-minute observation period allows full
10 distribution of the drug while monitoring for safety
11 and conversion. If there's no conversion to sinus
12 rhythm and no other important clinical issues are
13 observed, the second dose of 2 milligrams per kilogram
14 is infused over 10 minutes to a maximum of
15 226 milligrams.

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

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

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

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

12 In the ACT I and III studies, the subjects
13 were about two-thirds male, the average age was 60, and
14 they were predominantly white. About 40 percent were
15 from North America and about 60 percent from western
16 Europe. The baseline characteristics are generally
17 consistent with what would be expected for an AF
18 population. About 10 percent of the subjects had a
19 history of congestive heart failure; about 40 percent
20 had hypertension; 5 to 7 percent a history of MI; 11 to
21 14 percent with ischemic heart disease; just under 10
22 percent with valvular heart disease; and overall, 25 to

1 30 percent with a history of structural heart disease.

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

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

15 A significantly greater proportion converted
16 in the vernakalant group, 51.1 percent, versus 3.8
17 percent in the placebo group, with a p less than
18 0.0001. About 40 percent of the vernakalant treated
19 subjects convert after the first dose. An additional
20 20 percent of subjects who received the second dose
21 convert. The median time to conversion for vernakalant
22 responders was 10 minutes.

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

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

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

1 like.

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

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

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

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

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

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

22 The demographics of the study population was

1 similar to that in the phase 3 clinical trials.
2 However, the baseline characteristics reflected the
3 refined patient selection criteria in the European
4 label, consistent with treating physicians applying the
5 labeled guidance to select lower risk subjects for
6 vernakalant treatment. Also, the duration of AF was
7 8 to 12 hours, shorter than the meeting time in the
8 clinical trials. This is important, as shorter term AF
9 duration is associated with higher conversion rates.

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

16 The higher conversion rate in SPECTRUM, about
17 70 percent, is likely related to the study design, the
18 lower rate of structural heart disease, and the shorter
19 duration of AF in this study population. Also, across
20 these studies, we saw consistency in time to conversion
21 for vernakalant responders. The median conversion
22 times were between 8 and 14 minutes and slightly longer

1 in the SPECTRUM postoperative subjects.

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

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

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

1 development program. That conversion was accompanied
2 with lower rates of AF-related symptoms, and sinus
3 rhythm was maintained in the vast majority out to
4 7 days. The efficacy demonstrated in the phase 3
5 studies was confirmed in the post-approval experience.

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

8 **Applicant Presentation - Douglas Weaver**

9 DR. WEAVER: Thank you, Dr. Tershakovec.

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

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

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

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

14 We will begin where this submission left off
15 10 years ago, by presenting the 8 events of concern
16 outlined by the agency in 2008. Then I'll discuss any
17 deaths that occurred in the trials, including details
18 about the one that led to a clinical hold. After
19 careful review in each, the sponsor does not believe
20 that the 8 events and the ACT V death warranted a
21 clinical hold, and I will explain why.

22 The presentation will then cover the safety

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

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

15 To begin, there were 4 cases of hypotension,
16 3 events of bradycardias occurring at the time off or
17 following cardioversion, and one nonsustained
18 ventricular arrhythmia identified as concerning. The
19 4 hypotension events are shown here. I have
20 highlighted key details about each. The first three
21 would now be contraindicated under the proposed label,
22 as shown in the right column.

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

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

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

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

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

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

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

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

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

10 I'll now present the findings surrounding any
11 death that occurred within 30 days in the trials, that
12 includes one that led to the clinical halt. There were
13 9 in all, 1 in the placebo group and 8 in the twice
14 larger vernakalant group. Only one was considered by
15 the investigator to be treatment related. The sponsor,
16 however, judged two to be treatment related.

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

22 The first patient that was deemed related is

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

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

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

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

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

7 The patient was a 77-year-old man with a
8 history of hypertension, chronic alcohol abuse, and
9 otherwise was stated as unremarkable. He had a 1-week
10 history of dyspnea, orthopnea, fatigue, which the
11 investigator classified as class 3, meaning symptoms
12 with minimal exertion. He had palpitations for 2 or
13 3 days before admission. He also gave a history of
14 palpitations a month earlier.

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

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

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

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

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

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

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

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

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

6 Here are the baseline characteristics in the
7 all-patient population, those from the original studies
8 plus the 4 additional ones they've done since 2009:
9 the average age 62; heart failure in 16 percent; 30 to
10 35 percent had a history of MI or ischemic heart
11 disease; a little over 10 percent with valvular heart
12 disease; 40 percent had structural heart disease; half
13 the patients were on beta blockers; 4 to 5 percent
14 received class 1; and 12 to 13 percent class 3
15 antiarrhythmia drugs prior to enrollment. The
16 immediate post cardiac surgery patients represent about
17 10 percent of this entire cohort.

18 AEs were captured for three time periods: 0
19 to 2 hours; 2 to 24 hours; and 0 to 24 hours. The 0 to
20 2 hours captures a time of Cmax, which occurs at the
21 end of the infusion. The 2-to-24 hour period will be
22 that in which the placebo cohort may undergo electrical

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

3 As a reminder, following discontinuation
4 infusion, the drug is rapidly distributed at 30
5 minutes, the concentration has dropped to less than
6 half, and by 2 hours to about 20 percent, and at
7 24 hours, the drug is barely detectable by the assay.

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

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

1 heart rate was added to bradycardia.

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

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

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

1 cardioversion; whereas our analysis -- indeed, that
2 rhythm control has been the choice for treatment
3 here -- also examined the overall event rates of
4 0 to 24 hours, to include those events associated with
5 electric cardioversion after 2 hours.

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

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

22 For ventricular tachycardia, on the lower two,

1 there were more events for vernakalant in hour 0 to 2,
2 4.3 versus 2.3 percent in placebo. But in hours 2 to
3 24, there were more VT events in the placebo group, 9.6
4 versus 6.4. In the Holter analysis, the incidence of
5 both nonsustained polymorphic and monomorphic
6 ventricular tachycardia was similar for both groups.

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

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

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

4 Here are the bradycardia events. There are
5 more in the vernakalant group in our 0 to 2, 2.5 versus
6 0.2 -- that's the time of vernakalant
7 cardioversion -- and more for placebo at hours 2 to 24
8 shown in the middle, the time of electrical
9 cardioversion. Sinus arrest or pause, there were 8 in
10 the vernakalant and one in the placebo group. Each one
11 of these occurred at the time of cardioversion, six at
12 the time of vernakalant cardioversion, shown on the
13 left, and the two others in the middle panel, they
14 occurred after electrical cardioversion.

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

22 The bottom three rows show treatments for the

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

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

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

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

7 Let me provide the details surrounding any
8 patient who received a vasopressor. In the all-patient
9 population, there were three such cases in the
10 vernakalant group. One was a postsurgical patient with
11 1 minute of asymptomatic hypotension. The two others
12 occurred in patients who would be excluded in the
13 proposed target population. The other SAEs are drug
14 discontinuations that were either transit, received no
15 treatment, or managed by Trendelenburg positioning or
16 saline. There were 27 instances of atrial flutter;
17 three were recorded as SAEs, none in hypotension, no
18 required immediate electric cardioversion.

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

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

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

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

1 preventing a compensatory increase in output.

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

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

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

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

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

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

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

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

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

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

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

1 and was reconciled against hospital records by the site
2 monitors.

3 Reporting of all SATs was mandatory. Serious
4 adverse events were adjudicated, and to be
5 conservative, both the investigator-reported event as
6 well as the adjudicated event are included in the
7 tables you'll see. The sample size was set at
8 2000 episodes to provide an upper bound of the
9 95 percent confidence limit of 1 percent for each of
10 the events of interest.

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

17 The baseline characteristics reflect a much
18 narrower population that was defined by the EU label
19 than that enrolled in the earlier clinical trials.
20 Let's go over the medical history. The average age,
21 61.9; 3.7 percent with a history of heart failure much
22 lower than the 18 percent in the earlier trials;

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

3 The medium duration of AF was also shorter.
4 Over 40 percent were described as having lone AF, and
5 about 24 percent had first onset AF. About 4 percent
6 were immediate postoperative patients. Beta blockers
7 are the most commonly used rate control medications.
8 Class 1 and class 3 meds had been received in about
9 5 percent of patients as opposed to 16 percent in the
10 earlier trials.

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

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

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

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

10 There are only two instances, or 0.1 percent,
11 1 in 1,000 incidents, of hypotension. Both of those
12 occurred in the setting of bradycardia and are listed
13 as two of the bradycardia events above. Both resolved
14 following atropine treatment. None of them required a
15 pressor. There were two events of atrial flutter with
16 1-to-1 conduction. One was symptomatic and
17 electrically cardioverted; the second converted quickly
18 to 2-to-1 conduction and was asymptomatic.

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

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

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

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

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

1 in 25 countries. It's a class 1A recommended treatment
2 for recent onset AF in patients without heart failure
3 in the European guidelines. Independent investigator
4 initiated studies and postmarketing safety now include
5 12 reported cases of 1-to-1 atrial flutter.

6 There is no apparent relationship for the
7 number of doses. Half of these patients were
8 symptomatic and were converted with electrical
9 cardioversion. The others reverted spontaneously or
10 were cardioverted later. There have been 199 adverse
11 drug reactions reported, and they're summarized in the
12 briefing document. In the nine years, there have been
13 6 deaths reported in over 58,000 uses of the drug, each
14 of which occurred in patients with complicated or
15 serious conditions, but I'd like to provide a summary
16 of these for you.

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

1 pressure in the 80's, but he didn't receive any
2 treatment at that time. An hour and a half later, he
3 was reevaluated, and again no treatment was given.
4 About 5 hours later, he was treated with diuretics for
5 rales in the chest and shortness of breath, and then
6 the record shows he continued to deteriorate and died
7 14 hours after cardioversion.

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

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

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

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

6 **Applicant Presentation - Peter Kowey**

7 DR. KOWEY: Thank you, Dr. Weaver.

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

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

22 What usually happens today in patients who

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

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

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

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

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

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

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

1 in the emergency department or other acute care
2 settings.

3 One drug, ibutilide, has been approved for
4 this indication of conversion of recent onset atrial
5 fibrillation to sinus rhythm by the FDA. Ibutilide is
6 an IV drug that gained approval despite modest efficacy
7 at a high rate of ventricular proarrhythmia, as well as
8 the need for prolonged and intensive monitoring,
9 4 hours after dosing, all of which seriously limits its
10 use in the United States. Keep in mind that oral
11 dofetilide is also approved for AF conversion but is
12 not used in the acute care setting.

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

22 First of all, as the FDA briefing document

1 points out, there is a significant incidence of
2 pulmonary edema, hypotension, ventricular fibrillation,
3 asyctole and bradycardia after electrical conversion.

4 Electrical conversion can't be applied for many
5 logistical reasons, including the need for anesthesia.

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

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

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

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

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

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

1 in clinical practice. Vernakalant will be absolutely
2 no different.

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

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

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

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

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

17 **Applicant Presentation - Mark Corrigan**

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

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

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

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

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

3 **Clarifying Questions**

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

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

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

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

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

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

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

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

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

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

4 Dr. Corrigan, if you'd answer.

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

9 DR. LEWIS: No, no, no. I'm sorry. Since
10 2010, you've been approved, and 58,000 people have
11 received it, roughly.

12 DR. CORRIGAN: Right.

13 DR. LEWIS: Do you have any concept of how
14 many patients, in that time period, in the approved
15 countries, could have received vernakalant; like they
16 would have met the criteria, but the physicians did or
17 didn't use it? Like, I don't know if 58,000 is they're
18 using it in 90 percent of the indicated population or
19 10 percent of the indicated population.

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

1 DR. LEWIS: Thank you.

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

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

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

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

1 is very difficult to make.

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

4 Dr. Alexander?

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

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

22 A lot of the AF is very short duration. So

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

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

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

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

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

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

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

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

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

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

18 DR. LEWIS: Dr. Packer?

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

1 document? It is on page 66.

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

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

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

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

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

22 DR. PACKER: Class 2 heart failure with a 40

1 percent ejection fraction would be okay?

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

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

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

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

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

22 DR. WEAVER: I would say class 2 LV 40

1 percent, the patient would likely be treated.

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

4 DR. TERSHAKOVEC: Slide up.

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

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

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

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

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

1 ACT III pooled data.

2 DR. PACKER: You included class 2 patients?

3 DR. TERSHAKOVEC: Yes.

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

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

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

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

18 DR. TERSHAKOVEC: Dr. Weaver?

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

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

6 DR. WEAVER: Right.

7 DR. PACKER: -- and died.

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

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

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

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

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

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

1 6-7 hypotensive episodes. If you had one patient with
2 hypotension who died, you included that patient in the
3 no heart failure group?

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

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

13 DR. WEAVER: Correct.

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

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

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

22 DR. WEAVER: Different. So for the checklist,

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

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

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

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

8 DR. WEAVER: Not today.

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

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

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

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

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

5 DR. WEAVER: Yes, I would because --

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

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

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

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

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

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

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

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

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

1 failure, and the recommendation there is to 2B.

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

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

8 DR. LEWIS: Thank you, Dr. Camm.

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

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

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

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

3 DR. TERSHAKOVEC: Slide up.

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

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

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

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

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

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

22 DR. WEAVER: The data that we have does not

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

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

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

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

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

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

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

16 DR. LEWIS: Thank you, Dr. Weaver.

17 Dr. Moliterno?

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

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

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

8 DR. MOLITERNO: So 97 percent. Could you
9 continue with SPECTRUM and tell us how many received
10 1 dose versus 2 doses of the drug?

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

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

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

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

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

12 DR. LEWIS: Thank you. Dr. Gibson?

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

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

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

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

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

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

15 As you said, in the clinical trials, they were
16 powered primarily for the primary endpoint of the
17 efficacy, and for most studies, consider about
18 25 percent difference between placebo and vernakalant
19 for the efficacy endpoint.

20 The SPECTRUM, the large --

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

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

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

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

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

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

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

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

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

12 DR. GIBSON: The forest plots.

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

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

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

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

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

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

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

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

20 DR. RITZ: Yes.

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

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

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

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

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

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

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

18 **FDA Presentation - Preston Dunnmon**

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

1 resubmission of NDA 22034.

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

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

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

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

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

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

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

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

1 following the initiation of treatment.

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

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

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

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

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

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

1 safety concerns of other antiarrhythmic treatments.

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

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

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

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

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

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

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

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

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

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

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

1 constants of 1 to 10 seconds. Vaughan-Williams class
2 1B drugs like mexiletine demonstrate fast kinetics with
3 a dissociation constant less than 1 second. At the
4 other extreme, 1C drugs like flecainide demonstrate
5 slow dissociation kinetics from the sodium channel,
6 with dissociation constant exceeding 10 seconds.

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

16 Indeed, using the methodology that FDA thinks
17 was the most accurate, the dissociation constant for
18 vernakalant and its diastereomers was calculated to be
19 49.4, strongly suggesting that vernakalant, like
20 flecainide, is a Vaughn-Williams class 1C
21 antiarrhythmic drug.

22 The sponsor subsequently undertook two studies

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

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

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

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

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

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

22 In the second fatal case that occurred, in the

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

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

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

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

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

1 ventricular sodium channel blockade.

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

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

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

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

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

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

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

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

3 Unlike what you heard this morning as far as
4 this patient being described, I will be happy to talk
5 about this and show you the data. This person was
6 listed as not having had heart failure in the sponsor's
7 database. This person was not shown to have heart
8 failure from what they submitted to me in the MedWatch
9 reports on physical exam. And this person had an EF of
10 44 percent that the reader felt was only mildly
11 depressed because his resting heart rate was 156 when
12 they did the echo, and echos tend to underestimate EF
13 when people were going that fast. The reader of the
14 echo specifically noted that there were no segmental
15 wall motion abnormalities present.

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

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

3 So these patients only got one dose of drug
4 and did not convert, and stayed in sinus rhythm. This
5 subset had worse outcomes than the rest. Twenty-six
6 percent of these subjects experienced serious
7 cardiovascular adverse events within the 2 hours of
8 initiating vernakalant therapy. The mean placebo
9 adjusted increase in the QRS interval was approximately
10 20 milliseconds, on average, and the mean placebo
11 adjusted increase in the QTc greater than 30
12 milliseconds.

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

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

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

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

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

19 SPECTRUM enrolled 1,778 patients who underwent
20 2009 vernakalant treatment episodes. Seventy-nine
21 percent of these subjects were prospectively enrolled.
22 The 21 percent of them were retrospectively enrolled.

1 The data were largely collected through medical chart
2 abstraction.

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

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

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

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

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

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

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

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

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

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

1 scenario or for vernakalant-induced arrhythmias.

2 Likewise, the checklist states the use of
3 IV beta blockers is not recommended within 2 hours of
4 vernakalant administration or 2 hours after. However,
5 most subjects who received IV beta blockers within
6 2 hours of vernakalant administration received them for
7 acute rate control of rapid atrial fibrillation or
8 atrial flutter. In our assessment, it is not possible
9 to prospectively identify who may need these therapies
10 after the vernakalant has been administered.

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

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

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

3 Dr. Woronow?

4 **FDA Presentation - Daniel Woronow**

5 DR. WORONOW: Thank you, Dr. Dunnmon.

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

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

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

1 Ibutilide is also approved for rapid conversion of
2 atrial flutter.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 **FDA Presentation - Preston Dunmon**

15 DR. DUNNMON: Thank you, Dr. Woronow.

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

1 is a potent negative inotrope in dogs and in humans,
2 and has caused deaths in dogs and in humans.

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

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

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

1 vernakalant is unfavorable for the proposed indication.

2 Thank you.

3 **Clarifying Questions**

4 DR. LEWIS: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

16 DR. DUNNMON: Correct.

17 DR. RIDKER: Thank you.

18 DR. LEWIS: Dr. Packer?

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

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

6 In your slides, you had a reference on slide
7 5 -- there's no reason to put it up there -- that there
8 was a patient in 2010 with pulseless electrical
9 activity, where the patient had hypertension and left
10 ventricular hypertrophy, and developed pulseless
11 electrical activity. That patient had structural heart
12 disease.

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

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

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

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

8 DR. PACKARD: Yes.

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

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

22 The reason I bring this up, this is a case

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

6 This prodrome that I keep seeing over and over
7 again, with the itchy, clammy, diaphoresis stuff,
8 starting usually with a metallic taste in their mouth,
9 got started at about minute 10. At minute 12, they're
10 bolusing with saline for hypotension. At minutes 15 to
11 25, they're bolusing more saline because of more
12 hypotension. At minute 25, they're having tonic-clonic
13 seizures, loss of consciousness, no carotid pulse, with
14 the cardiac arrest being called and compressions
15 initiated.

16 Then this person slowly recovers after about
17 27 minutes, remembering that unlike flecainide, where
18 in the post 90-minute observation period, after that IV
19 infusion in the dogs, it recovered. This drug's
20 negative dp/dt did not.

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

1 taking these three sequential echos, where this person
2 had low normal ejection fraction early on at
3 30 minutes. It went down to less than 20 percent, and
4 then at minute 300, which was in 5 hours with negative
5 troponins, was back up to normal again.

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

13 DR. LEWIS: Dr. Davis?

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

21 DR. DUNNMON: Right.

22 DR. DAVIS: The question is being raised by

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

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

14 But then this fellow in ACT V that we put it
15 on hold for, which was the second CPR case within
16 2 weeks in that study, had none of that. And he died
17 without aortic stenosis, with the record showing no
18 heart failure, no segmental wall motion abnormalities,
19 an EF of 44 percent at a heart rate of 156 during the
20 study, which the echocardiographer read is mildly
21 depressed LV function. This person would not have been
22 capped out.

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

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

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

1 pulmonary edema. There could not be left ventricular
2 dysfunction defined as an ejection fraction less than
3 40 percent. They tightened up on this to do what
4 exactly we had asked them to do to give us less than
5 1 percent of these events. But even with this, they
6 ended up with cardiogenic shock in somebody with LVH.

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

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

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

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

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

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

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

1 electrically cardioverted, and that was his first
2 recovery study.

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

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

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

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

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

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

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

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

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

1 DR. LEWIS: Dr. Alexander?

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

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

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

1 told me about atrial fibrillation and electrical
2 cardioversion.

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

7 Let's go up to the top, Guédon-Moreau, again,
8 a small percentage of deaths, 0.4 percent; lethal brain
9 hemorrhage in a patient on dual anticoagulants; also an
10 86-year-old patient with hypertrophic cardiomyopathy
11 died of heart failure one day after electrical
12 cardioversion; a 78-year-old patient with valvular
13 cardiomyopathy who died 1 month after electrical
14 cardioversion.

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

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

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

3 Let's go to the next slide. Let's throw this
4 up against vernakalant deaths; 8 vernakalant deaths in
5 the clinical studies. Regardless of whether you think
6 they're causally related or not. we're going to do the
7 same analysis with electrical cardioversion, causally
8 related or not; 0.7 percent for vernakalant,
9 0.13 percent for electrical cardioversion.

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

13 (Affirmative gestures.)

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

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

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

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

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

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

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

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

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

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

15 (Dr. Davis gestures no.)

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

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

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

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

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

22 DR. RITZ: As a requirement of informed

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

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

9 The second question is I understand that
10 20 percent of the people who were screened were not
11 enrolled in the studies because they didn't give
12 consent. Are we confident that everybody who is
13 screened -- the people who were screened include every
14 person who got a drug at all of the registry sites? Do
15 we know that?

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

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

22 DR. TERSHAKOVEC: Slide up.

1 DR. FLOYD: When I look at this, I see that
2 the conversion rates are consistent across every
3 randomized controlled trial, 50 percent, but there's
4 70 percent in this registry analysis. And this seems
5 pretty clear evidence of selection bias in that because
6 informed consent was required, anyone who had early
7 treatment-related adverse effects, rendering them
8 incapable or lacking the desire to participate, they
9 would be excluded, especially if they died.

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

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

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

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

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

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

22 DR. TERSHAKOVEC: I can ask Dr. Leonowens to

1 address your question.

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

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

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

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

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

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

22 DR. TERSHAKOVEC: I can ask Dr. Weaver to

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

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

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

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

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

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

1 DR. FLOYD: Excluding ACT II.

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

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

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

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

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

14 DR. TERSHAKOVEC: Okay.

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

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

18 Dr. Needleman?

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

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

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

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

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

15 (Dr. Tershakovec gestures yes.)

16 DR. LEWIS: Thank you.

17 The last question, Dr. Mandrola?

18 DR. MANDROLA: This clarifying question goes
19 to the rhythm control strategy. Over the last
20 10 years, my impression of the rhythm control
21 strategy -- and this goes to unmet need -- is that
22 rhythm control, cardioversion being a rhythm control

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

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

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

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

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

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

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

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

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

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

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

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

4 Oh, you did? Sorry.

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

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

12 Dr. Gibson, did you have an unanswered
13 question?

14 (Dr. Gibson gestures no.)

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

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

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

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

5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

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

1 of your statement to advise the committee if you do not
2 have any such financial relationships. If you choose
3 not to address this issue of financial relationships at
4 the beginning of your statement, it will not preclude
5 you from speaking.

6 The FDA and the committee place great
7 importance in the open public hearing process. The
8 insights and comments provided could help the agency
9 and the committee in their consideration of the issues
10 before them. That said, in many instances and for many
11 topics, there will be a variety of opinions.

12 One of our goals today is for the open public
13 hearing to be conducted in a fair and open way, where
14 every participant is listened to carefully and treated
15 with dignity, courtesy, and respect. Therefore, please
16 only speak when recognized by myself, the chairperson.
17 Thank you for your cooperation.

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

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

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

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

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

22 The new safety data come mainly from one

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

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

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

22 Given the risks and the unknowns, there's no

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

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

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

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

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

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

22 DR. LEWIS: The slides are on.

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

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

5 MS. MILLER: Okay. Thank you.

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

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

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

22 Almost eight years ago, I went to the

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

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

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

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

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

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

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

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

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

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

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

22 I took to the drug immediately, although it

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

10 After five months on the lower dose, I began
11 to have episodes of AFib and tachycardia approximately
12 every 10 days. Sometimes my episodes lasted 2 or 3
13 hours, but mostly they were much longer. I was willing
14 to tolerate frequent episodes if I could stay on the
15 lower dose of amiodarone, which was 100 milligrams per
16 day. However, my EP said amiodarone was too dangerous
17 to take without perfect control. She put me back on
18 200 milligrams daily while I considered next steps.

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

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

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

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

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

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

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

11 **Clarifying Questions (continued)**

12 DR. LEWIS: Thank you.

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

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

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

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

12 The next question was on --

13 DR. LEWIS: The dose --

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

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

4 DR. TERSHAKOVEC: For SPECTRUM?

5 DR. LEWIS: For Europe?

6 DR. TERSHAKOVEC: For Europe.

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

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

12 DR. LEWIS: Thank you.

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

15 **Charge to the Committee - Norman Stockbridge**

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

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

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

6 **Questions to the Committee and Discussion**

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

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

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

22 Are there any questions or clarifications

1 about the questions?

2 (No response.)

3 DR. LEWIS: Then discussion is open.

4 Dr. Needleman?

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

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

22 If you look at other medications that we have

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

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

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

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

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

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

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

22 I think you get that inflammation from post-op

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

5 DR. LEWIS: Dr. Alexander?

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

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

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

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

18 DR. LEWIS: Thank you. Ms. Hazlett?

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

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

4 But the thing I think that has not been
5 addressed is our average age on the forum is 40. That
6 means we have so many people in their 20's and in their
7 30's. Let's just say they present in the ED an acute
8 episode of atrial fibrillation, and vernakalant is
9 offered to them, and the checklist has been gone
10 through. I like the checklist. I love checklist. I
11 like things that make things clear. However, these
12 patients may not have been worked up. They may never
13 have had an echo. They may not have had their stress
14 test. They may not have had anything to say we've got
15 no defects here.

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

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

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

10 DR. LEWIS: Thank you. Dr. Floyd?

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

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

1 consent.

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

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

16 DR. LEWIS: Dr. Moliterno?

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

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

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

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

22 DR. LEWIS: Thank you.

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

3 DR. LEWIS: Yes, you may.

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

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

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

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

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

10 DR. LEWIS: Dr. Stockbridge?

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

12 DR. LEWIS: Ms. Alikhaani?

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

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

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

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

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

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

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

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

1 didn't even get to the second dose.

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

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

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

18 DR. LEWIS: Thank you. Ms. Merandi?

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

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

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

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

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

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

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

6 DR. TERSHAKOVEC: Yes, that is correct.

7 DR. ALEXANDER: Thanks.

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

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

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

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

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

11 (No response.)

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

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

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

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

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

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

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

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

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

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

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

6 DR. RIDKER: Okay.

7 (Laughter.)

8 DR. LEWIS: Dr. Mandrola?

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

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

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

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

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

21 DR. LEWIS: Dr. Needleman?

22 DR. NEEDLEMAN: Matt Needleman again. What

1 are other options? We talked about -- I'll kind of go
2 backwards, pharmacologic cardioversion agents. We have
3 flecainide, 300 milligrams a day. I think that's maybe
4 30 percent effective, so that's much less effective
5 than this potential medication.

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

13 Ibutilide, also is probably in that less than
14 30 percent effective regimen, much less effective than
15 that. And having caused Torsades in patients who
16 shouldn't have been risk factors for Torsades, I have a
17 healthy respect for it. I won't give it without
18 preloading magnesium now and all these things that I've
19 kind of learned.

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

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

9 Something else was going on with him. I think
10 he was sick from some other metabolic or process.
11 Something else was causing him to be sick, and I think
12 he would have had a bad outcome no matter what.
13 Unfortunately -- Dr. Alexander brought it up earlier.
14 But I think we underreport the serious events with
15 cardioversion.

16 It's not necessarily the electrical part, it's
17 the sedation and -- I think the reason we get away with
18 it a lot is because we have an anesthesiologist there,
19 most of the time when I do it, micromanaging the blood
20 pressure and giving all sorts of different little doses
21 of medications to kind of get you through it. Cardiac
22 outputs, heart rates, and stroke volume, if you changed

1 the heart rate very suddenly, the cardiac output is
2 going to decrease very suddenly, and the body's got to
3 compensate for that. And during those few minutes
4 after cardioversion, it's a dangerous time, I think, no
5 matter how you get there.

6 So I think we just really need to realize that
7 our current treatments are very imperfect.

8 DR. LEWIS: Dr. Alexander?

9 DR. ALEXANDER: I think that certainly to do
10 justice to an evaluation of the effectiveness and
11 safety of vernakalant clinically, one has to compare it
12 to alternatives. That's largely because the benefits
13 of it are largely avoiding the alternatives, maybe,
14 which is having to be hospitalized, stay longer, get
15 anticoagulated, maybe or maybe not, and get sedated,
16 and have electrical cardioversion.

17 Actually, what's missing under A and B down
18 there is a process of care. In my mind, really, the
19 biggest benefit of vernakalant that I've heard is that
20 it would allow people to be quickly cardioverted in the
21 ER. That has all kinds of health economic, and avoids
22 a hospitalization for a patient, which likely has risks

1 in and of itself. So I do think that it's relevant to
2 compare vernakalant to the available alternatives.

3 We've talked a lot about cardioversion, and I
4 think that cardioversion with sedation, with the delays
5 that are necessary because of the need for sedation,
6 has I think some risks that are not always appreciated.
7 Others have brought up do we really need to cardiovert
8 all these people? Could we just watch and wait? Most
9 of them would end up back in sinus rhythm anyway. Then
10 the safety, also, I think is relevant to think about
11 what the alternatives are, watch and wait, the risks of
12 electrical cardioversion with associated sedation.

13 Again, I go back to this idea of can we
14 identify the right patients? I think there probably is
15 a patient cohort in whom vernakalant is an attractive
16 alternative. I'm just not sure we can identify it, and
17 I think we'll get to that later.

18 DR. LEWIS: Dr. Packer?

19 DR. PACKER: Julia, could I ask the sponsor a
20 question, especially the electrophysiologist? I just
21 want to be able to understand the world, and the issues
22 that you face, and the patients you see, because I want

1 to make sure that I understand this.

2 Let me just try to explain my thinking while I
3 wait. For patients who are elderly and patients who
4 have LV dysfunction and who have heart failure, my
5 sense is these people are off the table for this drug.
6 The efficacy is markedly diminished. The risks are
7 markedly increased. The risk-to-benefit relationship
8 in that population is really demonstrably unfavorable.
9 As John had said, if you give the drug and they don't
10 convert, then you're in many ways worst off than you
11 did, and those are the patients who don't convert, the
12 elderly patients and the patients with heart failure.

13 So let's just take them off the table. If I
14 could ask Peter and John, forget about the checklist
15 that the sponsor has put forward, just take it off the
16 table, could you tell us what your personal checklist
17 would be, and based on the totality of your experience,
18 what other options you have?

19 We rarely give the consultants or the sponsor
20 a chance to talk during this session. I guess you can
21 talk only if you're invited, so I'd like to invite you.

22 (Laughter.)

1 DR. PACKER: Forget about anything that was
2 presented today. If you had your own personal
3 checklist, and you had to develop it right now, what
4 would it be?

5 DR. TERSHAKOVEC: I'll ask Dr. Camm to start
6 because he has access to the drug in the EU, and then
7 Dr. Kowey after that.

8 DR. CAMM: I think the first thing that I
9 would do on seeing a patient in the emergency room is
10 ask a simple question of how well this patient was. I
11 don't mean whether they have symptoms or not, but just
12 how well is he from the hemodynamic perspective, and,
13 of course, would make the relevant measurements to
14 ascertain that.

15 The majority of patients that I would consider
16 for pharmacological cardioversion would have to be
17 symptomatic and would have to be well. When I went to
18 into it, I would want to have a fairly negative medical
19 history for most serious conditions, most serious
20 cardiac conditions, for example, because by definition,
21 that patient is going to need a much more significant
22 workup before I consider doing anything such as giving

1 pharmacological cardioversion, and to some extent
2 before considering electrical cardioversion.

3 So I think the major issue is, first of all,
4 significant medical history; secondly, extent of
5 symptoms; and thirdly, what underlying cardiovascular
6 disease they have. And if they're relatively
7 hemodynamically stable and they have no significant
8 past medical history, and they're symptomatic, and I
9 can cardiovert that patient, and have done with that
10 particular medical problem for that occasion, I would
11 then proceed to cardiovert that patient, and
12 pharmacological cardioversion would be a quite
13 reasonable approach.

14 Obviously, we'd have to match drug and
15 patient, and there are specific reasons why I might not
16 use a particular drug in a particular patient.

17 DR. LEWIS: Dr. Camm, before you sit down, may
18 I ask you a question since we've opened it?

19 DR. CAMM: Of course.

20 DR. LEWIS: To the point of operationalizing
21 this, no significant medical history is a pretty broad
22 comment.

1 DR. CAMM: Yes, of course it is.

2 DR. LEWIS: I think our point about some of
3 these people being very young, and this is their first
4 episode, perhaps, and not having had a lot of health
5 care, how would you operationalize no significant
6 medical history?

7 DR. CAMM: Well, I think it is difficult just
8 with my saying any significant medical history, and, of
9 course, there's a whole list of things that one could
10 put on any checklist. But personally, I don't have a
11 definitive list of issues that I go through. I see the
12 patient, I hear what they've got, and I decide from
13 that whether or not I might proceed. But I definitely
14 don't have a mental checklist with dozens of conditions
15 in it.

16 DR. LEWIS: Thank you.

17 DR. PACKER: Peter?

18 DR. KOWEY: Milton?

19 (Laughter.)

20 DR. KOWEY: Thank you for this opportunity.
21 And you're right, we don't usually get a chance to do
22 this. First of all, what John said is absolutely

1 correct. The initial evaluation of patient in the
2 emergency department history, I know this is going to
3 sound like an anathema, but a physical examination, a
4 global assessment of the patient in the emergency room,
5 background therapy, previous history of presentation,
6 all that stuff obviously comes into play.

7 I'm going to be perfectly honest with you,
8 Milton. I think it would be highly unlikely that I
9 would give this drug to somebody without an echo,
10 within the last few months, perhaps. It doesn't
11 necessarily have to be right this minute., but knowing
12 what I know about this drug and all the other options
13 that I might have -- even an electrical cardioversion,
14 I would be very reluctant to electrically cardiovert a
15 patient without having a fairly good idea, with all the
16 limitations of doing echos in people who were in atrial
17 fibrillation, granted. I think I'd like to have that
18 information before I cardioverted a person, either
19 pharmacologically or electrically.

20 What's been missing is exactly what you've
21 brought up, exactly what you brought up, which is we
22 depend on our clinicians to make an adequate assessment

1 of the patient, and to make a risk-benefit assessment
2 of the patient at the time. You can't globalize that.
3 You can't generalize that. That's what John was
4 saying. You have to individualize it. But I think
5 that, knowing what I know about the drug and the
6 clinical situation, that I can make that decision. As
7 a doctor, I can make that decision, and I can preserve
8 patient's safety adequately doing it that way.

9 DR. PACKER: Peter, if I could, just ask one
10 brief follow-up on. From a committee and from an FDA
11 point of view, the question isn't whether we trust you,
12 because we do; it's whether we trust all the physicians
13 out there to do this, so that's a problem.

14 But let me, if I could, just ask a very
15 specific question. I'm going to make this as clean as
16 I possibly can. A young person without any known
17 structural heart disease, comes in with 2 hours of
18 palpitations, racing heart rate, whatever symptoms you
19 want to give them, is found to be in rapid atrial fib,
20 and make that person 30 years old.

21 I'm going to put two options on the table, and
22 I just want to make sure that I understand how you

1 would choose. The patient is symptomatic. You can
2 say -- and I'm going to ask you not to do the
3 following. John has brought up a very good point; just
4 send them home and say come back when you've converted
5 yourself.

6 MALE VOICE: That's not what he said.

7 DR. MANDROLA: Not just that.

8 (Laughter.)

9 DR. PACKER: I'm joking. Why don't you
10 electrically cardiovert that person right then? Why
11 does this recommendation exist that prior to electrical
12 cardioversion, you have to anticoagulate, but prior to
13 pharmacological cardioversion, you don't? That makes
14 no sense.

15 DR. KOWEY: Oh no; that's a misunderstanding.
16 The same rules apply for anticoagulation in either
17 kinds of conversion.

18 DR. PACKER: Why not just electrically
19 cardiovert that patient immediately?

20 DR. KOWEY: Totally reasonable to do that. By
21 the way, let me just back up for a minute and tell you
22 that when a 30-year-old comes into my emergency room

1 with atrial fibrillation, I'm even more worried about
2 why, and should I maybe even be more likely to get an
3 echo on that person than I would in an older person
4 that it's a known flyer with atrial fibrillation.

5 That aside, absolutely, positively, if your
6 hospital is geared up to have somebody come down and do
7 adequate anesthesia for that patient, and put them to
8 sleep, and cardiovert them, absolutely, and some of the
9 guys in my department do that. I personally believe
10 that in most emergency departments that don't have big
11 electrophysiology sections and a lot of fellows running
12 around, which is what we use, that having something
13 available to cardiovert that patient, again, in the
14 setting of what John and I have very clearly outlined,
15 would be a tremendous advantage for some patients, but
16 it's just something that you need to individualize.

17 I think this issue of characterizing the
18 patient before you give the drug, everybody around the
19 table said the same thing, listening to the responses.
20 I think that that is absolutely paramount, but it is
21 what we would hope to be able to educate. This really
22 gets down to something that hasn't come up, which is

1 education here of the practicing physicians is going to
2 be of paramount importance.

3 What usually happens in this situation is the
4 EPS are the first people who adopt this stuff, and then
5 it sort of gets down to the cardiologists, and then
6 back down into the emergency department. That's what
7 happened with adenosine; remember? It's the same thing
8 that's happened with a lot of drugs that we use in
9 emergent settings.

10 So the process I think is in place. It's a
11 question of educating doctors appropriately.

12 DR. LEWIS: I think if we could direct
13 ourselves back to the question about comparing
14 vernakalant to ECF and ibutilide. Dr. Davis?

15 DR. DAVIS: Barry Davis, University of Texas.
16 I think one should look at the things that are
17 relevant. Unfortunately, indirect comparisons are
18 really not that great all the time, unless you can make
19 them as much alike as possible. It seems to me, here
20 listening to the whole discussion today, that there's a
21 lot of information all over the place. Obviously, it
22 would be nice if there was a head-to-head comparison of

1 these things. I don't think that's going to take
2 place.

3 It seems to me that everybody thinks that it's
4 effective, and a lot of the data looks like it really
5 is effective. But there are these safety concerns.
6 The biggest problem in my mind, the thing that was
7 brought before us today, was that the SPECTRUM would
8 allay these concerns, and for me that really doesn't.

9 SPECTRUM just has a lot of problems. It's
10 combined this combined prospective and retrospective.
11 It's selection bias. It's a mix of the kind of
12 patients that got in there, so I'm not sure. There
13 were some serious problems before this, and I'm not
14 sure that this solved it.

15 DR. LEWIS: Do any of the committee members
16 want to comment on their comfort with vernakalant's
17 safety versus ibutilide, or ECF?

18 DR. RIDKER: Just a clarification from
19 Dr. Kowey. Now, I got a little confused. How long can
20 a patient, in your mind, have AFib and get a
21 pharmacologic cardioversion before you want to
22 anticoagulate them? I'm just a little bit -- can we

1 clarify that?

2 DR. KOWEY: This is Peter Kowey again. The
3 conventional wisdom has -- I don't know if you remember
4 the paper in the animals several years ago said 48
5 hours was this magical time period. Well, we've
6 learned that's probably a little long, because if you
7 look at transesophageal data, for example, left atrial
8 clot tends to form a lot faster than 48 hours. So we
9 don't give people 48 hours anymore. We give people
10 several hours, a few hours.

11 The problem is -- and I don't know who said
12 this. Maybe it was Dr. Needleman -- trying to time
13 when somebody goes in -- maybe it was
14 Dr. Mandrola -- trying to time when somebody goes into
15 AF. When they say they did is not always that
16 reliable, and a lot of times, people get it wrong.
17 They think they were in AF earlier than they were and
18 vice versa.

19 So my inclination in this situation is, unless
20 I'm very sure, and it's within, say, 6 to 12 hours,
21 then anticoagulation is on the table. If you can't,
22 acutely anticoagulate within that time frame of

1 transesophageal echo before conversion.

2 DR. RIDKER: Right. That's why I want to get
3 to here. I'm often asked to do a TEE on very short
4 notice because we want to electrically cardiovert, and
5 I can't remember being asked to do a TEE because we
6 wanted to give ibutilide. I'm trying to understand why
7 that is.

8 DR. KOWEY: That's exactly the point. is that
9 you can get ibutilide into somebody a lot faster than
10 you can make the arrangements to electrically convert
11 somebody. So the hope is that if you had a drug in the
12 emergency department, they wouldn't have to go through
13 the rigmarole of getting the anesthesia people and
14 everything, and use up a lot of time, but the rules are
15 the same.

16 DR. RIDKER: Are you willing to do it without
17 the TEE.

18 DR. KOWEY: The rules are the same.

19 DR. RIDKER: But that's why I'm stuck because
20 it sounds like -- you've said you would like an echo,
21 and you might even prefer a TEE if you could get it
22 quick. But I'm not hearing that in the whole

1 discussion today about how this drug would get -- I
2 mean, a REMS that said you must have a TEE might change
3 my whole attitude towards this, I suppose, but that's
4 not what I'm hearing, even remotely.

5 DR. KOWEY: Paul, I tend to agree with you
6 about the echo. I already said it, okay? And I know
7 the sponsor hasn't necessarily gone there, so maybe I'm
8 going a little off the reservation. But my opinion is
9 that any question whatsoever -- Milton used the 30 year
10 old. Thirty year olds in AF, by the way, scare the
11 hell out of me. I mean, they really do because I don't
12 know why they're in AF, so I have a pretty low
13 threshold.

14 You know, as well as I do, the handheld echo
15 things in the ER now, you can hook up to your
16 smartphone. I mean, what are we talking about here?
17 Why not? If you really want to assure yourself that
18 you're in good territory, why not? And I agree with
19 you also. If you're not sure about the anticoagulation
20 issue, the best thing to do is just do the TEE, which
21 is low risk.

22 DR. LEWIS: Thank you. I think we are a

1 little bit off at least this question's topic, and I do
2 think that we need to separate that thought of wouldn't
3 it be great not to have to wait for an electric
4 cardioversion, and organizing it in our hospital and
5 just get a shot and run versus is this the drive we
6 want to do that with.

7 Dr. Unger has the next question.

8 DR. UNGER: Ellis Unger. I just wanted to
9 make a point or two, and then there's another point I
10 think I want to make when we discuss number 4.

11 Dr. Stockbridge pointed out that the approval standard
12 is not better than a comparator. But I will say that
13 in the approval standard is safe and effective, and you
14 saw this converts about half the people.

15 So the number needed to treat is about 2, and
16 about 1 percent of people have misadventures, so the
17 number needed to harm is about 100; and compared to
18 most drugs we approve, that's pretty good.

19 But when we do our little risk-benefit
20 calculation at the FDA, there's a section on other
21 therapies. So that's how we kind of massage this and
22 say, well, we don't like this compared to other

1 therapies. I just wanted to clarify that because it's
2 an unusual situation.

3 The other thing I wanted to do, I've written
4 two notes to Dr. Stockbridge during the meeting, the
5 possibility of no echo, no drug. And I would like to
6 hear -- and maybe not until question 4 -- a robust
7 discussion of why that would or would not mitigate the
8 risk, at some point. I don't know when we should
9 discuss that, but I want to make sure that we have that
10 discussion, because we're hearing it now from a number
11 of people.

12 DR. LEWIS: Can I pause for a moment because I
13 was hoping that before we got to the voting question,
14 this subject of echo would come up. The sponsor would
15 like to discuss the echo report, if I've got that
16 correctly, and then I want to give Dr. Dunnmon an
17 opportunity to respond to what they say.

18 DR. TERSHAKOVEC: So there were some questions
19 about the echo report and the different
20 interpretations, and I want to ask Dr. Weaver to come
21 up and show the echo report and the translation. This
22 is for the ACT V patient that we discussed.

1 DR. WEAVER: Thank you. I appreciate the
2 opportunity because I know a lot of this has been
3 driven by these deaths in these early studies, these
4 two deaths. I have to say that when I started to work
5 with the sponsor, when I saw this first patient, who
6 died, I wondered why. Why should this fellow, when I
7 know the mechanism and everything else, have died?
8 Then, why should he have not been resuscitated even
9 after he had his cardiac arrest?

10 So I went to the source records. Being an
11 investigator, I didn't stop with the monitored records;
12 I wanted to see what was in the source.

13 Can we pull up the echogram? Slide up,
14 please.

15 For those of you who can read Spanish, it's on
16 the left side here. When I saw this, compared to what
17 was in the medical monitor's report, I didn't have to
18 have it translated to say, "Sistolica moderadamente
19 reducida por hipocinesia, difusa hipocinesia." That's
20 moderate systolic dysfunction. That's not minor. It's
21 moderate, and the translation's over here on the right
22 side.

1 So not only did this guy have symptoms and
2 signs, he actually had an abnormal echo at the time of
3 this. So in my mind, he should have never been
4 enrolled in this study. He shouldn't have been
5 enrolled because of anticoagulation as well, but he did
6 have a cause, and that's why we have looked for what
7 are those things, signals that come up?

8 As Dr. Packer pointed out, heart failure looks
9 pretty powerful on those things. Structural heart
10 disease looks powerful. I didn't show you, but we've
11 done some pharmacovigilance studies. Heart failure
12 comes up in that as a significant risk factor for
13 developing a hypotensive event.

14 So I think we can't get confused that the
15 early sponsors did trials with almost a wide open
16 population of atrial fibrillation, and wide open was a
17 big mistake because you're going to have errors.
18 You're going to get burned, just like what happened
19 here. And that's why we've looked so hard for a target
20 population and tested it retrospectively, and then
21 prospectively tested it forward.

22 Paul, when you asked me that question about

1 would I do an echo, well, based on what I saw for
2 clinical events in SPECTRUM, I wouldn't. But like
3 Dr. Camm, when I look at a patient, if I have any
4 questions, I'm going to do something to understand this
5 person's physiology because I think I do understand
6 who's going to have this problem, and I think I can
7 obviate giving this to the wrong patient.

8 DR. LEWIS: Dr. Packer?

9 DR. PACKER: Doesn't this report scare you to
10 death?

11 DR. WEAVER: Yeah.

12 (Laughter.)

13 DR. WEAVER: It does.

14 DR. PACKER: Does it scare you the same way it
15 scares me?

16 DR. WEAVER: Absolutely.

17 DR. PACKER: Let's make sure; okay? Here's a
18 patient who got this drug, who after getting this drug
19 had an ejection fraction of 20-25 percent, and severely
20 so. This is the screening echo, which is not
21 terribly -- depending on how you look at it, 44 percent
22 ejection fraction LV is not dilated -- not dilated --

1 DR. GIBSON: And this is 44 percent at a rate
2 of 156, so I don't know what to make of that. And then
3 when he recovers and has a normal heart rate, his
4 ejection fraction is normal, right, If this is
5 patient B.

6 DR. WEAVER: Later on, yes.

7 DR. GIBSON: But that's what's most
8 frightening to me, is this patient had a normal
9 ejection fraction, eventually, had a normal heart rate,
10 and having a normal ejection fraction and a normal
11 heart rate would not have identified this patient as
12 being someone at risk. And that's what I find most --

13 DR. PACKER: That's what scares me as well.
14 What terrifies me is exactly what Michael said. The
15 whole point of this is this is a patient -- this is not
16 a patient who had a big dilated heart with an ejection
17 fraction to 20 percent who fell apart. This is a
18 patient who didn't have a dilated heart, ejection
19 fraction of 44 percent; I understand, atrial fib, but
20 later --

21 DR. GIBSON: Normal.

22 DR. PACKER: -- normal, and who had this

1 profound drop in ejection fraction even though this
2 echo is not terribly impressive. Therefore someone
3 could have gotten this echo and said, "This is good
4 enough. We'll give the drug."

5 DR. LEWIS: I'm going to give Dr. Dunnmon a
6 chance to see if he wants to add any comments.

7 DR. DUNNMON: Could you please bring up FDA
8 backup slide 50? Thank you.

9 I've seen multiple different translations of
10 mild or moderate. The thing that concerned us was the
11 fact that this was a not bad ejection fraction for
12 going 156. In their system, in multiple places, they
13 documented this person was not in symptomatic heart
14 failure. It's in the database. It's in the MedWatch
15 reports. And he was closely supervised while this was
16 going on. It wasn't like this snuck up on anybody, and
17 he was kind of away for a while from treatment. They
18 were right there on -- he had an electrophysiologist in
19 attendance. I mean, it was closely monitored, and they
20 could not stop this while this was going on.

21 The thing that I had described to you before
22 in this sequence of echos, it went 44 percent, 0 during

1 the CPR because the man was described as having no
2 contractile activity at all, with an AFib rate of 110
3 on the ECG that was done at the same time. He started
4 after 40 minutes of resuscitation with high doses of
5 pressors that he was not responsive to, started
6 sleeping this off.

7 You remember the dp/dt study I showed you in
8 the dogs, where this was still going after 90 minutes.
9 After about 45, he started coming around. That EF at
10 25 percent was after they loaded him with amiodarone
11 and shocked him, trying to get hemodynamic and rhythm
12 stability, and then the next day, he was 49. And then
13 you can see there, what I described to you earlier, his
14 MR assessments were mild until the week he died, and
15 he'd gotten a lot of fluid, and got dilated, and start
16 leaking.

17 The other patient that I showed you -- and by
18 the way, on this person's echo report, the abnormality
19 that was present was they said that he had LVH, and
20 every reader remarked on that, and he had a left atrium
21 about 50 millimeters. So it looked pretty classic,
22 really, like hypertensive heart with normal right-sided

1 chamber sizes and dimensions, normal pericardium,
2 thickish heart, kind of wound up in a ball going 156,
3 with no reported symptoms, at least to the system as it
4 reported this.

5 But then I showed you that patient B, where
6 that person was not in the clinical trials. That was
7 just a spontaneous case, where they happened to have an
8 echocardiographer in the room.

9 By the way, you can stop there. This is what
10 I told you before that was in your -- the applicant had
11 written on the left, where they were saying that this
12 was really an alcoholic cardiomyopathy with EF at 25
13 percent, LV dysfunction, and MR.

14 We did not have that assessment. Our
15 assessment was that this patient's recovery of his
16 function, following that 40-minute pulseless arrest,
17 does not support the implicit or explicit thought that
18 somehow there's a safety advantage here when you've got
19 a sodium channel blocker doing what we know it does to
20 the ventricle from the dog studies.

21 Now, could you please go to FDA backup
22 slide 52? This is that patient B, where the attending

1 physician remarks specifically that this person had no
2 history of cardiac disease, and I didn't see other
3 structural abnormalities documented in anything that
4 got sent to us at all. This started in the same
5 sequence.

6 These are not unique to these two people.
7 When you read the other adverse reports that are in
8 your appendix --

9 DR. GIBSON: But the thing about both of them
10 is they ended up with a normal LV function.

11 DR. DUNNMON Oh, yeah, and this one was
12 remarkable --

13 DR. GIBSON: So they not have benefited
14 from --

15 DR. DUNNMON: -- and it happened quickly.

16 DR. GIBSON: an --

17 DR. DUNNMON: Absolutely. So if you look at
18 that series of events, at some point he didn't have
19 enough of an ejection fraction to stop CPR from being
20 started, so I think that 20 was probably not his nadir.
21 But you look at that sequence of low normal, less than
22 20 percent, back up to normal at 5 hours with normal

1 troponins, with no echocardiographic abnormality here,
2 this is what we started thinking about, writing that in
3 a consent form that what is the predictor here that
4 you're going to have a poor outcome?

5 DR. LEWIS: Thank you Dr. Dunnmon and
6 Dr. Weaver.

7 Dr. Alexander?

8 DR. ALEXANDER: Yes. I was going to ask
9 you -- and you don't have to answer because it's sort
10 of a rhetorical question of how old this patient was;
11 because I think we're overplaying the importance of
12 ejection fraction in two ways.

13 One, it's one marker of cardiac function, and
14 there are lots of ways people can have low cardiac
15 reserve with a normal ejection fraction. I mean,
16 severe LVH, a 78 year old, you wouldn't expect them to
17 have any cardiac reserve in there. They could have
18 totally normal systolic function and tolerate a
19 negative inotrope like this really badly.

20 Then the other challenge I think with an echo
21 is that without vernakalant in these patients, their
22 EFs change. You make someone's heart rate go from 80

1 to 150, their EF changes. You change their pre- and
2 afterload, their EF changes. So what you really want
3 on all these patients is their EF when they were in
4 sinus rhythm before they got any of this. And I don't
5 know how long before. I mean, that's the other
6 challenge. If you want an echo before you give
7 vernakalant, I don't know whether that's in sinus
8 rhythm, right before they go into AF. I mean, that's
9 what you'd really like, and that's unlikely to be
10 available.

11 DR. LEWIS: Thank you, Dr. Alexander.

12 I'll make one quick comment that it is
13 concerning that two investigators, at least, enrolled
14 patients that arguably were, according to the sponsor,
15 misenrolled, who probably got a lot more background on
16 who to enroll and not enroll than our average ER doctor
17 might get; so I think we have to be very cautious. I
18 think I would trust Dr. Camm's judgment in any
19 situation, but we have to think about the wide use in
20 our healthcare system.

21 I'm going to summarize question 2, and then I
22 think we'll take a -- do I have more people that have

1 comments for question 2?

2 Dr. Needleman, did you have -- no, no. I'm
3 happy to do more comments.

4 DR. GIBSON: I'll just do one comment, which
5 is you focused a lot on HF_rEF as a risk factor, but
6 perhaps there's something going on with HF_pEF. For
7 instance, amyloid, if you give digoxin, will
8 concentrate the drug, and you have some toxicity. So
9 is there something here that is allowing that kind of
10 toxicity that's not obvious in terms of left
11 ventricular ejection fraction reduction?

12 DR. LEWIS: Dr. Needleman -- [inaudible - off
13 mic].

14 DR. NEEDLEMAN: Just to follow up on that one
15 patient. He was 77, and his presenting heart rate was
16 174. To me, that's an emergency situation. A 77 year
17 old shouldn't have a heart rate of 170. That's really
18 outside the normal. Does anybody think -- that's a
19 dangerous situation.

20 DR. PACKER: It sounds like a great case for
21 electrical cardioversion.

22 (Laughter.)

1 DR. LEWIS: Dr. Packer, I thought you didn't
2 have another comment?

3 (Laughter.)

4 DR. LEWIS: Dr. Needleman, are you done?

5 (Dr. Needleman gestures yes.)

6 DR. LEWIS: Dr. Ridker, I believe you have one
7 short comment.

8 DR. RIDKER: Yes. This is just to return to
9 Dr. Unger's question to us a minute ago about the echo
10 issue, and Dr. Alexander I think got halfway there.

11 We're going to go to the real questions in a
12 second, and this is an entree to that, that I think
13 it's important. I must say I came here today wondering
14 something related to this, which is would the FDA lift
15 the clinical hold and have the sponsor do the proper
16 study, where you got a baseline echo in lots of people
17 at high risk for recurrent AFib, so you knew the echo
18 at baseline, and you did something?

19 Is that within the realm of what you're asking
20 us or is that just off the table for this kind of
21 discussion? Because you were asking about what the
22 echo issues might be here.

1 DR. STOCKBRIDGE: If we thought there was a
2 reasonable study to be done, a theory for how to manage
3 this risk, and we wanted it studied, then we'd lift the
4 hold. There's no question we'd do that.

5 DR. LEWIS: Okay. I'm going to make a stab at
6 summarizing our wide-ranging discussion on question 2.
7 I think that in terms of comparing it to the other
8 alternative, we have heard, again, a little bit of a
9 mixture of points of view that ECF works great. It's
10 really just a management or a healthcare issue of
11 getting the anesthesiologist and mobilizing the
12 resources, and an inconvenience to the patient to have
13 to stay longer for all that to happen, and that harm
14 reduction should be our focus.

15 On the other hand, we've heard that ECF is not
16 necessarily as safe as we think it is, that there is
17 much underreporting of negative effects of it, as well
18 as ibutilide. Other drugs are thought to be less
19 effective, so there are not other drugs that are as
20 effective to help patients convert pharmacologically.

21 Is the risk of the drug worth getting out of
22 the ER more quickly? Then I think we did focus a

1 little bit on a discussion that will come more to our
2 fourth question, which is could we identify a
3 population for which the safety compared to the
4 alternatives would be acceptable? We've heard about
5 selecting people with no significant past medical
6 history that is relevant; nothing can beat the physical
7 exam. I think that summarizes it.

8 Dr. Unger or Dr. Stockbridge, do you have any
9 other comments or questions for this one?

10 DR. STOCKBRIDGE: I think we're good.

11 DR. LEWIS: Okay. We will take a break. We
12 will take a 10-minute break. Panel members, please
13 remember there should be no discussion of the meeting
14 topic during break amongst yourselves or with any
15 member of the audience, and we will resume at 2:10-ish.

16 DR. RIDKER: Julia, would there be a
17 possibility of skipping the break, by chance?

18 DR. LEWIS: I'll give you a little bit longer.
19 You want a 15-minute break.

20 DR. RIDKER: No, no. I was actually wondering
21 if we could skip the break because --

22 DR. LEWIS: Excuse me?

1 DR. UNGER: Our recorder would like a break.

2 DR. LEWIS: You want a break? Okay. Our
3 recorder needs a break. We'll compromise. We'll do a
4 10-minute break.

5 (Whereupon, at 2:01 p.m., a recess was taken.)

6 DR. LEWIS: Thank you for all taking that
7 short break. If there's no further discussion on this
8 question, we will now begin the next question, which is
9 the voting question.

10 We will be using an electronic voting system
11 for this meeting. Once we begin the vote, the buttons
12 will start flashing and will continue to flash even
13 after you have entered your vote. Please press the
14 button firmly that corresponds to your vote. If you
15 are unsure of your vote or you wish to change your
16 vote, you may press the corresponding button until the
17 vote is closed.

18 After everyone has completed their vote, the
19 vote will be locked in. The vote will then be
20 displayed on the screen. The DFO will read the vote
21 from the screen into the record.

22 Next, we will go around the room and each

1 individual who voted will state their name and vote
2 into the record. You can also state the reason why you
3 voted as you did if you want to. We will continue in
4 the same manner until all questions have been answered
5 or discussed.

6 I'll read our voting question. Do you
7 recommend approval a vernakalant for the rapid
8 conversion of recent onset atrial fibrillation? Does
9 anyone need a clarification of the question?

10 (No response.)

11 DR. LEWIS: Okay, then we are ready to vote.
12 Oh, I'm sorry.

13 DR. ALEXANDER: Does this include necessarily
14 both the postoperative patients and presenting in the
15 emergency room patients?

16 DR. STOCKBRIDGE: I think if you can name a
17 circumstance under which you're ready to approve it,
18 you should vote yes.

19 DR. LEWIS: We'll proceed with voting.

20 (Voting.)

21 DR. LEWIS: Please press the button on your
22 microphone that corresponds to your vote. You will

1 have approximately 20 seconds to vote. Please press
2 the button firmly. It looks like we've succeeded in
3 our vote.

4 DR. WANG: For the record, we have 2 yeses, 11
5 nos, and zero abstain.

6 DR. LEWIS: Now that the vote is complete, we
7 will go around the table and have everyone who voted
8 state their name, vote, and if you want to, you can
9 state the reason why you voted as you did into the
10 record. Dr. Ridker?

11 DR. RIDKER: Yes. Paul Ridker. I voted no.
12 I don't think it's worth going through a lot of the
13 details of why; we've talked about it a lot. I would
14 say one thing, though, which is that I don't want this
15 vote to imply that we should shut down pharmacologic
16 cardioversion in general as an approach, nor that this
17 drug as an approach should necessarily be abandoned.

18 I would like to say, for the record, I
19 probably would encourage the FDA to consider lifting
20 the clinical hold and allowing the sponsor to maybe
21 figure out some study designs that would answer some of
22 these critical questions, so that we could come back

1 here with more data on benefit-to-risk ratio, because I
2 suspect there are patients this is a good idea for; I
3 just haven't been convinced today of who they are. And
4 that would require a lift of the clinical hold to allow
5 them to do that.

6 DR. GIBSON: Yes, I agree with Dr. Ridker it
7 would be great to see more data, the drug evaluated
8 further. Dr. Gibson. Sorry. As an interventional
9 cardiologist, we're always weighing risk and benefit.
10 In order to take a risk, there has to be a very clear
11 benefit. For instance, we do things like put stents in
12 that have a 0.5 percent risk of stent thrombosis, which
13 carries a substantial risk of harm, and we weigh the
14 risk of bleeding in that context.

15 Here, there is a risk of a very infrequent,
16 potentially catastrophic fatal event, but I'm looking
17 for what's the advantage, and I'm not seeing -- it's
18 convenience. But when I look at our hospital, we have
19 a room full of 10 to 15 people getting cardioverted all
20 day. Getting them out quicker I'm not sure is
21 necessarily an advantage to the health status of an
22 individual patient.

1 I was struck by some of the basic animal lab
2 data, the fact that the negative inotropic could not be
3 separated from the antiarrhythmic effect. Mostly, I
4 was concerned and struck by the persistent inhibition
5 of dp/dt, all the way through 90 minutes, and I never
6 saw that come back up. I was left wondering when does
7 the LV function return?

8 I was also very worried about the two patient
9 narratives. Both seemed to have normal LV function at
10 the end of the day, and when I looked through their
11 histories and began to apply the checklist, I don't
12 know that the checklist would have identified those two
13 patients as having been people at risk.

14 If you're going to take a risk, you have to
15 say, well, are there other alternatives? There did
16 appear to be other alternatives that have treatable
17 side effects. The SPECTRUM data was submitted. I just
18 think it's hard to believe the mortality rate was that
19 low. Obviously, you had to be alive to consent, so I
20 think that's a big limitation; that we did not
21 adequately capture what may have been some events.

22 I do a lot of adjudication of events, and

1 people may not die within 24 hours. They may have
2 begun the spiral down at 24 hours, and they may die at
3 day 31, not within 30 days. They may have died from
4 pneumonia, or sepsis, or something, a complication, and
5 they may die somewhere else. You may not have the
6 medical records to review right at your hospital. If
7 you only complete 68 percent of the checklist, I
8 wondered about your ability to collect data about those
9 adverse outcomes.

10 So at the end of the day, I just didn't feel,
11 at this point, in this development, of this drug, there
12 was an unpredictable risk. We take risks, but here the
13 risk was unpredictable. And when you have an
14 unpredictable risk, I think it really makes it much
15 more concerning as a healthcare provider, and then you
16 have a side effect that did not appear to be easily
17 treatable. So in my mind, the benefits did not
18 outweigh the risks at this point in time in this
19 development plan, but hopefully the sponsor can make
20 some changes to change that.

21 Dr. Gibson. I voted no.

22 DR. LEWIS: Dr. Packer?

1 DR. PACKER: Milton Packer. I voted no. I
2 will not repeat what Michael said, and I would agree
3 with what he said and the way he said it. This is a
4 drug, in large part, of convenience, which is not
5 counterbalanced by a harm that's unpredictable, but
6 serious. I really tried very, very hard to find some
7 patient population, some low-risk patient population
8 that could be identified, even after the fact, that
9 would allow for a risk to benefit that would favor
10 using the drug in someone, and I couldn't find it.

11 DR. DAVIS: This is Barry Davis. I voted no.
12 I think Dr. Gibson summarized it excellently. It's a
13 benefit-risk calculation. It clearly has benefit, but
14 it does have risks. If this was the only drug around
15 or the only treatment around, yes, but there are other
16 options. And from what I've heard today, even though I
17 commented upon how you could reliably predict, I don't
18 think that there's any sort of way of getting a handle
19 on this just yet. I would think they could go back to
20 the drawing board and maybe design something that might
21 better say that there's a certain population that would
22 benefit.

1 DR. MANDROLA: John Mandrola. I voted no for
2 the same reasons that have already been stated. It's
3 just not a favorable benefit-risk ratio. I don't think
4 I need to reiterate what others have said.

5 DR. LEWIS: Julia Lewis. I voted no. I
6 thought the totality of evidence supported the
7 hypothesis that this drug has a potential for a fatal
8 side effect in a disease that you can live with
9 potentially, although I respect Sue's comments and how
10 difficult it can be, and that there are other
11 treatments for.

12 DR. ALEXANDER: This is John Alexander. I
13 voted yes, and my rationale is actually not that
14 different than what some of the other people have said.
15 I think the benefit is that the drug clearly converts
16 atrial fibrillation, although it's only a transient
17 conversion of atrial fibrillation; it does nothing to
18 prevent long-term atrial fibrillation. There's clearly
19 a serious safety signal in some populations of
20 patients.

21 However, I was more reassured by the SPECTRUM
22 data, and I think there is a low-risk population, where

1 the convenience factor of this drug, that would provide
2 an important option for providers and patients,
3 outweighs the relatively low risk of serious
4 complications. Patient selection is key, and I think
5 more work needs to be done on identifying the patient
6 population that has a favorable risk-benefit profile.

7 I think there's a pretty clear really low-risk
8 population, I think there's a pretty clear really
9 high-risk population, and I think there's this huge
10 gray zone, which is a big problem. So more work needs
11 to be done to clarify who are the low-risk patients
12 where it would be favorable.

13 DR. MOLITERNO: David Moliterno. I also voted
14 no, and I don't think I need to repeat what others have
15 said. But distilling it down, I would say it's the net
16 benefit, meaning benefit minus potential harm versus
17 other available options. So for me, it was a
18 relatively easy decision.

19 MS. ALIKHAANI: My name is Jacqueline
20 Alikhaani, and I voted no, primarily because I'm very
21 concerned about the seriousness of the adverse side
22 effects and the lack of diversity in the clinical

1 trials.

2 MS. HAZLETT: My name is Nedra Hazlett, and I
3 voted no for the safety concerns. The potential risks
4 were too great compared to the benefits, which seemed
5 no better than things that exists that are safer.

6 DR. FLOYD: James Floyd. I voted no. I think
7 this drug clearly has efficacy, but I think it also
8 clearly has dose-dependent effects, negative inotropic
9 effects, that can lead to death. For me, the issue is
10 effect modification. I think that we were shown
11 evidence that clinical heart failure, LV dysfunction,
12 structural heart disease, that these account for a lot
13 of the serious safety issues, and also account for
14 reduced efficacy. So that's clearly a population where
15 you would not want to use this drug, and then we're
16 left with the really healthy patients.

17 Even there, we heard a number needed to treat
18 of 2 and a number needed to harm of maybe 100; maybe
19 it's 500. But given the asymmetry of the benefit
20 outcome and the harm, that still is not acceptable to
21 me. There could still be opportunities for further
22 clinical development, and I would like to give advice

1 along those lines.

2 If you can identify the population where you
3 think the efficacy is preserved, where the harms are
4 minimized, I think the key is to do the study that's
5 designed for that purpose and actually powered to
6 exclude the clinically acceptable amount of harm.
7 Often we do these studies with a few hundred patients.

8 We see one death, two deaths, and we have wide
9 confidence intervals. I think if that is really the
10 hang-up, then probably the study that's designed needs
11 to exclude what we think is the amount of harm that's
12 unacceptable, which of course is really hard to
13 quantify and people might disagree what that is.

14 I also want to point out I was actually quite
15 concerned that even in the ACT V study, I believe,
16 where there were stringent exclusion criteria, there
17 were still protocol violations. And I worry about the
18 use of this drug once it's out in practice, where
19 people who aren't as familiar with the benefits and
20 harms as we are, study physicians are going to violate
21 the protocol even more than that. So that was a major
22 concern of mine.

1 DR. NEEDLEMAN: [Inaudible - off mic].

2 DR. LEWIS: I don't think your mic is on.

3 DR. NEEDLEMAN: Sorry. Matthew Needleman. I
4 voted yes for the indication. Quality of life is an
5 important goal, and it may be worth taking risks for.
6 There's no perfect option for cardioversion. Every
7 option has I think significant limitations.

8 The checklist also had significant
9 limitations; I agree with Dr. Packer's concern that
10 even in mild heart failure, we saw that there could be
11 limitations. But as kind of a blue collar
12 electrophysiologist taking care of a lot of AFib
13 patients, it's nice to have options to treat people.

14 We've all known patients with normal ejection
15 fractions who keep coming in with symptomatic AFib, who
16 want to get out of it quickly and get back to their
17 lives. So having an option like this I think would be
18 good for a very select group of patients. I understand
19 the concern of the committee releasing this to the
20 wild, but I think in a very select group of patients,
21 this has a role.

22 DR. MERANDI: Hi. Jenna Merandi, and I voted

1 no for this as well, just like many of the other
2 reasons stated. Specifically around the risks
3 outweighing benefits for this particularly, I think if
4 there is further data available, it would give us the
5 opportunity to perhaps build a robust REMS program with
6 different elements to assure safe use, perhaps, that
7 would allow us to better identify who should receive
8 this therapy versus those that should not.

9 I think one of the comments mentioned that
10 providers just need to be really educated on this, I
11 think that it goes much more beyond education. A lot
12 of the providers that are going to see these patients
13 first might be your new learners, and residents, and
14 fellows, and things of that nature; as already
15 mentioned, people that might be less familiar with this
16 therapy and the risks that are associated with it.

17 So I really do think before moving forward, we
18 would need to know exactly who falls into those
19 categories, and then have a robust program that can
20 actually be operationalized to really capture it versus
21 just relying on education because that doesn't always
22 work.

1 DR. LEWIS: If there are no more comments on
2 the voting question, I will read the next discussion
3 question. If vernakalant was approved, what
4 restrictions would you place on patients or on the
5 conditions of use?

6 I think, Dr. Ridker, this could also be
7 applied to your comment about if you were going to
8 relieve a clinical hold and do a clinical trial in the
9 United States, what restrictions would you put on the
10 population entering the study.

11 DR. RIDKER: Right. I think a creative trial
12 could be done here that would actually convince me this
13 is a very good agent, and I think you'd have to sort of
14 say -- I was thinking about this. I would take my many
15 patients in clinic who are return AFib patients, that
16 keep coming back with AFib, so they get cardioverted or
17 whatever. I know who they are; they're very high-risk
18 people if they're recurring.

19 Probably you have to grab their echo when
20 they're in sinus rhythm beforehand and exclude the
21 people that we are all concerned about risk. So now
22 you have a randomizable cohort based on a normal echo

1 and all the other exclusions, like the ones that
2 Dr. Camm laid out so nicely, and then you randomize
3 those folks to this drug I can't pronounce -- I'm
4 sorry -- or placebo. And I suspect you'd probably come
5 out in good shape.

6 So again, I've already said I would
7 encourage -- I do believe pharmacologic cardioversion
8 has a role. I think there's a future in this. I just
9 know we have to get there. Our colleagues in Europe
10 and Canada have these options, and I'm very sympathetic
11 to that; having multiple is generally a nice thing to
12 have. I do think there's a clinical trial that could
13 get done that would do this, but that requires lifting
14 the clinical hold for this issue.

15 DR. LEWIS: Would you include an ECV arm?

16 DR. RIDKER: I guess that would be an even
17 better study, but it raises some other issues,
18 obviously, but it's an interesting thought.

19 DR. LEWIS: Dr. Alexander?

20 DR. ALEXANDER: As somebody who voted for
21 thinking about approving it, I would want to restrict
22 use to patients with no structural heart disease, and

1 that I mean probably more than mild. So it would
2 require assessment of all of these things. I wouldn't
3 just take known LV dysfunction. I would exclude
4 everybody with LV dysfunction. I would exclude people
5 with more than moderate aortic stenosis -- I'm
6 sorry -- yes; more than moderate aortic stenosis, more
7 than moderate LVH, and any recent MI, clinical
8 diagnosis of heart failure.

9 Then I would want use to be in a setting that
10 could deal -- one of the things I was struck by is, if
11 you think vernakalant is as dangerous as it is, it
12 needs to be used in an environment that's not that
13 different from the environment in which we do
14 cardioversion. It needs to be used in an environment
15 that can use pressors, and inotropes, and intubate. So
16 I would want to restrict use for places that can do at
17 least some of those things, performing ACLS and care.

18 Paul, I think more study would be really
19 useful. Studying people in this low-risk population to
20 confirm safety in that low-risk population would be
21 really useful. I think we'd want to have more
22 discussion about what the right control group is.

1 What's the use of placebo? If you're trying to confirm
2 safety, I'm not sure there's a whole lot of use of
3 placebo. Depending on what outcome you're interested,
4 having a cardioversion arm would be really interesting,
5 but it would have to include process of care, length of
6 stay, cost, things like that to be useful, I think.

7 DR. LEWIS: Dr. Floyd?

8 DR. FLOYD: I voted against approval and
9 further study, but if this drug were approved, I do
10 agree with the comments that it probably should only be
11 used by the people with the most expertise in the risks
12 and benefits; I'm thinking probably electrophysiologist
13 but also some general cardiologists. There is a part
14 of REMS that isn't invoked often. I think it's under
15 elements to assure safe use, where you can require
16 registration of physicians before they can prescribe
17 it.

18 So instead of this reliance on passive
19 education, actually have physicians take an online
20 course, saying they understand the risks, quantify the
21 harms, and know what can happen. You give the drug,
22 and then you can't get them out of cardiogenic shock;

1 know that that's a real risk. So it doesn't have to be
2 an EP doc, but something with more teeth than just
3 saying we're going to educate people I would say is
4 important.

5 DR. LEWIS: Dr. Moliterno?

6 DR. MOLITERNO: Thank you. My comments echo
7 the prior two speakers, that if the agency did choose
8 to approve this drug, I would probably focus more on
9 conditions of use. Not to sound prideful, but I
10 probably would restrict it to cardiologists initially
11 who had a deep understanding of this drug, and then --

12 DR. FLOYD: I should not be allowed to use
13 this drug.

14 (Laughter.)

15 DR. MOLITERNO: -- fair enough; come to
16 me -- and then collect data based on that experience
17 gained by cardiologists in the United States, and go
18 from there.

19 DR. LEWIS: Dr. Needleman?

20 DR. NEEDLEMAN: Not to rehash what
21 Dr. Alexander and Dr. Floyd said, I completely agree
22 with their comments. In addition to the REMS program

1 and the ICU setting, I would also not use it in elderly
2 people at all, so maybe patients less than 60.

3 DR. LEWIS: Dr. Gibson?

4 DR. GIBSON: I do think the risks of
5 electrical cardioversion may have been underestimated.
6 I guess that's because when I cardiovert people,
7 they're usually in the cath lab, so maybe I have a very
8 different view of cardioversion. But nonetheless, if
9 there was an effort to reevaluate this, I do think
10 electrical cardioversion would be a good comparator,
11 and I do think you might see that the results are more
12 durable with this agent compared to electrical
13 cardioversion. With the sedation and everything else,
14 you do get some hypotension with electrical
15 cardioversion.

16 So rather than comparing yourself against
17 placebo, which has no safety concerns, compare yourself
18 to something that does have some potential safety
19 concerns to put this in better context.

20 DR. LEWIS: Ms. Merandi?

21 MS. MERANDI: Just to add on from what
22 Dr. Floyd said about thinking about a REMS program for

1 this, also thinking about the role of the patient and
2 how they can be educated, and how they could be aware
3 of the risks and things of that nature through
4 mandatory patient counseling and things of that nature;
5 also the role of the nurse and what type of mandatory
6 education would be required upon them in terms of
7 monitoring, how long they should be monitoring, what
8 they could of be expecting, and things of that nature;
9 so just making sure to include both the patient and
10 other interdisciplinary staff when thinking about this.

11 DR. LEWIS: Dr. Mandrola?

12 DR. MANDROLA: You're going to eliminate the
13 elderly. You're going to take away anybody with low
14 blood pressure, anybody with mild LV dysfunction, which
15 is, in my hospital, everybody in atrial fibrillation.
16 And you're going to restrict it to electrophysiologists
17 or registered docs. That leaves you with a very
18 healthy cohort of 40- to 50-year-old people who could
19 easily be treated with atenolol, and some peace and
20 quiet, and sent home, and two-thirds of them will be in
21 sinus rhythm in 24 hours. Sorry.

22 DR. LEWIS: Dr. Packer?

1 DR. PACKER: If the FDA were going to approve
2 it, I think there is a mechanical framework for a name
3 patient registry; is there not?

4 (Dr. Stockbridge nods yes.)

5 DR. PACKER: This goes beyond the certified
6 physician. This is a certified physician and a named
7 patient registry. The way that I'm thinking about this
8 is it obviously is not going to be suitable for the
9 vast majority of people in the world, but one could
10 imagine that there's a patient population of patients
11 who have just rare paroxysmal atrial fibrillation that
12 you would not put on a long-term beta blocker even,
13 maybe; who would come in every year or two. They could
14 then be put into a name registry, and when they come
15 in, they could get the drug. Because it's a name
16 registry, you could follow them in terms of safety and
17 in terms of how they do.

18 Name registries might actually provide a path
19 forward that would provide comfort if the FDA were so
20 inclined.

21 DR. LEWIS: Ms. Alikhaani?

22 MS. ALIKHAANI: Yes. I would like to see more

1 work on better identifying and categorizing the
2 high-risk patients; also more consistency with the
3 checklist. Also, I don't know if this is something
4 that they did, but considering the high number of
5 adverse side effects, I'm not sure that there was a
6 strong patient research partner engagement team as part
7 of the research leadership teams. So I think maybe
8 have a consortium of patients to help advise the
9 research effort.

10 DR. LEWIS: Dr. Alexander?

11 DR. ALEXANDER: Sorry. I didn't put my card
12 down.

13 DR. LEWIS: Okay.

14 Are there any more comments from the panel on
15 the last discussion question?

16 DR. STOCKBRIDGE: Should I take from this
17 discussion that if we weren't to approve vernakalant at
18 this point, that most of the committee members would
19 sort of like to see a prospective study done to
20 evaluate a risk mitigation plan? Is that fair?

21 DR. LEWIS: I think Dr. Stockbridge is asking
22 us to clarify our comments. Are we willing to suggest

1 that the U.S. population should be available for a
2 clinical trial? Does someone want to comment first?
3 Dr. Alexander?

4 DR. ALEXANDER: Yes. I would say whether or
5 not you decide to approve vernakalant, there's more
6 work to do to characterize in whom it's appropriate and
7 in whom it's not.

8 DR. GIBSON: Yes. Gibson. I agree, and
9 again, I'd like to see some more work done in the
10 animal studies to know when the dp/dt comes back up as
11 well, the recovery of the LV. But I think a more
12 appropriate comparator, as I said, would be electrical
13 cardioversion.

14 DR. STOCKBRIDGE: And do you have some notion
15 of what an acceptable performance would be? No events
16 in 30 patients? No events in 10 patients? What are
17 you thinking?

18 DR. LEWIS: We're getting close to a question
19 here, but I think we could have a further discussion.
20 I will comment, I actually am concerned about lifting
21 the clinical hold only because I think that the animal
22 data supports what was seen in, albeit, a few number of

1 humans, but humans, and I think it would be challenging
2 to ask a patient to volunteer. But I think other
3 people should comment.

4 Dr. Floyd?

5 DR. FLOYD: As I mentioned earlier, I think if
6 a clinical hold were lifted, the trial would have to
7 have clear objectives. I think it would be unethical
8 to randomize, say, 30 or 40 people because the zero
9 events doesn't tell you much compared to the
10 information you have, and there's no point in doing
11 that trial, except to collect physiologic information,
12 maybe.

13 So I think if a trial is being done, I think a
14 randomized design is preferable to observational, based
15 on what we've seen. It really needs to be powered to
16 exclude some amount of harm that some people would feel
17 comfortable using the drug once you demonstrate that;
18 zero events out of 100 or 200.

19 The rule of zero events, I think it's one over
20 the number times 3 is the upper bound of the confidence
21 interval. That gives you a back-of-the-envelope
22 calculation. That may be so large a population that

1 the sponsor can't actually enroll that many patients
2 because of the serious consent issues with the risk of
3 death, and I think that gives an answer in and of
4 itself.

5 DR. GIBSON: But I do think we have 58,000
6 patients worth of data up to now, and in kind of a
7 Bayesian kind of way just say, well maybe we should
8 rethink this. But again, it's hard to beat placebo in
9 terms of safety. I do think you have to put it in the
10 context of other therapies, and then set some
11 noninferiority margin with respect to safety relative
12 to electrical cardioversion.

13 DR. LEWIS: I think Dr. Ridker was next.

14 DR. RIDKER: I agree with what Dr. Floyd just
15 laid out in terms of the big structure and probably
16 would do it against electrical cardioversion. But I
17 think if you were smart about this, you would also
18 build in a second endpoint that's being monitored along
19 the way, which is just get echo data during the actual
20 infusion.

21 If you saw, we were very persuaded by these
22 one or two cases, where it appeared that somebody

1 somewhere saw an echo go from functional to
2 dysfunctional, back to functional. If you design this
3 clinical trial, and then also were to monitor that
4 along the way, and you saw some patients having that
5 happen, it might change what you thought of this drug.
6 And if it turns out that that's not happening, and this
7 is just bad luck, anecdotal something, okay, you
8 proceed. So that's probably how I would look at this.

9 DR. LEWIS: Dr. Packer?

10 DR. PACKER: I had previously, as a wild idea,
11 proposed an imaging study, open label, no control,
12 imaging study, looking at LV function during the
13 infusion, in order to quantify exactly what's going on
14 because we don't know.

15 My personal sense is if you took a group of
16 normal people and you saw that everyone had their
17 ejection fraction fall from 65 to 30, and then it came
18 back after an hour, that would give you a different
19 feel. And if you saw them go from 65 to 60, or
20 whatever you want, you would have a better sense of how
21 much of a negative inotrope this was, even in people
22 with normal hearts.

1 That would be so informative to this sponsor
2 as to whether they would actually want to pursue this.
3 The problem is that, as has already been mentioned,
4 that would be ethical only if you had adequate informed
5 consent. I guess I would have to ask myself would I
6 consent to that study, and I don't know.

7 DR. LEWIS: Dr. Davis?

8 DR. DAVIS: Barry Davis. I think it would be
9 useful if he could do this study comparing to ECV, but
10 there are so many problems. The most important one is
11 the one that Dr. Stockbridge mentioned, which is what's
12 your outcome there? It seems to me that you'd be
13 talking thousands and thousands of patients if you're
14 talking about a very low-level safety outcome.

15 Then the kind of patient that's going to sign
16 up for this, they'd have to be willing to be randomized
17 to ECV. The whole point of vernakalant was that they
18 wouldn't get the ECV. So it would require a lot of
19 thought as to what the appropriate endpoints are and
20 what the sample size is. It may be prohibitive.

21 DR. LEWIS: Dr. Moliterno?

22 DR. MOLITERNO: David Moliterno. I think many

1 of these questions are great, and are academic, and I'd
2 love to have the detailed information, particularly
3 Dr. Gibson's questions about the recovery of dp/dt and
4 when you could address it. I think Dr. Stockbridge is
5 right and Dr. Davis, how many patients do you need,
6 though, to find the signal beyond that.

7 I think the overall argument in conversation
8 is a little bit moot since there hasn't been a clinical
9 hold in many European countries over the last decade.
10 So should the sponsor or academicians in Europe wanted
11 to address this, they could have. I think three
12 different companies have owned this drug, and they
13 haven't.

14 DR. LEWIS: Dr. Alexander?

15 DR. ALEXANDER: Thank you. I just want to
16 echo support for the echo or imaging study. In the way
17 I've been thinking about this, there's a cohort of
18 high-risk patients and a cohort of low-risk patients.
19 But it would be very different, in my mind, if
20 everybody's AF dropped by half, and some people had
21 reserve to tolerate it and some people didn't.

22 I have sort of been working under the

1 hypothesis that there's a cohort that's at risk of LV
2 dysfunction from the drug and a cohort that's not, but
3 that may not be the case, and wouldn't take that many
4 patients to answer that question, potentially.

5 DR. LEWIS: I'm going to attempt to summarize
6 our discussion of that question. I think that the
7 committee both looked at it as how you would restrict
8 its use, as well as how you would lift the clinical
9 hold. There was interest in exploring the mechanism of
10 action of this drug, either by echo or by comparison
11 with an active comparator, possibly placebo.

12 In terms of using it outside a clinical trial,
13 I think that virtually all the committee members wanted
14 some restrictions in its use if it was approved, either
15 by only cardiologists or only EP people, or people that
16 are not only both those things but also REMS certified
17 doctors. I think it's an extremely good point that
18 it's not just the doctors that need to be educated and
19 certified, but also the multidisciplinary team that
20 will be caring for this patient.

21 The question did come up about whether or not
22 this would, A, be enrolled, with the big harm that you

1 would have to reveal to the patient the potential
2 death, and also would you narrow the population so low,
3 to such a small population that would potentially get
4 this drug, that it's maybe not worth discovering a
5 small safety signal, but a deadly one.

6 Do you guys have any further questions or
7 clarifications that you want from the panel or
8 discussion?

9 DR. STOCKBRIDGE: I think we're good.

10 DR. LEWIS: Are there any last comments you
11 want to make?

12 DR. STOCKBRIDGE: Just my thanks and
13 appreciation, and hope that you all have a safe trip
14 home.

15 **Adjournment**

16 DR. LEWIS: Panel members, please take all
17 personal belongings with you, as the room is cleaned at
18 the end of the meeting day. All materials, however,
19 that you leave on the table will be disposed of.
20 Please also remember to drop off your name badge at the
21 registration table on your way out, that they may be
22 recycled.

1 We will now adjourn the meeting, and I want to
2 thank you all for participating and for an excellent
3 discussion.

4 (Whereupon, at 2:53 p.m., the meeting was
5 adjourned.)

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22