FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE (CRDAC) MEETING

Virtual Meeting

Wednesday, December 16, 2020

9:00 a.m. to 1:37 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Joyce Yu, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

MEMBERS (Voting)

Jacqueline D. Alikhaani, BA

(Consumer Representative)

Volunteer and Advocate

American Heart Association

Los Angeles, California

C. Noel Bairey Merz, MD, FACC, FAHA, FESC

Director

Barbra Streisand Women's Heart Center

Cedars-Sinai Medical Center

Los Angeles, California

Thomas D. Cook, PhD, MS, MA

Professor (Clinical Health Sciences)

Clinical Trials Program

Department of Biostatistics and

Medical Informatics

University of Wisconsin-Madison

Madison, Wisconsin

C. Michael Gibson, MD, MS

Professor of Medicine

Harvard Medical School

President

Combined non-profit Baim and PERFUSE

Research Institutes

Boston, Massachusetts

Edward K. Kasper, MD, FACC, FAHA

Director of Outpatient Cardiology

Johns Hopkins Medicine

E. Cowles Andrus Professor in Cardiology

Johns Hopkins School of Medicine

Baltimore, Maryland

Julia B. Lewis, MD

(Chairperson)

Professor of Medicine

Division of Nephrology

Vanderbilt Medical Center

Nashville, Tennessee

David J. Moliterno, MD

Professor and Chairman

Department of Internal Medicine

University of Kentucky Medical Center

Lexington, Kentucky

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

Eugene Braunwald Professor of Medicine

Harvard Medical School

Director, Center for Cardiovascular Disease

Prevention

Division of Preventative Medicine

Brigham and Women's Hospital

Boston, Massachusetts

Ravi I. Thadhani, MD, MPH

Chief Academic Officer

Massachusetts General Brigham

Professor of Medicine and Dean for

Academic Programs Mass General Brigham

Harvard Medical School

Boston, Massachusetts

ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

(Non-Voting)

Jerome A. Rossert, MD, PhD

Vice President, Head of Clinical Renal

AstraZeneca

Gaithersburg, Maryland

TEMPORARY MEMBERS (Voting)

Cynthia L. Chauhan, MSW

(Patient Representative)

Wichita, Kansas

Scott Emerson, MD, PhD
Professor Emeritus of Biostatistics
University of Washington
Seattle, Washington

Steven E. Nissen, MD, MACC
Professor of Medicine
Cleveland Clinic Lerner School of Medicine at
Case Western Reserve University
Chief Academic Officer
Sydell and Arnold Miller Family Heart,
Vascular & Thoracic Institute
Cleveland Clinic
Cleveland, Ohio

Christopher M. O'Connor, MD, MACC, FESC, FHFA, FHFSA
President and Executive Director
Inova Heart and Vascular Institute
Professor of Medicine, Duke University
Falls Church, Virginia

FDA PARTICIPANTS (Non-Voting)

Ellis F. Unger, MD

Director

Office of Cardiology, Hematology,

Endocrinology and Nephrology (OCHEN)

Office of New Drugs (OND), CDER, FDA

Norman Stockbridge, MD, PhD

Director

Division of Cardiology and Nephrology (DCN)

OCHEN, OND, CDER, FDA

Aliza Thompson, MD, MS

Deputy Director

DCN, OCHEN, OND, CDER, FDA

Mary Ross Southworth, PharmD

Deputy Director for Safety

DCN, OCHEN, OND, CDER, FDA

Ququan Liu, MD, MS

Mathematical Statistician

Division of Biometrics II (DB-II)

Office of Biostatistics (OB)

Office of Translational Sciences (OTS)

CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. LEWIS: Good morning and welcome. I'd like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her email and phone number are currently displayed.

My name is Julia Lewis, and I will be chairing today's meeting. I will now call the December 16, 2020 meeting of the Cardiovascular and Renal Drug Advisory Committee to order. Dr. Joyce Yu is the designated federal officer for this meeting and will begin with introductions.

Dr. Yu?

Introduction of Committee

DR. YU: Good morning. My name is Joyce Yu, and I am the designated federal Officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation. We'll start with Ms. Alikhaani.

MS. ALIKHAANI: Good morning. I'm

Jacqueline Alikhaani. I live in Los Angeles, and I'm a heart survivor, heart patient, and citizen scientist and a long-time volunteer with the American Heart Association. I also serve as an ambassador for PCORI, the Patient-Centered Outcomes Research Institute. Thank you.

DR. YU: Dr. Bairey Merz?

DR. BAIREY MERZ: Noel Bairey Merz, clinical cardiologist and physician scientist in Los Angeles at the Cedars-Sinai Smidt Heart Institute. I have interest in women's heart disease and heart failure with preserved ejection fraction. Thank you.

DR. YU: Dr. Cook?

DR. COOK: Thomas Cook, University of Wisconsin-Madison, Department of Biostatistics and Medical Informatics. Thank you.

DR. YU: Dr. Gibson?

DR. GIBSON: Hi. I'm Mike Gibson, an interventional cardiologist, clinical trialist, and professor of medicine at Harvard.

DR. YU: Dr. Kasper?

DR. KASPER: Good morning, everyone. I'm

Dr. Ed Kasper. I am a heart failure cardiologist at Johns Hopkins.

DR. YU: Dr. Lewis?

DR. LEWIS: Dr. Julia Lewis. I am a nephrologist at Vanderbilt University Medical Center.

DR. YU: Dr. Moliterno?

DR. MOLITERNO: Good morning. David Moliterno. I'm an interventional cardiologist and the chairman of the Department of Internal Medicine at the University of Kentucky.

DR. YU: Dr. Ridker?

DR. RIDKER: Good morning. Paul Ridker. I'm a cardiologist at the Brigham and Women's Hospital in Boston and Harvard Medical School.

DR. YU: Dr. Thadhani?

DR. THADHANI: Good morning. Ravi Thadhani, chief academic officer at Mass General Brigham and nephrologist in Boston. Thank you.

DR. YU: Ms. Chauhan?

DR. CHAUHAN: Good morning. Cynthia Chauhan, patient representative. I have heart

failure with preserved ejection fraction stage 3, renal failure stage 4, and other comorbidities. I live in Wichita, Kansas.

DR. YU: Dr. Emerson?

DR. EMERSON: Scott Emerson, professor emeritus of biostatistics at the University of Washington in Seattle.

DR. YU: Dr. Nissen?

DR. NISSEN: Steve Nissen. I am the chief academic officer of the Heart and Vascular Institute at the Cleveland Clinic.

DR. YU: Dr. O'Connor?

DR. O'CONNOR: Christopher O'Connor. I'm the president of the Inova Heart and Vascular Institute, heart failure cardiologist, and past president the Heart Failure Society of America.

DR. YU: Dr. Rossert?

DR. ROSSERT: Good morning. Jerome Rossert from AstraZeneca.

DR. YU: Thank you, everyone. We'll now introduce the FDA participants.

Dr. Unger?

DR. UNGER: Good morning. I'm Ellis hunger. I'm a cardiologist and director of the Office of Cardiology, Hematology, Endocrinology, and Nephrology in the Office of New Drugs, CDER FDA.

DR. YU: Dr. Stockbridge?

DR. STOCKBRIDGE: Norman Stockbridge, director of the Division of Cardiology and Nephrology.

DR. YU: Dr. Thompson?

DR. THOMPSON: Good morning. Aliza Thompson, deputy director of the Division of Cardiology and Nephrology.

DR. YU: Dr. Southworth?

DR. SOUTHWORTH: Good morning. I'm Mary Ross Southworth. I'm the deputy director for safety in the Division of Cardiology and Nephrology.

DR. YU: And Dr. Liu?

DR. LIU: Hi. Good morning. I am Ququan Liu, a statistical reviewer in the Office of Biostatistics.

DR. YU: Thank you.

Dr. Lewis?

DR. LEWIS: Yes.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from

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

Dr. Joyce Yu will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

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

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is

being provided to participants in today's meeting and to the public.

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

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

of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

For today's agenda, the committee will discuss spironolactone for the proposed indication of heart failure with preserved ejection fraction, a serious and often fatal condition for which no drug is approved to improve outcomes.

The data supporting the new indication are post hoc analyses of the National Heart, Lung, and Blood Institute, NHLBI, sponsored TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist, the TOPCAT trial, which nominally failed to meet its primary endpoint. Spironolactone is currently marketed in the U.S. for the treatment of heart failure with reduced ejection fraction, hypertension, primary hyperaldosteronism, and the management of edema.

This is a particular matters meeting during which specific matters related to spironolactone

will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the drug.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Jerome Rossert is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Rossert's role at this meeting is to represent industry in general and not any particular company. Dr. Rossert is employed by AstraZeneca.

With regard to FDA's guest speakers, the agency has determined that the information to be provided by these speakers is essential. The following interests are being made public to allow the audience to objectively evaluate any

presentation and/or comments made by the speakers.

Dr. Bertram Pitt has acknowledged that he has stock options in KBP Pharmaceuticals, Sarfez Pharmaceuticals, and Relypsa/Vifor. He has also acknowledged being a principal investigator or co-investigator for Bayer, Sarfez Pharmaceuticals, KBP Pharmaceuticals, and Relypsa/Vifor, and a scientific advisor for Bayer, Sarfez Pharmaceuticals, KBP Pharmaceuticals, Relypsa/Vifor, and PhaseBio.

In addition, Dr. Pitt has acknowledged receiving consulting fees from Bayer regarding finerenone; KBP Pharmaceuticals regarding KBP-5074; Sarfez Pharmaceuticals regarding spironolactone; PhaseBio regarding an aldosterone synthase inhibitor; and Relypsa/Vifor. He has also acknowledged that he holds a patent regarding site-specific delivery of eplerenone to the myocardium.

Dr. Martin Rose is the founder and the member of the consulting firm, Rose Regulatory Consulting, LLC, which was established in February

2020. Dr. Rose has advised that his consulting activities have been unrelated to spironolactone and heart failure with preserved ejection fraction in adults. His past and current clients include: 4D Molecular Therapeutics; Altimmune; Asklepion Pharmaceuticals; Avrobio; Incarda Therapeutics; Myocardia; Quark Pharmaceuticals; SC Pharmaceuticals; Stealth Biotherapeutics; Triceda; X4 Pharmaceuticals; and Hyman, Phelps and McNamara PC.

Dr. Marc Pfeffer has acknowledged being a principal investigator or co-investigator on a completed research grant via subcontract to the Brigham and Women's Hospital from the New England Research Institute, which was supported by a contract with the National Heart, Lung, and Blood Institute of the National Institutes of Health.

He has also acknowledged being a consultant to AstraZeneca; Boehringer Ingelheim and Eli Lilly Alliance; Corvidia; DalCor; GlaxoSmithKline; Novartis, Novo Nordisk; Peerbridge; and Sanofi. He has also acknowledged that he owns stock options in

DalCor and Corvidia. In addition, he receives research grant support from Novartis on topics unrelated to today's presentation.

As guest speakers, Drs. Pit. Rose, and Pfeffer will not participate in committee deliberations, nor will they vote.

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

DR. LEWIS: We will proceed with the FDA opening remarks from Dr. Norman Stockbridge, the director of the Division of Cardiology and Nephrology.

Dr. Stockbridge?

FDA Opening Remarks - Norman Stockbridge

DR. STOCKBRIDGE: Yes. Good morning. I want to thank the committee for participating in today's meeting. I also want to express my appreciation to the folks who are presenting the case today.

There is no application. We are considering the TOPCAT study, which was conducted by the NIH, and staff from the NIH and principal investigators Bert Pitt and Marc Pfeffer are here to assess. The assessment was conducted mostly by Jerry Liu and Martin Rose voluntarily and not part of their assigned work. Dr. Rose in particular has continued to work on this since his retirement from FDA a year ago, and my thanks to all of you.

Yesterday we discussed the case for approval in which the study did not formally reject its null hypothesis. The case today is superficially similar in that respect and perhaps with a similar indication. This time, however, the basis for giving consideration to the claim stems from the regional heterogeneity and results.

A few thoughts on this one. We adhere to intention-to-treat principles and count every one randomized, except when we don't. It is not unusual to reject some of the data in a study. Usually it's a site or a few sites at which the conduct was bad, and usually, but not always, the decision to exclude low-quality sites is made before the formal unblinded. And of course, usually it isn't entire continence being called into suspect.

Two, in trials that were overall successful, there is precedent for questioning whether foreign data are applicable to the U.S., that is whether the disease or care elsewhere is similar enough to the U.S. Particularly noteworthy is the case of ticagrelor in which we discounted the aberrant results in the U.S. and approved its use with concomitant therapy similar to that in the rest of the world.

Thus, as discussed yesterday, we sometimes consider persuasive the results from studies that failed to reject the null hypothesis and sometimes

we discount the results in some sites. TOPCAT is thus fundamentally not different from these cases but does stretch the limits I think, and I'll be interested in hearing your discussion today of this matter. Thank you.

DR. LEWIS: We will now proceed with the guest speaker presentations, immediately followed by the presentation from the FDA.

Dr. Rose?

(No response.)

DR. LEWIS: Dr. Rose?

DR. ROSE: Thank you. I was just looking for my mute button.

Guest Speaker Presentation - Martin Rose

DR. ROSE: Good morning, Dr. Lewis, other members of the panel, Dr. Stockbridge, and other participants from FDA. It's my pleasure and an honor to be back at FDA in a virtual sense for the first time since I left a year ago.

I am not seeing my slides on the screen. Okay. Thank you.

DR. YU: Hi, Dr. Rose. This is Joyce. I'm

progressing your slides for you, but just give it a minute. When I click next, you may see a delay.

DR. ROSE: Thank you. Okay.

DR. ROSE: Alright. You've heard about my conflicts. We heard a lot about HFpEF yesterday. Let's skip this slide.

Heart failure animal models have indicated that MRAs like spironolactone can reduce interstitial fibrosis, ventricular remodeling, vascular oxidative stress, and improve endothelial functions. These findings supported the TOPCAT trial. The goal of TOPCAT was to assess the effects of spironolactone on morbidity, mortality, and quality of life.

TOPCAT was sponsored by NHLBI. It was a double-blind, parallel, 2-arm, randomized-controlled trial. It was conducted at 233 centers in 6 countries, the U.S., Canada, Brazil, and Argentina, which we'll call the Americas, and Russia and Georgia, which will be called Eastern Europe.

The study drugs were spironolactone versus

placebo. The spironolactone was a formulation made specifically for the study by URL Mutual Pharmaceuticals, which is no longer in business. It was a 15-milligram tablet, so a lower dose than the smallest tablet that's currently marketed, which is 25 milligrams, and that was done because it was thought that HFpEF patients shouldn't be started at 25 milligrams a day.

The starting dose in the trial was 15 milligrams once a day. There was a forced uptitration to 30 milligrams once daily at week 4 if certain safety parameters were satisfied, and then an optional titration at month 4 to 45 milligrams daily with no further uptitration.

Here's the inclusion criteria. Patients were men or women at least 50 years old with at least 1 of 3 heart failure symptoms at screening -- and they're up on this slide -- and at least 1 of 4 heart failure signs in the last 12 months or at screening, and again, they're up on the slide; and LV ejection fraction at least 45 percent per local reading obtained within

6 months prior to randomization and after any MI or other event that might affect ejection fraction.

There was one additional criteria. Patients needed to have one of these two characteristics. They needed to have an elevated natriuretic peptide level within 60 days before randomization. That could be BNP greater than 100 picograms per mL, or greater than or equal to, or NT-proBNP greater than or equal to 360 picograms mL.

There were no special criteria for subjects with atrial fibrillation, or in the alternative they had to have at least one hospital admission in the last 12 months for which heart failure was a major component of the hospitalization. Transient heart failure in the context of MI did not qualify, and of course some patients had both. These are the exclusions, serum potassium greater than or equal to 5 in the last 2 weeks or 5.5 milliequivalents per liter in the last 6 months; untreated systolic blood pressure greater than 140; and some other that are related to safety.

Randomization was 1 to 1 and was stratified by whether the patient qualified by previous hospitalization or BNP elevation and was balanced by site. If a patient met both the previous hospitalization and BNP elevation criteria, they were lumped into the previous hospitalization stratum.

The primary endpoint was time to the first event of the composite of CV death; hospitalization for the management of heart failure, which we'll call HHF; or aborted cardiac arrest. The final analysis was a log rank analysis with no covariates performed in the intent-to-treat population. Endpoints were adjudicated blindly at the Brigham in Boston. Randomization was stratified by which stratum the patients were in, either the hospitalization stratum or the BNP stratum. It was also balanced across sites.

Actually, I've given all this. Let's go to the next slide. Thank you. There was no evidence that the study was event-driven. There were four planned looks at the data, including three interim

looks. The final p-value after the three interim looks was 0.0498.

These are the results. The study enrolled patients from 2006 through early 2012 and followed them to their first semi-annual visit in 2013. The study ended as planned with no early termination. 3,445 patients were randomized and the mean follow-up was 3.3 years.

This is the CONSORT slide for the trial. Give me one second while I catch up with my notes here. Lost to follow-up and missing vital status data were similar in the treatment arms and acceptable, but not as small as in some recently completed CV outcome trials. Unknown vital status was more than twice as common in Eastern Europe as in the Americas. You can see that down at the lower right.

It is noteworthy that the mean follow-up was 3.7 years in Eastern Europe and 2.9 years in the Americas. That's a function of the extremely rapid enrollment in Eastern Europe. You'll hear more about that later. Because of the longer mean

follow-up time in Eastern Europe, the region had 55 percent of the overall person-years of follow-up for study endpoints despite having only 49 percent of the study subjects.

Here are the subject characteristics at baseline, which were closely balanced in the two treatment arms. Later we'll see these data broken down by region, and there will be some notable differences between the two regions. Here again are disease-related characteristics at baseline, and these, too, were closely balanced in the treatment arms. There's nothing remarkable here.

These are the overall results. The top line is the result for the primary endpoint. You'll see that there was a lean in favor of spironolactone, but the confidence interval crosses 1 and the p was 0.014. The various components of the primary endpoint are shown below. There were trivial numbers of aborted cardiac arrest and we're not going to be talking about that anymore after this slide.

The results leaned, again, in favor of

spironolactone for both CV death and hospitalization for heart failure and were nominally significant for hospitalization for heart failure. Cumulative hospitalization for heart failure was a secondary endpoint. You can see there were lots of those, and there the results were nominally significant for spironolactone with a p-value of 0.03. The other endpoints were very close to equal to the treatment arms.

Let's go to the next slide. These are the regional results. This is the first time you've seen them here. In the Americas, the result for the primary endpoint was nominally significant with a primary endpoint event rate of 10.4 versus 12.6 events per 100 patient-years or percent per year. They're the same.

CV death favored spironolactone and again was nominally statistically significant. Hospitalization leaned in favor of spironolactone and was nominally statistically significant, and cumulative hospitalization for heart failure also was nominally statistically significant for

spironolactone.

The results were very different in Eastern Europe. The event rates were much, much lower. You can see that the primary endpoint event rate was about a fifth of the rate in the Americas and went the wrong way and went in favor of placebo. CV death also went the wrong way. Hospitalization for heart failure went the right way, but all the confidence intervals were wide and crossed 1.

These are data from the placebo arm of published HFpEF trials, and I have up there the placebo arm rates and other characteristics in TOPCAT from the Americas and Eastern Europe. The event rates are the bottom three rows in the chart. You'll see that the other studies, I-Preserve, CHARM-Preserved, and PEP-CHF, had event rates that were more similar to TOPCAT in the Americas. There are some issues in interpreting the data here because the endpoints were not the same across all of the studies and the way the data were presented were not the same across all of the studies.

Hang on while I catch up with my notes.

In CHARM-Preserved, rates of CV death and hospitalization are reported as percent with events over a median of 36 months. So you can't precisely translate that to events per 100 patient-years, but if you divide by 3, that's a rough estimate. In PEP-CHF, the event accrual period was a little over 2 years. So if you divide those numbers by 2, you can approximate events per 100 patient-years.

As you can see, for CV death, you get about 3.8 percent in CHARM-Preserved for CV death, and in PEP-CHF, you get a little over 4 and a half percent. That's much more like TOPCAT from the Americas, which is 4.9 and larger than Eastern Europe 1.6.

For heart failure hospitalization, the number for CHARM-Preserved translates to around 6 and the number for PEP-CHF translates to around 6. Again, that's much closer to 9.7 than it is to 0.95. The results from TOPCAT in the Americas are much more in line with the previous studies than TOPCAT in Eastern Europe, and my screen just went dark.

Can you folks still hear me?

DR. YU: Yes, we can hear you.

DR. ROSE: Okay.

DR. LEWIS: Yes, we can hear you.

DR. ROSE: Okay. Is this a local problem for me?

DR. NISSEN: Just click on your screen, and it'll probably come back.

DR. ROSE: Thank you.

DR. NISSEN: It's your screen saver.

DR. ROSE: Okay. Good. Thank you.

DR. LEWIS: Yes.

DR. ROSE: Excellent. I need to remember to do that. Okay. Let me get back in here. Good. Thank you.

Was that Steve Nissen who made a suggestion?

DR. NISSEN: It was indeed.

DR. ROSE: It was indeed. Thank you, Steve.

DR. NISSEN: It was indeed. Thank you. Yes.

DR. ROSE: Alright. Let me bring that up again. Next slide, please.

These are regional subject characteristics at baseline in the trial. Of course, I'm trying here to explain the regional disparities. This is just TOPCAT that you're seeing. It's the Americas versus Eastern Europe. The mean age in the Americas was 72 versus 66 in Eastern Europe. That age of 72 is more in line with previous heart failure studies -- previous HFpEF studies. The percent of patients with age over 75 is considerably greater in the Americas than in Eastern Europe. Again, advanced age, as you know, is a characteristic of HFpEF.

Down at the bottom, you can see the stratum data for the number of patients in each stratum. The elevated NP stratum was 45 percent of subjects in the Americas and 11 percent of subjects in Eastern Europe. Hospitalization for heart failure was 55 and 89. There were small differences in blood pressure. There were modest differences in eGFR, probably because the patients were older in the Americas. There was a marked difference in history of coronary disease, 45 percent of The

Americans versus 72 percent. There was a lot more atrial fibrillation in the Americas than in Eastern Europe, more diabetes -- these of course are characteristics of patients with HFpEF -- and more renal disease.

There was a history of myocardial infarction in 32 versus 20 percent. I mentioned Eastern Europe first. There was a very large disparity in the percentage of patients with angina between the Americas and Eastern Europe. Diuretic use was higher in the Americas. Aspirin use was much higher in Eastern Europe. Down near the bottom, statin use was higher is in the Americas, but the significance of that is unclear.

These slides, this is a series of slides that looked at the pharmacodynamic effects of spironolactone, which include hyperkalemia, or at least increases in serum potassium, and increases in creatinine and decreases in blood pressure. These slides are shown to approximate or give a hint as to whether people were taking their study drug.

As you can see, in the Americas, which are in red, there was a fairly prompt increase in serum K in the spironolactone arm but not in the placebo arm. In Eastern Europe, which is in blue, the increase was blunted. They started at a higher baseline over there possibly because they weren't taking much diuretics in the Americas, but the difference between drug and placebo is much lower than in the Americas.

This is regional serum creatinine over time, and you see the same pattern. The Americas start out with higher levels of serum creatinine probably because they tended to be a bit older, and as you can see, creatinine goes up about a tenth of a milligram per liter, and in Russia and Georgia, there's a miniscule change.

The next slide is blood pressure versus time, and again you would expect blood pressure to go down in the spironolactone arm. And that's exactly what you see in the Americas in red; changes from baseline in the spironolactone arm and in the placebo arm are similar in Russia and

Georgia

In these slides, those data suggest that patients in Eastern Europe may not have been taking their study drug, and it looks like that was fairly widespread to produce those kinds of numbers on those pharmacodynamic characteristics. This is a table showing pretty much the same data, looking at it a different way. These are time to events and are odds ratios for various events.

So the data for the Americas are at the top half of the slide and the data for Eastern Europe are at the bottom of the slide. So a doubling of baseline serum creatinine at some point during the trial occurred at a rate of 6.8 percent per year in the spironolactone arm versus 4.2 percent per year for placebo with a hazard ratio of 1.6, which was statistically significant.

Again, down below you can see serum creatinine at 3.0 milligrams per dL at any time, not so dramatic, and serum potassium greater than 5.5. Now this is at any time, 25 percent versus 8.9 percent with an odds ratio of 3.46, which was

highly significant, and serum K less than 3.5, which you would expect to see less often in treatment patients. That too was statistically significant between drug and placebo in the Americas. The next line is serum canrenone, less than the lower level of detection.

There was a repository study. A small percentage of subjects had frozen serum. What you're seeing are the results of the serum canrenone analysis in subjects who said they were diligent in taking their study drug. This was only a small subset of subjects. Serum canrenone is a metabolite of spironolactone. It's very long-lived. It should be detectable in the serum of a patient for several days after their last dose of study drug, so it's somewhat insensitive to timing of the blood draw. All these patients said they were taking their drug on a daily basis. In the U.S., 2 out 76, or 3 percent, had undetectable levels of canrenone.

If you go down to Eastern Europe, you'll see that all of the hazard ratios for the various

pharmacodynamic effects have confidence intervals that cross 1. There was no difference between drug and placebo for any of these. Serum canrenone, 20 out of 66 subjects, or 30 percent, had undetectable levels of serum canrenone and, again, these are people who said they were regularly taking their study drug. So these data reinforce the previous data you saw, suggesting that there was a much higher rate of non-compliance with study drug in patients in Eastern Europe.

These are more or less the same data. Let's skip this slide and this slide. Those pharmacodynamics and pharmacokinetic data were observed despite the fact that people in Eastern Europe were taking nominally higher doses of spironolactone than subjects in the Americas. These are the data for mean daily dose in milligrams at months 4, 8, and 12. You'll notice over time that the mean daily dose falls in each column here and that the placebo dose at any particular month is always a little higher than the spironolactone dose.

That's easy to understand. The dose, regardless of which row you're looking at, is higher for placebo than for spironolactone and higher in Eastern Europe than in the Americas. So despite having higher nominally doses, especially at month 18, they had lower rates of showing the spironolactone pharmacodynamic effects.

To summarize the effectiveness here, the overall results in TOPCAT for the primary endpoint, the composite of CV death, heart failure hospitalization, or aborted cardiac arrest favors spironolactone over placebo but did not meet statistical significance in the primary endpoint analysis, however, 49 percent of subjects were enrolled at sites in Russia and Georgia.

The trial data indicate that results from this large subgroup of patients, and hence the study as a whole, would not be predictive of the results of treatment with spironolactone in the intended U.S. patient population because, at baseline, subjects from the Americas were older and more likely to have had the common risk factors and

complications associated with HFpEF than those from Eastern Europe, and the former were also much more likely to have been enrolled in the study on the basis of elevated natriuretic peptides.

There was something I didn't tell you. At an earlier point in the study, the DSMB became concerned about the very low rate of events in Eastern Europe. They had a meeting with NIH leadership about two years into the study, which resulted in a look at some of the hospital records for the qualifying hospitalization in Eastern Europe, specifically in Russia, by a Russian-speaking physician at NIH. He or she looked at 22 of those records, and in either 18 or 19 of them, it looked like the subjects were in the hospital for coronary disease or for something related to coronary disease rather than heart failure.

So that's what this is referring to. Anecdotal evidence from hospital records suggest that some prior hospitalizations that supported enrollment of Russian patients were for ischemic

heart disease, not heart failure. Baseline medical history and medication information that you saw indicate that there was a higher rate of ischemic heart disease in Eastern Europe than in the Americas.

Subjects from Eastern Europe had notably lower rates of CV death and hospitalization for heart failure during the study compared to subjects in earlier heart failure HFpEF, but subjects from the Americas had rates of these events that were in line with the earlier trials. These points strongly suggest that some or perhaps many patients in Eastern Europe did not have the same disease as patients in the Americas or in earlier heart failure trials.

Pharmacodynamic data from the study and limited PK information regarding canrenone from the repository study indicates that the rate of non-compliance with study medication was likely to have been substantially higher in Eastern Europe than in the Americas. Accordingly, the data from Eastern Europe are less likely to be predictive of

the true effects of spironolactone in U.S. patients with HFpEF than the data from the Americas.

Thus, only the data from the Americas can be reasonably extrapolated to U.S. patients with HFpEF, and these are the only data from the study that should be considered relevant to our evaluation of effectiveness and perhaps some aspects of safety.

And again, I'm arguing that based on the characteristics of the data, not on the address of the study sites. I'm not suggesting that data from Eastern Europe can never inform decisions about whether drugs ought to be approved for use in the United States. I'm saying that these data are not predictive of the true effects of spironolactone in U.S. patients. By these data, I mean of course the data from Eastern Europe.

The data from the U.S., from the Americas, indicates that spironolactone was superior to placebo for the primary composite endpoint and had beneficial effects on both time to the first heart failure hospitalization and CV death, unlike the

data you saw yesterday where there was no notable effect on CV death. Spironolactone also reduced the rate of cumulative heart failure hospitalization, including second and subsequent hospitalizations during study period.

Moving on to safety and risk-benefit, I'm not going to show you the safety data from TOPCAT because they provided no new signals of harm for spironolactone, a drug that's been on the market in the U.S. since 1960 and already studied for HFrEF. The safety information from the RALES study in HFrEF are already in labeling.

Given the important nature of the benefits of spironolactone in patients with HFpEF, the benefits of spironolactone outweigh its risks. I favor approval of a modified indication for spironolactone that includes the treatment of patients with HFpEF to prevent CV death and hospitalization for heart failure.

I need to thank a number of people. I'm not going to read all of these off, but they're from FDA and two are from NHLBI. Robin Boineau has

moved along to another part of NIH since then, and I'd like to thank the TOPCAT investigators, Bertram Pitt, Marc Pfeffer, and Brian Claggett, who were very helpful in my preparation of this presentation.

In particular, I'd like to thank, from FDA though, Norman Stockbridge and Mary Ross Southworth. Norman was always very supportive of this effort, which has gone on for over a year I think, and Mary Ross likewise was extremely supportive, and others at FDA are listed there as well.

There are two names I left off here. One is Alexis Childers, our project leader, or "the" project leader at FDA. Sometimes I still say "our" or "we" when I refer to FDA. Forgive me. I haven't been gone that long; and also Joyce Yu, from the advisory committee staff who was terrifically helpful in the logistics of making this presentation. Thank you, Joyce.

I think that's my last slide.

DR. LEWIS: Thank you, Dr. Rose.

Dr. Pitt?

Guest Speaker Presentation - Bertram Pitt

DR. PITT: Yes. Thank you.

Can I have my first slide? Yes, these are my conflicts, which you've already heard. Let me move on to the next slide.

Before I go further, I would really like, on behalf of the TOPCAT investigators, to express our appreciation to the committee and the FDA for allowing us this opportunity, and especially to Dr. Rose, who you just heard, who presented all of the details and insights into the results.

Now, these are the primary results that you've already heard of the overall TOPCAT, and when we saw this, we were obviously quite disappointed because we had, from prior knowledge in HFrEF as well as the pilot studies in HFpEF, and since then meta-analysis of spironolactone HFpEF, the clues that spironolactone was effective in reducing cardiovascular death and heart failure hospitalizations. I'm going to be relatively brief because Dr. Rose has done such an extensive job in

presenting the overall data, but I'd like to make a few points.

This is just heart failure hospitalizations that showed a significant overall benefit in the trial. So despite all the difficulties that you heard about from the regional difficulties, there was a significant overall result for hospitalizations.

Now, Dr. Rose mentioned that we stratified patients on natriuretic and heart failure, and when you look at the strata that was prespecified, where there are objective criteria for heart failure, you can see there was a highly significant reduction in the overall endpoint with a hazard ratio of 0.65, a 35 percent reduction of events with a highly significant p-value.

Now, the numbers are small, but nevertheless this is the one objective criteria that we would believe really signifies heart failure, but when we look at heart failure hospitalization, there is no really trend. The explanation from that, and I think you can infer from some of the things that

Dr. Rose said, is differences related to regional differences.

Now, we didn't understand this during the trial, but subsequent to the trial, we've gotten some further insight. It turns out that the centers that were recruited in Russia and Georgia for this trial, for the most part, were primary care centers that didn't have experience in heart failure. There were some, and there are some excellent investigators I must say, but the majority were groups that were involved in hypertension, coronary artery disease, and had not had prior experience with doing trials in heart failure.

There were other things that we learned subsequently. Many physicians in Russia and Georgia earned their salaries, in part, by getting involved in trials, so there's a certain incentive to join the trials. And patients have an incentive to join the trials because that is one of the ways that they can get good care. So there is an incentive both for the physician to get people into

trials and for patients to join trials.

And as you've heard in Russia and Georgia, there were these marked discrepancies in baseline characteristics that Marc Pfeffer is going to talk about further, but we think that many of these people did not have heart failure, and that is why when we use heart failure hospitalizations in that strata, we don't see anything, but when we use objective criteria, we clearly do. So it is, at least with the objective data, a very strong signal that this drug is effective.

Now, several times during the course of the trial, Marc and I asked the DSMB if there were any major differences between regions, and we unfortunately never got the information to make a course correction because if we had known what you saw a few moments ago, we would have early on in the trial been able to make a course correction, but we didn't learn this until too late, and we couldn't make any course corrections.

So the data from Russia and Georgia, although there was some very good sites and good

investigators, overall I think does not reflect HFpEF and does not reflect the effect of spironolactone in HFpEF. So I'm going to turn it over to Marc, who is going to amplify further and give you further details and understanding of what we believe is really happening.

Marc?

Guest Speaker Presentation - Marc Pfeffer

DR. PFEFFER: Well, thank you, Bert, and if I could have my slides.

I know you've spent two days on this topic. I'm going to try not to be too redundant, but I do have to paint a picture of how the whole thing emerged, how heart failure with preserved emerged, and then what you just heard from Dr. Rose, that didn't just happen overnight, and it took a little bit of digesting.

So I am here as an individual, as is Dr. Rosen and as is Dr. Pitt. Now, I have to say that Dr. Pitt and I have worked together on this since before the trial started. Dr. Rose I just met through my ranting and raving about how the FDA

should take a role in this. I couldn't understand how a government-sponsored study doesn't get a government-sponsored review, and of course it was just my misunderstanding of the whole system. But now I have to thank Dr. Rose for really taking its part.

Why do we even care about an FDA indication? Well, we do care because we think we have a therapy that will help human beings. Obviously, the FDA doesn't write prescriptions, but those initials, F-D-A, mean integrity, and it would have a force if they believe. And that's what this session is. I honestly didn't know if the FDA would look at our data and say, well, the Americas aren't that great either, so we're open to that, and we're very pleased to have the opportunity to have our data voted.

On behalf of the three individuals, I want to thank the FDA and I want to thank everybody involved. I also want to thank -- before I even start -- the NIH. It's only the NIH that could take on this question of a drug that's selling for

pennies as an approval of 60 years ago, and it was a contract to NERI, New England Research Institute. So I'm very pleased to be here.

You heard my conflicts. Well, I have an intellectual conflict, which is probably stronger than any potential financial one. I of course believe that what we found did change the practice of medicine. Now, I can't rant and rave anymore. Let's look at some data. Let's go on.

This thing called heart failure with preserved, it didn't have that name, and actually in the good old days, the syndrome was congestive heart failure. You didn't need an ejection fraction. It was just congestive heart failure. In the mid-1980s, a very prominent nuclear medicine lab said, "Why are all these doctors sending us patients with a diagnosis of heart failure to measure ejection fraction? We find about a third of them don't have reduced ejection fraction. They have basically normal, intact." One said normal; one said intact. And it wasn't that the syndrome wasn't there, it's in the mid-80s we're first

recognizing it.

Let me put that in the context. We only started seeing treatment of this congestive heart failure being associated with improved prognosis in the late 1980s. And let's give credit to Dr. Cohn and the CONSENSUS for V-HeFT, and the Veterans Administration, and the CONSENSUS investigators, Dr. Swedberg, his team. But it was only then, and they didn't use ejection fraction. That was plain old congestive heart failure.

I have SAVE and SOLVD there because we were both at the FDA the same day. That's the beginning of using ejection fraction. SOLVD said I want to look at people who are symptomatic/ asymptomatic, and you heard from Dr. Stockbridge that the asymptomatic arm, which didn't have a survival benefit, did get approval. And I'm putting SAVE up because we put a number, an EF of 40, to treat people with that to prevent heart failure.

Now, when those two got their indication, physicians then had to look for ejection fraction to say, "Okay, I should be using an ACE inhibitor

of people below 40." So it's a very operational number. It's like blood pressure. We treat certain blood pressures because we have data that says treating this level of blood pressure is beneficial for people. So it's a number that moves around, and in the 1980s and '90s, it was 40. Okay. That served us well, but all the studies were looking at all-cause mortality. I know those words aren't used anymore: mortality, survival.

Then in this CHARM, which is down at the bottom, now we're starting to go into preserved. I was part of CHARM. We were at the FDA. There was no discussion of CHARM-Preserved because we didn't hit the magic 0.05; we were 0.05 something. In those days, you were studying mortality. CHARM was a transition. It was one of the first programs where it said, yes, we'll study all-cause mortality, but for the components we're going to look at the composite of CV death and hospitalization for heart failure.

The field had advanced to say we don't only have to change alive or dead, and it introduced the

term "preserved." It was the best definition we had at the time and it was an operational definition. That's how we found the people. The diastolic mafia wanted us to call it "diastolic heart failure," but we didn't have a way to identify patients by diastolic heart failure.

So that's the beginning, and now further efforts. You heard one yesterday, and we'll tell you about TOPCAT today.

Well, the lessons from CHARM really carried over. The number one lesson was that people with the higher ejection fraction didn't die as frequently as people with the lower. The event rates are still much higher than the general population and they're much higher than hypertension and diabetes, but compared to lower EF, the death rates were different.

We also learned very important lessons. These patients are all studied at the same sites and same time. The lesson was quality of life as reduced. We did an important study of quality of life led by Eldrin Lewis that said, "Ejection

fraction does not determine your quality of life." So we had this large population, and you've heard a lot about that. They do have higher event rates than the normal population, than good old hypertension risk factors, and they do have morbidity/mortality.

Okay. Anytime you go to a medical brand round -- this is a slide that gets a lot of laughs -- no treatment, convincing data, a lot of theories. It's ha-ha and let's move on. It's not ha-ha for the people who have this disorder, but we do need to find more robust data. That's for sure.

I'm going to take you back through history, and we're going to walk through this together. I think it's important because in 2013 when we opened our books for the results of TOPCAT, we are a committee, we're a large group, and presenting the results and representing the group, you have to have consensus. And in 2013, even internally, between the investigators at the National Heart, Lung Institute, NERI, the Brigham and Women's, and Dr. Pitt, we didn't have a clear consensus. I was

going one way, but I'm representing the whole group.

So here's what we said in 2013, representing all parties as we first learned about our data. I'm going to go through this very quickly, and I'm going to try not to have the redundancies that we had. You've heard this. You've seen it if you're an investigator, "Okay. Oh. Yes, it's probably something here, but that's it." We didn't make our primary. I know the rules. I've sat on your side of the table, too, and I certainly have my integrity. How far can I push this? There it is.

Okay. Let's look at the components. You're allowed to do that. Let's look at the components, and we said didn't make it on the primary. Really, you have to take the rest as exploratory. How am I going to divide that p of 0.05? How many ways can I divide it? But let's take a look and, yes, hospitalizations for failure had a nominal value but of course the primary was not significant, and the hierarchy wouldn't allow us to go down there.

We had the CHARM experience, and I think

this is one of the first where we're saying let's look at subsequent hospitalizations. And when we did that, the difference was more apparent but, again, this is not prespecified. This is in our primary analysis but there's something going on here to help patients, but you can't really be definitive.

So here's the conclusion in 2013, and I think it was the right conclusion. We did not alter the primary. We did observe reductions in hospitalization. And this last point I want to bring up very carefully because I think Dr. Pitt and I have been very clear about this. If you choose to use this therapy, you must monitor serum potassium and creatinine. If I understate that as we move forward, I shouldn't. We're very clear that this drug requires monitoring. So if you want to use this based on the information I have, you have to be careful.

Now, I'm saying it that way because it's in the absence of any other data, more definitive data. So in 2013, I made this statement

representing the whole group because we felt this is the best we have available. I got to present. Dr. Pitt was the first author on the paper. We knew this regional problem right then and there. We couldn't put it in the paper, but we did put it in the appendix.

So I'm showing you our appendix and your briefing book, table 7, which I'd like to go over this for a second. This is the prespecified adjusted model, and you can see we take the 0.13/0.14 down to 0.06.

Now, with the next slide I'm going to go one step further, which is not prespecified because we didn't know we were going to see this regional thing, and I just want to show you the magnitude. This is your briefing book. It is in our first publication in the appendix. I'm delighted that every number I showed to the decimal point, it's the same as the FDA briefing book, and I thank Brian Claggett for that. But if you add that one adjustment, just add the adjustment, then all the results, we now have a significant reduction in the

primary.

But let's look at how big that region is. That's a four-fold difference. But I make a point for those of you who are the purists. I'm only asking you to go one step. Take the whole population, make that adjustment, and you still have a significant reduction in the primary outcome.

Let's go to the next step. So now one year later, in one year, more of the group is convinced. It takes a while. And I'm showing the authors here on purpose because now signing on with this with Dr. Pitt and myself are every country leader and the leaders of NERI and the National Heart, Lung, and Blood Institute. NERI was most resistant to this because it was the trough, but now by one year later, everybody's on.

I'm going to show you now the data, most of which you've seen but giving you my twist. Thank you. This was what I learned day one, and this slide has nothing to do with spironolactone. Let me say that again. There's no spironolactone on

this slide. This is just asking placebo patients.

And by the way, I don't use the word "Eastern Europe" because I don't want to put other countries that weren't even involved. I'm very specific, Russia and Georgia, and I'd like to be more specific, and here are the sites in Russia and Georgia because it's not even all of Russia and Georgia. But from now on I'm going to use Russia/Georgia. And by the way, when we started the trial, Russia and Georgia were one country. There was a war that happened in the middle of this trial.

In what we call the Americas, you see this event rate and you see the multifold difference. If you take any trial and divide it by countries, somebody's at the high end, somebody's at the low end, 10-15 percent, 20 percent; you will not have 3-, 4-fold differences. There's something wrong.

I want to use this slide for another second here to say why we only had six countries, and this is a very important part. I have friends. You heard many of my friends yesterday. I have

international friends. Dr. Pitt has International friends. They were willing to work with us for a low-cost generic. They weren't going to be paid a lot. We could not get our Western European colleagues and our Scandinavian friends in because the drug is generic, and there was no sponsor to accept it at the other side of the border. So I just throw that in as an aside.

Could I have the next slide? Okay. The difference in the primary, the p-value here is stopped at 1 in a thousand. We could go further. It's every outcome we looked at, and it's not 10-20 percent. It's going to be 3-, 4-, 5-fold differences. This is now in both groups irrespective of treatment.

Let me go to the next slide. I want to show you something here. When I look at a trial, I asked myself, how sick are the patients? Well, just go to the mortality. I don't need adjudicated responses; just who lives, who dies. Well, in the four countries we call the Americas, the death, the 95 percent confidence interval from every single

one overlapped. In Russia and Georgia, 95 percent confidence interval of the deaths don't overlap with any of the countries in the Americas. So they were totally different.

I'll even point out here the Georgia population was even lower than Russia and no overlap in their 95 percent confidence interval. So I'm not giving you any statistics here, but I'm just showing you how different mortality was and of course the primary endpoint.

You heard Dr. Rose. This is adjusting for follow-up, and I'm showing you very prominent trials in hypertension/diabetes all had 30,000 people with hypertension plus other risk factors. If you ask about hospitalization for heart failure, well, it's about 1 percent a year after. If you take a population selected for heart failure, it's multifold higher, except Russia and Georgia. They were just like good ole hypertension/diabetes risk factors. I'll point out HYVET. That is people over 80 with a systolic blood pressure over 160. Yes, they're a sick population, but heart failure,

if you have the diagnosis of heart failure, you have multifold chances of coming back with that diagnosis again.

I'm not going to do what Dr. Rose did. He did it so well. All I'm going to say is the reason we have 38 variables, I just picked what we showed in table 1 in the New England Journal and said, "Okay. Now let's look at it this way," and 34 of 38 are different. 34 of 38 were different; some are the same. Ridiculous how different they were.

You heard about the follow-up. The follow-up was longer because they randomized so fast. They were paid per; randomized that fast. I was beating up on all of my friends, "How come you're not -- Marc, don't you understand with your inclusion/exclusion, if somebody has hypertension and not treated, we have to take them out? If somebody has renal function, we have to take them out? It's not as easy as you think." But despite that, we still did get a large number.

Now, another point. If you randomize someone to placebo or active therapy and you're

uptitrating blinded, don't be surprised if you get to a higher dose level with placebo, which is exactly what happened in the Americas and didn't happen in Russia and Georgia.

Okay. I told you prognosis. Dr. Rose told you prognosis. I told you patient population. He showed you pharmacologic responses of spironolactone. I kept asking Dr. Pitt, "Bert, do you need to have heart failure to have these? Even if you have hypertension, won't you get the changes?" "Sure, you'll see the pharmacology of spironolactone in any human being." So let's take a look.

There's only a couple I want to do here in a little more detail. Hyperkalemia, well, you randomize someone to spironolactone, 3-fold more people will have a serum potassium greater than 5.5 over the course of time. It does require monitoring. You have to watch. In Russia and Georgia, we didn't see that at all. Dr. Pitt kept telling me, "Marc, one of the advantages is we'll have less people having hypokalemia." He's right.

You have half the chance of having hypokalemia; not so on Russia and Georgia. So this is the whole population.

Now, I'm going to ask you to remember this number. I'm looking at a different slide. I'm sorry. Thank you. You know what? I apologize. I've been looking at the different slide. This is the 3-fold more hyperkalemia and the half hypo, and I'm going to ask you to remember the 0.3 overall change, and I apologize.

Can I have the next slide, please? It's not the first talk I've given, but it's probably one of the most important ones. Doubling of creatinine. Now, I actually didn't know that spironolactone had that much of an impact, but here it is, large numbers of people, a 60 percent higher chance of us showing a doubling of your creatinine if we monitor you.

Now, that was a concern, and our DSMB, who I thank very much, said, "Boy. You better make sure no one has an increase over 3, and you better cut back on the dose, and you better monitor after

every dose," and we did. And because of that, we can say we didn't hurt people's kidney function more than placebo. And that's another important safety feature, use this drug; you must monitor. We had no greater increase in numbers of people going on to dialysis than placebo; no action, Russia/Georgia

I bring this up. This is the way we presented it. The only difference here in the presentation at the American Heart is I added a little bracket after the interaction, and I'm telling you where it is on your page 25 26 because people are making a note out of that non-significant interaction, so let me explain that.

If you look at the confidence interval in Russia and Georgia about the drug effect for the events, it's from 0.7 something to 1.5 something, so wide that I can't show you an interaction looking at the confidence interval versus the Americas. The absence of an interaction doesn't mean there's not an interaction. If you want an

interaction, we have less than 0.01 for every pharmacologic action of spironolactone, less than 0.001, and we probably could have had more decimal places but Brian wouldn't let me. But the absence of this interaction doesn't mean that the drug didn't behave differently. I think Dr. Rose showed you and I showed you how differently the drug did behave.

Here are the outcomes. The primary is now in the Americas. The confidence interval, upper limit less than 0.99; CV mortality less than; and everything less than with a lot of events for total hospitalization less than. So I'm showing you that, and that's your table, and this is what I want you, if you agree with me, to focus on.

Differences in patients, prognosis, response, and this is the conclusion of the second presentation, now the second time at the American Heart. Now I am saying randomization of spironolactone reduced CV deaths and hospitalizations in patients, so I'm emboldened now. I'm going further. I'm going beyond the

data, but it says "post hoc analysis by region," not enough to convince many people but certainly something to share with the world.

So now we're in 2017, '16 actually. My good friend, Dr. Jean Rouleau, who was with us from the very beginning, and not for any money -- "Marc, if you want to do this, we'll do it. We'll get the Canadian sites" -- he was kind enough to run a repository in addition to all those other things, and the Montreal Heart had the blood. We didn't have a lot. We had 206 something from the U.S. and no samples from Georgia, Argentina, and Brazil.

So I said, "Jean, it's time we should do something. Do you want to measure troponin? Do you want to look for --" he said, "Marc, what are you talking about? We are going to measure canrenone." So I thank him for that, and let me show you what he showed you. You heard a little this, but let me do it my way.

One of his young investigators did all this work, Simon de Denus. The first thing, we're only talking about people whose case report forms said

they're taking the drug, and let's look at the dose response; those who told us in the Americas they're taking 15, and here's their level; those who said they're taking 45 higher; and those 30 in between. Do the same thing with the few samples we had from Russia, and we're only talking about those they told us were taking the drug and those they told us were taking 45-30, and there's no dose-response.

The next is even more telling, and you heard this. This is with zero detection in people that the case report form said they're taking it. And our confidence interval at the lower limit is very sensitive, so if you have it in your blood, we're going to detect it. And yes, there are 3 percent of the patients in the U.S. and Canada who said they're taking it and we can't detect it, 10-fold more, from the good sites in Russia that are sending us the samples.

Here's one that you didn't see. If canrenone was measured in your blood, if it was in your blood, we then went back and said was the potassium changed from baseline? Now, I don't care

what country you come from. If canrenone's in your blood, there's a 0.3 rise in your serum potassium. If canrenone is not in your blood, we don't see that.

So that 0.3 I ask you to remember. That's what we got in all of the Americas. This is a sample of some of the blood from some of the sites, but in all the Americas we got 0.3. In RALES we got 0.3, and in the human beings, where we know you had canrenone in your blood, have a 0.3.

I'm coming towards the end, but I want to say now the next step. I think the blood levels let us say we have false reporting. That's hard to say. That's harsh. I could be even harsher, but I think now I can say false reporting; no trials without flaws. I have all the experiences of I wish we did this.

What I'm not talking about here is a flaw. I'm talking about serious misconduct. So really we're talking about a cancer, a cancer that has clear margins. The margins are Russia/Georgia that warrant censoring their data. Then you have the

question, is he right? Can we censor? What are we left with if we censor Russia and Georgia? Well, we're left with human beings who have the syndrome and who, for the most part, took the drug.

So now I'm in emboldened. I'm emboldened. I'm not even showing Russia and Georgia, and I'm going to be talking about the patients from the Americas. Do we have enough information? Well, we have 522 people that had at least one adjudicated event. Let's take a look at that. Okay. Here's what we've presented.

We said if we just look at the Americas, we have what I believe is a reduction in the primary and what I believe was due to both components, CV death and hospitalization for heart failure, and I'm going to do something I've never done, p-values on that. I've always said it's a post hoc, but here, the p-values, adding that. The FDA's review of this would embolden me to do that.

Why is that important? Well, we're individuals. We are sickened and saddened that the unscrupulous behavior of some people that we can

identify is not allowing more broader use of a morbidity/mortality-saving generic therapy for a large segment of people with heart failure. It's sad, but let me go to the next slide.

Here is something from your former commissioner and my friend, a highly respected colleague, and I think it's a very important point for all clinical trialists. We the clinical trialists don't drive what happens. We give you the data, and it's for Dr. O'Connor to figure out do I have enough here; what were the warts; and societies; and the regulators; and payers. If we had the FDA, if you agree and you say, "Yeah, I think there's something here for human beings," that's how you improve public health.

So Dr. Pitt and I standing on our platform yelling to do this doesn't have the same clout as those three initials, F-D-A and the integrity of the FDA. That's what you're going to ask, "Are you going to put your stamp on this?" If you do, that will be translated into improved use and improved public health. So that's why we're here today, to

ask you whether you consider what we just said a reasonable thing.

I ended up in 2014 by thanking the committees and I thanked all the national leaders. I'm going to end up in 2020 on my next slide, and my last slide, by adding to that, thanking the FDA for this independent review. And I also took out, in red, the Russian/Georgia national leaders. I note I don't thank them, and I really don't. And I think we're saddened that human beings were not helped because of what happened there. But if we can now make amends and do that, I think we'll be promoting public health.

So thank you, FDA; thank you, Julia and your committee; and much appreciated. That will be my last slide.

DR. LEWIS: Thank you, Dr. Pfeffer.

We will now proceed with the presentation.

Dr. Liu?

DR. LIU: Can you hear me? Hello?

DR. LEWIS: Yes, we can. We can hear you.

DR. LIU: Alright. Thanks.

FDA Presentation - Ququan Liu

DR. LIU: Good morning, everyone. My name is Ququan Liu, and today I will make a short presentation to share our interpretation of the study from a statistical perspective. The details of the study were described in the earlier presentation. My presentation will focus on discussion of statistical issues in the study.

First, I would like to acknowledge the FDA review team. Here are the issues we see in the trial. The TOPCAT trial did not meet its prespecified success criterion for the primary endpoint. The subgroup analyses favored spironolactone over placebo in the Americas. Notable heterogenous treatment effect was observed in subgroups of randomization stratum, regions, baseline ejection fraction, and body mass index.

There are major differences in the baseline demographic and disease-related characteristics in two regions. There were also major differences in the primary event rates and cumulative heart failure hospitalization event rate in two regions.

These observations led to the discussion on whether the Americas result in TOPCAT can support a claim on spironolactone for heart failure with preserved ejection fraction. While there may have a clinically plausible explanation for the regional disparity, there are reasons to be skeptical. I will discuss them in my presentation.

There was no precedent of excluding a whole region with half of the study population. If spironolactone is approved for this indication, this might set a precedent on what is considered substantial evidence for approval. We would like to seek the committee members' input on whether TOPCAT can support the approval of spironolactone in treatment for heart failure with preserved ejection fraction.

Here is a brief recap of the study. The TOPCAT trial was to evaluate the efficacy of spironolactone in patients with heart failure with a preserved left ventricular ejection fraction. Study participants were recruited at 233 sites in 6 countries. According to the study protocol, 3,515

subjects were to provide 80 percent power to detect a 20 percent relative reduction, assuming the 3-year event rate of 17.4 percent in the placebo group. The trial randomized 3,445 of subjects and 671 of them had confirmed primary events. The primary efficacy endpoint is a composite endpoint of CV death, aborted cardiac arrest, or hospitalization for heart failure adjudicated by the clinical committee.

This is the main result of the primary efficacy analysis. 1722 subjects received spironolactone and 1723 subjects received placebo. 320 subjects in the spironolactone group and 351 subjects in placebo had primary events. The hazard ratio is 0.89 with a 95 percent confidence interval of 0.77 to 1.04. The p-value from a log rank test is 0.14.

According to the final version of the protocol, there were 19 prespecified subgroup analyses. The figure here shows the results of this subgroup analysis. The forest plot is difficult to read, and we will take a closer look

at the four separate groups with a notable difference on treatment effect in the next slide.

Among 19 prespecified subanalyses, notable differences on treatment effect was observed in four subgroups. They are randomization stratum, region, ejection fraction, and body mass index. Patients enrolled based on elevated BNP; patients with lower ejection fraction; patients with higher body mass index; and patients in the Americas seemed to benefit from the treatment. Patients enrolled based on prior hospitalization for heart failure; patients with higher ejection fraction; patients with low body mass index; and patients in Eastern Europe seemed to show no benefit from the treatment.

The p-value for interaction in the randomization stratum group is 0.01. The p-value for the other three interactions ranged from 0.08 to 0.12. Out of 19 prespecified subgroup analyses, three of the subgroups showed at least the same level of disparity as the region. The subgroup analyses were not adjusted for multiplicity.

This slide shows the subgroup analysis by region and randomization stratum. The top table is the subgroup analysis of the region. Treatment benefit of spironolactone was only shown in the Americas with a hazard ratio of 0.82 and a 95 percent confidence interval of 0.69 to 0.98. However, the treatment benefit was not shown in Eastern Europe with a hazard ratio of 1.1 and the 95 percent confidence interval of 0.79. to 1.51.

The bottom table shows the subgroup analyses of randomization stratum, which was discussed in many published papers. Patients were stratified at randomization by whether they qualified with a history of heart failure hospitalization or BNP elevation. This randomization stratum has a significant interaction with treatment. The p-value is 0.01. Spironolactone showed no treatment benefit in the subgroup of patients qualified with a history of heart failure hospitalization. The hazard ratio is 1.01 with a 95 percent confidence interval of 0.84 to 1.21. Patients qualified by BNP elevation were mostly in

the Americas and seemed to benefit from spironolactone. The hazard ratio is 0.65 with a 95 percent confidence interval of 0.49 to 0.87.

This slide shows the patient enrollment by randomization stratum by hospitalization for heart failure or BNP elevation. From the plot on the left side, you see that, overall, 72 percent of patients were qualified for the study by a history of hospitalization for heart failure. Less than 30 percent of patients were enrolled based on elevated BNP.

Within the Americas, approximately half of patients were enrolled based on the history of heart failure hospitalization and half of patients based on elevated BNP level. Within Eastern Europe, the majority of patients were enrolled based on a history of hospitalization for heart failure at approximately 89 percent.

The plot on the right shows that among patients qualified by a history of hospitalization for heart failure, 60 percent of patients were in Eastern Europe. Among patients that qualified by

BNP elevation, 81 percent of patients were in the Americas and only 90 percent of patients were in Eastern Europe.

This slide shows the subgroup analysis of a primary endpoint by randomization stratum in region. The first two rows in the table shows the treatment effect by randomization stratum in the overall population; the middle two rows are treatment effect by randomization stratum in the Americas population; and the last two rows are the treatment effect by randomization stratum in the Eastern Europe population.

There is a lack of treatment effect in patients qualified by history of hospitalization for heart failure. That is shown in the overall population and in both regions indicated by the red font in the table. The rate of primary events in the placebo group were very different between two regions. The primary event rate in the Americas is much higher than the rate in Eastern Europe, 36 percent in the Americas and only 8.7 percent in Eastern Europe.

This is one of the reasons that undercuts the applicability of the data from Eastern Europe. However, if we look at the patients enrolled by prior hospitalizations for heart failure in the Americas, they show no benefit from the treatment even though these patients in the Americas had a much higher event rate than those in Eastern Europe, and they had very different baseline characteristics. This seems contradictory to the hypothesis that Americans and Eastern Europeans are different populations and therefore led to different outcomes. The treatment benefit in the Americas was [indiscernible] by patients enrolled based on elevated BNP.

Region of Americas consists of four countries from two continents and seemed to have a heterogeneous population within the region itself. This table shows the populations by continent. North America includes the USA and Canada. South America includes Argentina and Brazil. Eastern Europe includes Georgia and Russia. The primary event rate in the second column in the table is the

percentage of events and the third column is the incidence rate in cumulative hospitalizations for heart failure.

As shown in the table, there were differences on the primary event rate and incidence rate for cumulative hospitalizations for heart failure among three continents. North America has the highest rate, South America has the intermediary rate, and Eastern Europe has the lowest rate. There are differences in patients' baseline and disease characteristics between North and South America such as age; heart failure class; diabetes at baseline; body mass index; baseline ejection fraction; baseline systolic blood pressure; history of prior MI; and use of [indiscernible]. So Eastern Europe should be excluded due to the heterogeneous population from the Americas. The difference between South America and North America may also be a concern.

Here is how we interpreted the TOPCAT trial results. Analysis on the primary endpoint was not significant. The hazard ratio for the primary

analysis in the overall population is 0.89. The p-value is 0.14. Further testing, including subgroups, inflates the type 1 error rate. Tests for interaction between treatment and region has a p-value of 0.12. There is insufficient evidence to conclude that two regions are different enough such that the overall results that the primary endpoint was not significant should not be considered.

A nominal p-value for the primary endpoint in the Americas was 0.26 without correction for multiplicity. Subgroup analyses do not carry the same level of evidence as a prespecified hypothesis that the study was designed to test. Patients qualified by a previous hospitalization for heart failure in both regions seemed to show no treatment effect.

This is contradictory to the explanation that different populations between two regions led to different outcomes. Patients qualified by BNP elevation were mostly in the Americas and seemed to benefit from spironolactone, however, the BNP stratum constitutes less than only 30 percent of

the total population.

Conclusions based on the result in this stratum need confirmation. Subgroup analysis can be difficult to interpret. There are many differences in patient baseline characteristics between the Americas and Eastern Europe, and such differences might confound the results, therefore we should not overinterpret any subgroup results.

Here is our conclusion. The review presented here is from the Office of Biostatistics. These are the group analyses that show the considerable difference between regions. However, this was not a hypothesis that the study was designed to test for, and therefore does not carry the same level of evidence as the prespecified hypothesis.

There may exist some clinically plausible explanation to the regional disparity, however, it is difficult to conclude that the treatment is effective for the U.S. population based on this single study. The statistical review team does not consider that TOPCAT has provided sufficient

evidence to support the conclusion that spironolactone improves outcomes in patients with HFpEF. Thank you for your attention.

Clarifying Questions

DR. LEWIS: Thank you.

We will now take clarifying questions for all presenters. Please use the raised-hand icon to indicate that you have a question and remember to clear the icon after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter if you can. If you wish for a specific slide to be displayed, please let us know the slide number if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my question," so we can move on to the next panel member.

Dr. Emerson?

DR. EMERSON: Thank you. This is Scott Emerson, and I have several questions that are

going to be -- I guess the statistical reviewer for the FDA might be most prone to this.

Just to give a little bit of preface. The only subgroup that I'm going to consider is the same subgroup we went with yesterday, which is given that this is an approved drug, how do the people with ejection fraction at the lower end -- so I'm very much questioning the threshold that's used for HFpEF rather than HFrEF. And just as we largely said yesterday, we didn't think that the HFrEF threshold should be down at 45 percent.

So now, could I see the slide of all the different subgroups? That pertains to, I guess, figure 4 in the briefing book. While we're trying to get up that slide, I'll also note that we of course saw data yesterday that the sponsor was using, the MRAs, as an example of support for why we should believe that Entresto was behaving the same way.

I'm looking for the really big one where it had the ovals on it. I'm sorry. This will have it. The point is that's less than the median, and

the median in this study was 56, very similar to the 57 that we saw yesterday, and we're seeing basically similar results. So this is the subgroup that I am particularly interested in, but I also just want to talk about the slide that pertains to table 8, which is the slide of the adjustment 1 and adjustment 2 of the events.

Do we have that slide? Maybe we'll have to go to Dr. Pfeffer's to get that slide. I apologize. It might have been Dr. Pfeffer's slide 24; I don't know. At any rate, it is figure 8 in the briefing book; table 8 in the briefing book I should say.

DR. NISSEN: Yes, you're talking about the adjusted analysis.

DR. EMERSON: Exactly.

DR. NISSEN: Yes.

DR. EMERSON: So can we see that slide?

DR. YU: Hi, everyone. This is Joyce, the DFO.

Dr. Emerson, while we try to find the slide, if everyone following you could try to be a little

more specific with the presenter and the slide number, that would be really helpful for us while we're trying to look through everything.

DR. EMERSON: I apologize. I'm at a slight disadvantage this morning. Where is the table that you gave the adjusted analyses? I was wrong on slide 24, obviously.

DR. LIU: I think it's probably slide 13.

DR. EMERSON: This is great. This is it.

DR. LIU: Right? Yes.

DR. EMERSON: Yes, this is it.

I need to explain a couple things here, and I apologize if everyone is intimately familiar with survival analysis, but I'm going to explain what we're seeing here. The unadjusted hazard ratio estimate is 0.89. We do adjustment 1, which was prespecified as an exploratory analysis. The hazard ratio is 0.87. We note that in the adjustment we have several measures that are correlated with what region it is, and that when we add in region, we get a hazard ratio of 0.85.

Now, these differences in these hazard

ratios are not attributable necessarily to imbalances in randomization. Instead, when you have a variable that is strongly prognostic of outcome and you do not adjust for it, that attenuates the treatment effect that you would have seen if you adjusted for this prognostic variable. And as we see here, the region is highly prognostic, very highly prognostic, and this is called the non-collapsibility of the hazard ratio. If we had been looking at differences in means, we should have expected the estimates to stay the same, but that's not true for hazard ratios.

So this is quite compatible with no imbalances in randomization but that we get a deattenuation of the hazard ratio when we adjust for an extremely prognostic variable. But as Dr. Pfeffer quite rightly pointed out, the only thing that we're doing here that wasn't prespecified is we're doing an adjustment for region. We are not looking at a subgroup. We are instead just averaging the effect within strata.

Now, the thing that I need to be forthright

about here is that as we do this, because the number of events were lower in the stratum, that is the Russian/Georgia, that is effectively down-weighted because it's the number of events that govern how much data you have. So even though half the subjects came from Russia and Georgia, since only -- I think it was a very low number -- 8 percent of the events or something came from there, this does have a tendency to down-weight but not ignore the region.

So now, all of this is to argue what I'm going to ask for if we have it. Do we have an analysis of adjustment variables, but now add in an ejection fraction with the interaction -- that's the subgroup I'd be most interested in -- and what do we see then? I'd like to really see the ejection fraction, less than the median -- or 57, or 55, or whatever eventually would be done -- once we're adjusting. We're not eliminating the subgroup; we're just adjusting for it, but adjusting for the region and what our effect is.

DR. LIU: Hi. This is Ququan Liu. Do you

like me to answer this question?

DR. EMERSON: Yes. Do you have that?

DR. LIU: Yes. Actually, no. We didn't look at the different interactions. For example, we looked at the interaction between treatment and randomization stratum, which also can make the treatment effect change considerably, the hazard ratio, change considerably.

DR. EMERSON: Okay. So again -- and this is something obviously that the FDA can look at long after this meeting and decide what they say, but I would suspect, strongly, based on what we've seen so far, that by using this adjusted analysis but putting in the only subgroup that I personally will consider -- and again, this is based on the approved therapy and an adjacent group of the people with lower than normal ejection fraction.

I would bet $100 that you would see a very significant effect in that group. This would be most comparable to what we talked about yesterday. And again, this is not looking at the subgroup, but I am adjusting for the rate -- not looking at the

subgroup by region. I am adjusting for it. So that's --

DR. LIU: This is Ququan -- I'm sorry.

DR. EMERSON: I'll leave it at that, but that's the very, very important analysis to see, to my mind.

DR. LIU: This is Ququan Liu again. Actually, the analysis done related to the EF, we looked at the secondary interaction of EF by randomization stratum. The result shows that in the BNP stratum, patients with lower ejection fraction seemed to benefit more from treatment than patients with higher ejection fraction. Here, the ejection fraction, I used the median. The hazard ratio is 0.56 in patients with lower EF and the hazard ratio is 0.76 in the patients with higher EF.

DR. EMERSON: So again, then we would expect that what we're seeing -- and graphs along these lines presented by the sponsor yesterday, but we are seeing the similarity of a treatment response for the lower ejection fractions --

DR. LIU: Sure.

DR. EMERSON: -- and again, if you did this adjusted analysis, you would have more precision to do this, but you're telling me you didn't even really need that precision, although admittedly the BNP stratum is highly confounded with region.

DR. LIU: Umm-hmm.

DR. EMERSON: So thank you, and I'll try to even put down my hand.

DR. LEWIS: Okay.

Dr. Rose, you had your hand up briefly. Did you have a comment in response to Dr. Emerson?

(No response.)

DR. NISSEN: Marty, you may be muted.

DR. ROSE: I am muted. I did, but he dealt with it. Thank you.

DR. LEWIS: Okay. Dr. Gibson?

DR. GIBSON: Yes. To show benefit, you have to have the disease and you have to get the drug. I thought the BNP data was compelling in characterizing whether people had the disease, but what I would be interested in is more of a modified

ITT analysis, looking at those people who also actually got the drugs. So if you were canrenone positive -- I know it's a modified ITT analysis for people who really received the drug, but I do think it would be informative; so kind of a 2-by-2, or if you were BNP positive, you had the disease, and you had a positive assay for canrenone. Now, we may be limited by the fact that not everyone had a canrenone assay, but any data on that?

DR. PITT: We have very small numbers from U.S. It's just in Russia and Georgia. You saw the data, and we couldn't make that analysis. Just so few people had the canrenone measurement.

DR. GIBSON: Great. Okay.

DR. LEWIS: Excuse me, Dr. Gibson, before you go on.

Dr. Pfeffer, do you have another answer for Dr. Gibson's question?

DR. PFEFFER: I have an answer for Dr. Emerson, and then Dr. Gibson, of course.

For Dr. Emerson, we took that table that was in your briefing book that you referred to on

page 26, and we added ejection fraction at your request just now. And my lifeline is Dr. Claggett, and he did just what you said, and it keeps everything, overall. Let me just for the whole committee, this means take everything in the data set. Don't exclude anything. Don't exclude the cancer in Russia and Georgia. The overall becomes 0.85, which is just what it says there, and it doesn't change the p-value or the confidence interval. So we did add ejection fraction into the model.

DR. EMERSON: This is Scott again. I would want the interaction, the interaction with. So that is the one subgroup that I am considering, by lower ejection fraction versus high ejection fraction.

DR. PFEFFER: Okay. I'm going to get you that.

DR. EMERSON: Oh, okay.

DR. PFEFFER: My lifeline is working, and my lifeline is Dr. Claggett. But if we restrict to the EF less than 56, which is below our median,

that confidence interval becomes 0.63 to 0.96. The hazard ratio becomes 0.78 and the p becomes 0.02.

So your hundred dollar bet, which I think no one would have taken from you, is that the lower EF has a greater benefit, but that doesn't mean that there's no benefit above the median. I'm just answering your question.

DR. EMERSON: So --

DR. PFEFFER: Go ahead. I'm sorry.

DR. EMERSON: Yes. I was just going to say, I'll agree that doesn't prove there's no benefit above, although the graphs that we saw yesterday suggested certainly you lost statistical significance on the MRA, but I'll concede that the MRA graph they showed us yesterday did stay below. The estimate stayed below.

DR. PFEFFER: Okay.

Brian, can I get an interaction on that term?

Then for Dr. Gibson, we just eked out the canrenone from 300 people, so there's no analysis we can do by canrenone, except I think the one I

gave you about the rise in potassium for anyone on canrenone is a pretty robust analysis.

DR. GIBSON: Yes. So you could substitute in some way the rise in potassium, yes.

DR. PFEFFER: Now, I have an answer for -- this is medicine in progress. I have an answer. The interaction for the EF by the category we just did in the full model is 0.22. I don't think that allows me to say what your eye told you, you saw, that it behaved differently, statistically behaved differently by that categorical EF.

DR. EMERSON: Yes. And I'll say that I'm driven instead by my scientific predisposition to say I don't totally believe where the threshold between HFpEF and HFrEF is. So I was interested in that, separate from whether this interaction was significant or not.

DR. PFEFFER: Well, since you brought up -- let me clarify. This is not a spectrum across the whole range of ejection fraction from multiple studies. This is just within TOPCAT. I don't have very low EF in TOPCAT, within the range

of TOPCAT. Thank you.

DR. LEWIS: Thank you.

DR. GIBSON: Can I just make one additional comment before I am done? It's Dr. Gibson.

DR. LEWIS: I'm sorry. Of course, Dr. Gibson.

DR. GIBSON: The interaction p was 0.12. That was viewed as not significant. However, my understanding is that interaction p-values are notoriously underpowered. By way of historical precedent, I do want to point out that REDUCE-IT, one of the trials recently before the committee, did prespecify a p-value of 0.15 as what they would have held as statistically significant for an interaction term, comparing primary versus secondary prevention. They came in at a p of 0.14. So I just wanted to say that some interaction terms that are in that range can't be dismissed as indicating no heterogeneity.

DR. LEWIS: Thank you, Dr. Gibson.

DR. EMERSON: Dr. Lewis, may I follow up on that interaction p-value point?

DR. LEWIS: Yes, Dr. Emerson.

DR. EMERSON: I'll do it real quickly.

DR. LEWIS: Okay.

DR. EMERSON: This again, it's a reasonable thing when you're trying to screen for interactions and what you'll look for confirmation later. But if interaction is your major question, you're done in by the low power, and raising the type 1 error doesn't really make it enough better. But if what you're interested is the subgroup analysis, which is a different question -- it's one thing to say does the treatment work in this subgroup. It's a harder question to answer, and is that statistically different from what it works in the other group?

So I think that's sort of cross-purposes [ph] here to look at that p-value.

DR. LEWIS: Thank you, Dr. Emerson.

Dr. Pfeffer, do you have another comment to Dr. Gibson's question --

DR. PFEFFER: No, I have no --

DR. LEWIS: -- or is your hand still up?

DR. PFEFFER: I'm sorry --

(Crosstalk.)

DR. LEWIS: So everybody put their hands down if you're finished.

DR. PFEFFER: I guess I --

DR. LEWIS: Go up on the upper left-hand corner.

Dr. Nissen?

DR. NISSEN: Okay. Thank you.

Whenever we look at making a decision based upon data which are controversial, we always want to look at study conduct. And one of the things that caught my eye was the amount of missingness of data; that is patients who were not retained. They were either withdrawn consent or lost to follow-up, which I calculate to be about 13 percent of patients who essentially were non-retained.

So I have really two questions. The first one is, were their regional differences in missingness? Were there more patients for whom consent was withdrawn or who were lost to follow-up in the Georgia and Russia compared with the

Americas? Let's get that question first.

DR. LEWIS: Do any of the speakers have that information?

Marc?

DR. PFEFFER: I have vital status only, which doesn't really answer Dr. Nissen's question. I did say all studies have warts. I have the vital status missing, Steve, and I'll get that in a second.

DR. NISSEN: The reason I'm asking -- and this is for the statisticians, Scott and others -- is I'm concerned about informative censoring here, and I want to make sure we understand whether that was a possibility.

DR. PFEFFER: We had more vital status missing in Russia and Georgia. I wish we had all Russia and Georgia missing vital status. That doesn't mean we did a great job in the Americas. I think we were down to like 12 or 15. I'm sorry. I'm trying to find that.

DR. NISSEN: Yes. But I'd like to know the percent missingness in the two regions. We're

discussing regional heterogeneity here. We need to understand what regional missing is.

DR. ROSE: Marty Rose. I have the CONSORT diagram as slide 13 in my presentation, and there is some information there.

DR. PFEFFER: Yes, I see it --

DR. NISSEN: By region?

DR. PFEFFER: Yes, by region.

DR. ROSE: By region.

(Crosstalk)

DR. PFEFFER: -- 37 vital status unknown in the Americas, 2.1 percent; 95 vital status unknown in Russia and Georgia, 5.7. And as I said, I wish it were a hundred percent.

DR. NISSEN: Okay. I understand. We're going to come back to that issue, Marc. I really want to explore that. You want clarifying questions now, so we're going to come back.

My second clarifying question is, availability of BNP measurements in these two regions. I saw the unknown vital status, which was why I wanted to know, but look up above here on

this slide. You see withdrawn consent, 9.3 and 8.8 percent in the two strata, and then unknown vital status 3.9 and 3.8. Well, okay. So we need to see a complete picture of missingness in the two regions. It's really important because it implies the potential, at least here, for informative censoring. I hope everybody understands where I'm going here. And maybe at some point you guys can get that data to us.

My second point relates to the fact that the indications for randomization were different in Europe and in the U.S. In the United States, more people had BNP, but in this era when the study was done, were there differences in availability of BNP? Did every site involved here have BNP available to them?

DR. PITT: I can answer that, Steve. Steve, I can answer that. In the beginning, there was very little availability in Russia and Georgia, and we tried to make it available to some sites, but there was still relatively few. So it was a big discrepancy in availability.

DR. NISSEN: Okay. So that answers my question, and to me that's an elephant in the room because a lot is made of the fact that they had different indications for randomization in these two different regions, but the availability of the test wasn't uniformly available. So does that reflect physician decision making or simply test availability? And we'll come back to that later on when we actually results.

DR. LEWIS: Ms. Chauhan?

MS. CHAUHAN: Yes. My question isn't nearly so erudite. The presenter, the statistician from the FDA, your last slide, your conclusions, am I hearing you correctly that if Georgia and Russia had shown similar results to what the Americas showed, then we wouldn't even be having this meeting?

(No response.)

DR. LEWIS: Dr. Liu?

DR. LIU: Hi --

DR. ROSE: I'm sorry.

DR. LIU: This is Ququan --

DR. ROSE: So let me take a stab at that.

DR. LEWIS: Sorry. Who's speaking? Whoever is speaking, could they identify them self?

DR. ROSE: This is Marty Rose.

DR. LEWIS: Okay. Please try to remember. For the person taking the transcription, everybody say their name.

DR. ROSE: Certainly.

DR. LEWIS: Thanks, Dr. Rose.

DR. ROSE: Okay.

So if the overall results were negative, as they were, if the overall results did not show a significant difference between spironolactone and placebo, and the results in the two regions were similar, I don't think we'd be having this meeting.

MS. CHAUHAN: Okay. So given that, I have trouble appreciating that last slide that says that it doesn't -- I mean, this is my interpretation as a layperson. This is Cynthia Chauhan. That last slide kind of says it doesn't matter, and it seems to me it matters tremendously that we're getting really different results when we

look at how it was conducted. That's been a long-standing concern of mine with international trials anyway. So I'm just --

DR. ROSE: I mean --

MS. CHAUHAN: -- I'm alarmed.

DR. ROSE: I'm one of many people, but what last slide are we talking about?

DR. LEWIS: Dr. Liu.

MS. CHAUHAN: The statistician from the FDA's conclusions, where she said that she doesn't think -- I understood her to say that we don't have a valid case to review here, and I don't see that. She said does not consider that TOPCAT has provided substantial evidence. And I guess I'm questioning her conclusions. And I am not a statistician. I do not pretend to be one, but I care deeply about the population.

DR. LEWIS: Ms. Chauhan, when we get into our discussion section, perhaps our statistician can maybe help clarify that.

MS. CHAUHAN: Okay. I appreciate that. Thank you.

DR. LEWIS: Dr. Ridker?

DR. RIDKER: Yes. Thank you, Dr. Lewis. I have both a comment and a very specific clarifying question.

My comment is first, like the investigators, I want to thank the FDA for having this meeting on what's a very important study conducted by our federal government, and I have enormous respect for Drs. Pitt and Pfeffer, who as individuals contribute about as much to heart failure as anybody I can think of for the last 35 years.

I also want to say I totally understand their frustration. Although Dr. Pfeffer probably was being very kind, he seemed to target his unhappiness, if you like, with Ukraine and Russia. I would certainly share that. And by the way, I am persuaded that we should probably not worry about that test for interaction. I think there's plenty of evidence that there's clearly a difference between Russia, Ukraine, and the rest of the world.

But I think Dr. Pfeffer and the investigators have every right to be just as

unhappy, frankly, with NERI, and maybe their own DSMB, and maybe even the NHLBI, as much as it pains me to say that, because something failed in this trial besides the Russia part. It seems like the monitoring of the trial failed, and we might want to hear from them later about why they didn't learn of all these problems.

DR. LEWIS: There was essentially no monitoring. I mean, there was no monitoring, as we know it in pharmaceutical trials, done in this trial.

Dr. Pfeffer, am I correct?

DR. PFEFFER: Well, the contract to evidence in Russia did pay them for monitoring. They were paid for the activity. I have to say that this is NIH sponsored by a contract. If you compare this to industry-sponsored, I think it's fair to say $30 million compared to $300 million. And the problem was the sites knew in Russia and Georgia that they were not being monitored. I do think monitoring is overdone, but here it was underdone, and we paid the consequences.

DR. RIDKER: Dr. Lewis, what I'm really getting at, and this particular part of my issue, is that many of us who run trials on NIH budgets recognize that you can do lots of data monitoring without having to go to the site. I'm just making the point for the record. It sounds somehow or another that either NERI didn't do it or the DSMB elected not to tell the investigators, and the NIH should think about moving forward and make sure that this kind of problem doesn't happen again.

My question though, my clarifying question, is that it's interesting to me that none of the presentations, including that of the FDA, addressed toxicity. Now, I recognize that spironolactone has been around for a long time, but I as a cardiologist also recognize you get significant hyperkalemia and you get worsening of renal failure in patients with CKD. And there was very nice publication from this group about the fact that those with CKD was the group that seems to get -- no surprise -- mostly hyperkalemia and worsening of renal failure, and Dr. Pfeffer

probably pointed out that nobody went on dialysis because they did a very good job of monitoring.

But in terms of labeling of the drug -- so what I'm getting at here, and it makes me a little nervous, is when I apply the logic of this potential fraud issue, which by the way I'm very willing to apply, I lose half the data; if we apply the logic of yesterday, that this is really about not HFpEF but about reduced ejection fraction and the data from my friend, Scott Solomon, European Heart Journal, out of this trial suggests a very similar kind of thing, that there was this gradation of ejection fraction; and then if we did apply the third criterion, which was do we really want people with low GFR to be on this, we're down to about, the way I calculate it, roughly 20 to 25 percent of the total data.

I just want the investigators to comment on that and if my math is wrong because it's ultimately benefit to risk ratio, and we haven't talked about the toxicity issue, it seems to me, at all. And the GFR data I think is the US-only

patients if I remember the paper correctly.

DR. PITT: This is Bert Pitt. I wonder if I can comment to Dr. Ridker's comments.

DR. LEWIS: Yes, go ahead.

DR. PITT: Certainly, as Marc pointed out, there is hyperkalemia, but we didn't have any renal failures related to it. Now, in relationship to the worsening kidney function, which you referred to, and the rise in creatinine, that has been shown, for the most part, to really be a hemodynamic effect and it's reversible, and it's been seen in numerous ACE inhibitor trials, ARB trials, MRA trials. In fact, in the recent FIDELIO trial where there was a clear benefit on renal outcomes as well as cardiovascular outcomes, there was an initial increase in creatinine, a fall in GFR, and those are all hemodynamic related effects. And in the end, the slope of the fall in GFR actually was less on the MRA.

So I think a lot of the things that you're commenting on relating to renal function are [indiscernible] hemodynamic effects, and there's a

long-term benefit underlying renal function.

DR. LEWIS: We'll maybe come back to that, Dr. Ridker.

DR. RIDKER: Okay.

DR. LEWIS: I'd like to comment on it in our discussions.

DR. RIDKER: Yes, I assume [indiscernible] a nephrologist.

I have one second quick clarifying question, which is related to the --

DR. LEWIS: Sure.

DR. RIDKER: This is pertinent to our issue about FDA approval versus what the academic community is actually doing. I don't know the answer to this but maybe Bert or Marc does. I'm of the sense that a lot of people are using spironolactone in heart failure, because you guys have been so successful and talking about these issues already.

Do you have any idea, in relatively concurrent data -- I don't know the answer to that. Is that being found as background therapy in a lot

of heart failure trials or not?

DR. PFEFFER: In preserved systolic function heart failure, preserved EF, I think there are a lot of reasons to give. You can say just hypertension. So it's hard to know why people are, but I think the number I would guess is about 25 percent in trials, but in real life probably miniscule.

DR. PITT: I would agree on that. This is Bert Pitt.

DR. RIDKER: Okay. Thank you. We'll come back to the other issues later. I appreciate it.

DR. LEWIS: Thank you.

Dr. Merz? And someone is not muted. Actually, it sounds like kids. It sounds wonderful, but if they could please mute.

Dr. Merz?

DR. BAIREY MERZ: Thank you, Dr. Lewis. Noel Bairey Merz. This is a question not to the statisticians, but Rose, Pitt, or Pfeffer could probably address it.

If you look at the censored data that pretty

much everyone showed, meaning censoring Georgia and Russia, it was powered -- or it demonstrated a benefit that met statistical criteria, suggesting that either the effect size was larger than anticipated or the event rate was higher. You were able to gain statistical significance in a post hoc analysis with substantially less enrollment by eliminating half.

That to me suggests that you could consider an independent review adjudication similar to what we reviewed yesterday, but this would be independent review adjudication of probability of meeting actual inclusion criteria. And it could be done blinded, although you might consider the site in the adjudication process. I mean, that would be for you to decide.

I think that would be valuable. It extends what Dr. Gibson was suggesting, but you could potentially do it for the entire cohort and you'd have better data and you'd be less cherry-picking.

Thank you. I guess comment from anyone, and did you already do that, for example? Thank you.

DR. PITT: This is Bert Pitt. I think going back to the Russia and Georgia sites and looking at what was called heart failure, even if you reviewed the records, it would be very, very difficult because what they probably did, we believe, is people who had obesity or a little bit of ischemia, who was short of breath, or whatever, they called them heart failure. They justified it in order to get into the trial. So I think it's going to be very difficult going back to those sites in Russia and Georgia and getting much meaningful data.

DR. BAIREY MERZ: Well, Bert, hang on. This is Noel again. I'm not suggesting that you go back and try to get original documents. What we reviewed yesterday was one additional analyses of yesterday's trial, where an independent panel was commissioned and they adjudicated probability of events that had insufficient documentation; so a panel of experts looking at the incomplete data, and then giving likelihood and probability. So this is different, but thank you for that response.

DR. ROSE: May I? This is Marc Pfeffer.

Julia, may I comment?

DR. LEWIS: Yes. We're running past time, but if you guys want to keep going, we'll catch it up I think.

DR. PFEFFER: The CEC for TOPCAT was the same CEC for the trial you've looked at yesterday. What we didn't do is analyze the entry hospitalization, and I've never been fooled by people before. And in the Americas, if you were hospitalized for heart failure, you had a crummy outcome, but we didn't analyze what the -- we didn't adjudicate the initial hospitalization; we just took people's word for that. And we can't go back and get that information.

We did do an analysis of what happens to people who are hospitalized, and the CEC agreed after, and it's a multifold increased risk of death. A hospitalization for heart failure is a big deal if people aren't trying to fool you with the forms.

DR. LEWIS: Okay. Dr. O'Connor?

DR. O'CONNOR: Thank you. Chris O'Connor

here. Thank you, Marc, Bert, and Marty for great presentations. I agree you've made a compelling argument that Georgia/Russia has really jeopardized data, so in my mind I'm not looking at that as carefully. I have two questions. One is given the borderline significance in the primary endpoint overall and then in the adjusted analyses, I'm looking for a sweet spot, and I think heart failure hospitalization is a potential sweet spot for indication.

You had a very strict Hicks criteria for adjudication of heart failure hospitalization. Do we know if the investigator-called heart failure hospitalizations paralleled the CEC? Because we know this type of strict adjudication throws out a lot of events. Then my second question is, why do you think the patients who had a heart failure hospitalization entry in the Americas had such an attenuated benefit on the primary endpoint?

DR. PFEFFER: This is Marc Pfeffer. Julia, may I?

DR. LEWIS: Yes. And we're really going to

have to keep everything short, guys. We are running out of time.

DR. PFEFFER: Okay.

I don't know, Chris, why there was that imbalance there, but the overall hospitalizations were reduced, and as I just said, a hospitalization, as in every other study, meant something prognostically for the patients who experienced an adjudicated hospitalization. I don't at this moment have our batting average for the ones that didn't make that line. I could try to get that for you.

DR. LEWIS: Thank you.

DR. O'CONNOR: Thank you.

DR. LEWIS: Dr. O'Connor, do you have another question or are you done?

DR. O'CONNOR: No, I'm done. Thank you.

DR. LEWIS: Okay. Dr. Thadhani?

DR. THADHANI: Thank you very much, Dr. Lewis.

Just very quickly, again, for the presenters, just a follow-up question. The point

estimates for heart failure across the sites, no different, but of course when we look at the results in a different way, we find those differences.

The question I had was BNP. Given the remarkable differences in outcomes in BNP, just for my own edification, is BNP routinely used for HFpEF as a diagnostic criteria in the fashion -- certainly, we know it's much lower, and more importantly kind of standard of care in that category. It would be helpful to hear from the cardiologists on that note. Thank you.

DR. PFEFFER: Bert, do you want to do it or should I?

DR. PITT: This is Bert Pitt. I would just comment that BNP is used not for a criteria for HFpEF versus HFrEF, but to document that there is heart failure, if that's what you're asking.

DR. LEWIS: Yes. It was one of the entry criteria yesterday.

Dr. Nissen, do you have a compelling question?

DR. NISSEN: Yes.

Dr. Thadhani, you were done?

DR. THADHANI: I can follow up later. Thank you, Dr. Lewis.

DR. LEWIS: Okay. Great. Thank you.

DR. NISSEN: A very quick question. I know we're running out of time. Typically, when there's a very marginal effect in a trial, the statisticians at FDA will impute missing data as a sensitivity analysis. Was that done here, FDA statisticians; and if so, what did it show?

DR. LIU: Hi. This is Ququan Liu. In terms of the missing data, I believe there's not that much missing data in that study. What specific missing data are you referring to?

DR. NISSEN: I'm sorry. There's an enormous -- the missing data here is so large I can't even figure out why this is in front of us. There's 13 percent of the patients for which we don't have outcome data. That's a huge amount of missing --

DR. LEWIS: Dr. Liu, do you want to comment

on that? Do you have the ability to do that analysis? Is it available?

DR. PFEFFER: Julia, this is Marc Pfeffer. I have that. Withdrawn or lost to follow is 7 percent in the Americas and 11 percent in Russia and Georgia.

DR. NISSEN: Marc, if I look at the CONSORT diagram, it looks like it's 13 percent. If you had up the withdrawn consent plus lost to follow-up, I think that's right.

DR. PFEFFER: Okay. From where I'm sitting in my house, I can't answer that, except the CONSORT diagram is the supplement; that is right. What I'm getting is from a very reliable source who's doing the numbers for me right at this moment.

DR. LEWIS: Okay. If they can do the analysis that Dr. Nissen requested, that would be fantastic.

Our transcribers need a 15-minute break, so we will take the full 15 minute break. If I got it right this time, Dr. Nissen, I think that gets us

to about 11:54 or 11:55. And it is our only break as well, so we're going to take a break.

I will now remind you that there should be no chatting or discussion of the meeting topic with anyone during the break. We will resume at 11:55 Eastern Standard Time.

(Whereupon, at 11:41 a.m., a recess was taken.)

Open Public Hearing

DR. LEWIS: We will now begin the open public hearing session.

Both the FDA 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 is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you

may have with any company or group that may be affected by the topic of this meeting. For example, financial information may include a company's or group's payment of your travel, lodging, or other expenses in connection with your participation in the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to

carefully and treated with dignity, courtesy, and respect. Therefore, please only speak when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SACHDEV: Thank you, Dr. Lewis, and good afternoon, everyone. My name is Vandana Sachdev, and I'm a cardiologist in NHLBI. I'm here with my colleague, Dr. Jerry Fleg, and we're speaking on behalf of ourselves, presenting our views and not official views of NHLBI, NIH, or DHHS. We have no conflicts.

This is an overview of the points that we'll be addressing. NHLBI has been very committed to addressing the growing public health challenge posed by heart failure, especially HFpEF. Morbidity and mortality rates for the clinical syndrome of HFpEF remain very high. Community-based studies demonstrate even higher

rates of mortality, hospitalization, and emergency department visits compared to what we saw in the TOPCAT Americas study.

The use of ejection fraction to define HFpEF is an oversimplification of a complex syndrome. We've learned in the last few years that several factors must be part of this definition, first, evidence of heart failure, some signs and symptoms, or recent hospitalization; second, cardiac-specific finding such as a high BNP; and also the exclusion of other diagnosis that might be responsible for symptoms, and things such as amyloid must be excluded before making this diagnosis.

The current understanding of HFpEF is that of a spectrum of sub-phenotypes with dynamic functional changes. This is an area of active research within NHLBI. The data from TOPCAT suggest that all HFpEF patients with congestion, as evidenced by a high BNP or recent hospitalization, stand to benefit from the use of spironolactone. Unfortunately, the general consensus of the scientific and clinical communities is that all

trials have been negative and there are no approved treatments for HFpEF. We have the opportunity today to critically evaluate and change this perception.

HFpEF, as many of you know, is a heterogeneous syndrome with multiple comorbid conditions: obesity, hypertension, diabetes, chronic kidney disease, and atrial fibrillation, and the risk of death is higher with an increasing burden of comorbid conditions. It's worth noting that there is a large body of accumulating evidence on the use of MRAs and chronic kidney disease and diabetes. In fact, Dr. Pitt has already referred to this.

Two recently completed studies of finerenone, a selective MRA used in patients with chronic kidney disease and diabetes, showed an improvement in renal outcomes and an improvement in cardiovascular outcomes. A recently initiated study will test cardiovascular outcomes specifically in HFpEF patients. I bring this up because selective MRAs such as finerenone and other

drugs such as sacubitril/valsartan, while they may have efficacy in HFpEF patients, these are costly drugs that will not be disseminated for many years.

Spironolactone, on the other hand, is low cost and widely available. In terms of current guidelines, based on the TOPCAT regional analysis and a meta-analysis of 14 other randomized-controlled trials, MRAs are given a 2B indication for HFpEF treatment. Despite clear evidence of a reduction of heart failure hospitalizations with MRA treatment in the America's, TOPCAT results have had only a modest impact on provider prescribing patterns. This question came up just a short time ago.

In the figure shown here from a Get With The Guidelines publication, the release of trial data at the end of 2013 resulted in the number of HFpEF patients receiving an MRA upon hospital discharge, increasing from 12 percent to only 15 percent by the end of 2016. This is shown in the red circles in this graph. In this particular report women, older patients, and black patients with HFpEF were

less likely to be discharged on an MRA.

In recent years, MRA treatment for HFpEF has been increasingly accepted by the cardiology community. This is shown by a rate of 24 percent of MRA use in the recently discussed PARAGON trial, and a newer ongoing trial had an even higher rate of 37 percent. However, it's very important to remember that many HFpEF patients are seen only in primary care. Drug labeling can have a significant impact on physician prescribing behavior. Despite a favorable risk-benefit ratio for spironolactone, physicians are less likely to start a new drug if it does not have an approved indication.

As was discussed yesterday, the left ventricular ejection-fraction based taxonomy of heart failure is imprecise for a disease like this that is more of a spectrum of phenotypes. Heart failure patients in fact can have both systolic and diastolic dysfunction independent of ejection fraction. We believe the TOPCAT data and results from other studies support the use of spironolactone in carefully defined HFpEF patients

with BNP elevation or a recent heart failure hospitalization. Increasing use of spironolactone in these patients will reduce heart failure hospitalizations, leading to significant societal and economic benefit. An approved indication for spironolactone will also encourage key opinion leaders and societies to promote more widespread use of this treatment.

Finally, I want to emphasize that TOPCAT was a significant investment of time and resources by all involved, but the benefits of these efforts are not achieved by data creation alone. Converting data and knowledge into practical application is a vital part of the return on investment for public research. We commend Dr. Rose, the FDA staff, and this committee for their continuing efforts to translate knowledge into action.

That's the end of my comments. Thank you. I'll turn it back over to Dr. Lewis.

DR. LEWIS: Thank you very much.

Speaker number 2, your audio is connected now. Will speaker number 2 begin and introduce

yourself? Please state your name and any organization you are representing for the record.

DR. FLEG: Yes. This is Dr. Jerome Fleg, and I am also a cardiologist at National Heart, Lung, and Blood Institute. I'm here mainly to answer questions, but I would bring up one additional point that Dr. Sachdev did not touch on, and that is that given the primary endpoint consisted of both cardiovascular death and heart failure hospitalization, we should not lose sight of the fact that even in the overall trial, even including Russia and Georgia, there was a 17 percent significant reduction in heart failure hospitalizations, which account, in fact, for about two-thirds of the primary outcome of events in TOPCAT and probably in the real world as well.

I know that it may in some ways defy approving a trial as it only met a major secondary endpoint rather than the primary. One could certainly conceive of the benefit that would accrue from approving this drug for HFpEF even if only for reduction of heart failure hospitalizations and not

necessarily mortality. So I would just like to bring that additional point to bear. It was actually a 17 percent reduction in heart failure hospitalizations, and if you look at total cumulative heart failure hospitalizations, it was about a 25 percent reduction.

I'll stop there, and I will be happy to take any questions for Dr. Sachdev and myself.

DR. LEWIS: Okay. I'm sorry. I didn't realize, Dr. Fleg, you were part of speaker number 1's presentation, but thank you for your additional comments.

Speaker number 2, we will now put your audio on. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SEYMOUR: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Meg Seymour, a senior fellow at the center. Our Center analyzes scientific and medical data to provide objective health information to patients, health

professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

Today the committee is asked to consider a new indication, spironolactone, for heart failure with preserved ejection fraction. If approved, spironolactone would be the first product with an indication to improve outcomes in patients with HFpEF, however, as we have all read in the briefing materials, the trial failed to reach the prespecified primary endpoint. Though consideration for approval is not unprecedented in such cases as FDA pointed out, it is unusual.

That is not the only thing that is unusual about these data. These results varied widely between the two regions where the study was conducted. For example, the rate of the primary endpoint was 5.4-fold fold higher in the Americas. FDA stated there are good reasons to be skeptical of accepting the TOPCAT results from the Americas.

There is no precedent for excluding an entire region, rather than a single study site,

especially when that region constitutes half of the study sample. Further, the lack of interaction by region means that it's not possible to conclude that the two regions are different enough to exclude half of the results.

The demographics of the study lead to further questions about the data. The sample population from the two regions varied on numerous crucial demographics, which complicates interpretation of the data and the question of data exclusion. The bottom line, what is the risk of approving this indication if it might not work? What can be done to improve the quality of the data prior to FDA making a decision about whether or not to approve this indication? Thank you.

DR. LEWIS: The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. I will pause here. We have an opportunity right now if any of the presenters have had the opportunity to gather data to address Dr. Nissen's question about the impact of the missing data.

DR. PFEFFER: I have. I'm trying to raise my hand, Julia. I have, and I have to thank my colleague.

The fact that we're looking at the region is very important to me, that I don't want to talk about missing data in Russia and Georgia because I think that doesn't add anything. But if we're down to what is left, if we just look at the Americas, then Dr. Nissen is correct. We have to look at the missing data, and that's exactly why I wanted the FDA to take this independent look at what is left.

I would have to say that no trial's perfect, and we are missing vital status and important data on 7 percent of our patients. And Dr. Nissen, I think it's because in that diagram, we're adding the vital status unknown to missing data. The number for the Americas is 7 percent. That's 7 percent too high, but that's what it is.

DR. NISSEN: Marc --

DR. LEWIS: Yes, Dr. Nissen?

DR. NISSEN: -- what is the missing data on the European side -- I mean on the Georgia/Russia

side?

DR. PFEFFER: I didn't try to get that for the reason that even if they gave us the data, I don't trust the data, so I'm not even going to ask my statistician to get that. But I'll get it for you if you want it.

The point we have here is, yes, we can go with the overall, which you've heard; overall adjusted, which you've heard; and overall heart failure hospitalization, which you've heard. But I think the story is we censor Russia/Georgia, or we don't. So that's a point you have to agree on, and then if we do, what's left? Eleven percent is the number from Russia and Georgia.

DR. NISSEN: Thank you.

Questions to the Committee and Discussion

DR. LEWIS: Okay. Thank you very much, Dr. Pfeffer and Dr. Nissen.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with the

questions to the committee and panel discussion. I would like to remind the public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. I am now going to read the first discussion question.

Please comment on the various prespecified and post hoc analyses. Which ones contribute to the strength of evidence supporting the indication? Which ones do not?

Are there any questions about the actual wording of the question? Does anyone need a clarification from the FDA on the wording?

(No response.)

DR. LEWIS: I don't see anybody's hands raised, so if there are no questions or comments concerning the wording of the question, we will now open the question to discussion. I just want to remind you all to raise your hands if you want to begin the discussion.

Dr. O'Connor?

DR. O'CONNOR: Thank you, Julia.

Chris O'Connor here. I'd like to comment that I think the analysis excluding Georgia/Russia is very compelling to me in the component of heart failure hospitalization, and the question that I will come to later is what is the patient population? But from the standpoint of the analyses provided by the investigators, I think the exclusion of Russia and Georgia is compelling, the adjusted model, and I think the signal on heart failure hospitalizations is compelling to me. Thank you.

DR. LEWIS: Thank you, Dr. O'Connor.

Dr. Emerson?

DR. EMERSON: I'd like to first address which do not, and it's the compliance. While it's regrettable that the compliance was low in Georgia/Russia, we should not be adjusting for compliance anyway. As I stated before, where I have the greatest sympathy is for doing an adjusted analysis, and that is, however, a data-driven decision in the sense that it was not a prespecified analysis.

I think my other interest is in the lower ejection fraction, and that's driven by results outside this trial as well as inside this trial. I can't ignore the circular aspect of yesterday's results included results from these sorts of studies, and then today using that again.

I would not be in favor of a subgroup analysis, but I need to be honest, that the adjusted analysis, because the low event rate is there, is down-weighting that other group because of the statistical model that's used. So we just would have to acknowledge that fact, that by that down-weighting, am I allowing a subgroup selection to masquerade as just adjustment for a different stratum? That's all that I'd have.

DR. LEWIS: Thank you, Dr. Emerson.

Dr. Moliterno?

DR. MOLITERNO: Thank you, Dr. Lewis. I don't have anything novel to say, though. I think like yesterday and others have said today, that which I'm most compelled by is that which is biologically plausible again, and that's the

ejection fraction group below the median and the benefit there consistent with prior in the current study. I highly respect the arguments today about regional variation in outcomes, though obviously that takes an element of speculation about the whys, so I'm drawn most to the biologic aspect at the lower ejection fraction. That's all. Thank you.

DR. LEWIS: Thank you, Dr. Moliterno.

Dr. Nissen?

DR. NISSEN: Okay. Well first of all, Marc and Bert, you guys are two people I admire greatly, but I really disagree with your interpretation of the trial, and particularly the censoring of half of the data, the data from Eastern Europe and Russia. And I understand why you think what you think, but I want to ask everybody a rhetorical question.

If a large pharma company came in and said, "Well, we did this trial and we got a p-value of 0.14. But gee, if we take out a whole bunch of these low-quality sites, bingo, the study's now

positive," what would we say? And the fact that the study was done by the NIH doesn't change my thinking.

We have rules about how we do these things, and those rules are there for a reason. If you let me throw out low-quality sites from any study that we've ever done, I can amplify the favorable effects. If you take out the bad, all these sites that underperform and that do things that they shouldn't be doing, that perhaps didn't follow the rules about enrollment -- the sites were chosen in advance. They were vetted appropriately. To say, "Well, they're dirt-ball sites, and therefore we're just not going to accept their data," is just not compelling.

So I agree with FDA's statistician that there really isn't compelling evidence to just throw out half of the sites. Even though they probably didn't do as well, the idea that they don't contribute anything and can be therefore thrown out doesn't make sense to me. So those are the data that I don't consider compelling.

I also don't consider compelling the analysis based upon the reasons for enrollment. We heard that if you got enrolled because you had a high BNP, lo and behold, the drug had a favorable effect as opposed to being enrolled because you got enrolled for having a prior hospitalization. Then we find out that the Eastern European sites, many of them didn't have the ability to measure BNP. Well, of course, they enrolled patients based upon the other criterion because they didn't have the BNP available, so that's not a compelling analysis either.

So those are two examples of analyses that I don't think rise to the level of regulatory action.

DR. LEWIS: Thank you, Dr. Nissen.

Ms. Chauhan?

(No response.)

DR. LEWIS: Ms. Chauhan, I think you're muted. You're muted in the upper left-hand corner of the Adobe Connect.

(No response.)

DR. LEWIS: Ms. Chauhan?

MS. CHAUHAN: I --

DR. LEWIS: Oh, there you go.

MS. CHAUHAN: Okay. Am I on now?

DR. LEWIS: Yes, ma'am.

MS. CHAUHAN: Cynthia Chauhan, patient representative.

In spite of Dr. Nissen's thoughtful comments, I really agree with Dr. O'Connor that it is compelling. I'm not a trialist. I understand a lot about trials, but I think if you have a massive misuse of the trial in order to get care to patients you care about, that has to be taken into account when you're looking at the results, and I think that's what probably happened over there. So I agree with Dr. O'Connor about moving forward with this. That's all. Thank you.

DR. LEWIS: Thank you, Ms. Chauhan.

Dr. Thadhani?

DR. THADHANI: Thank you, Dr. Lewis.

Just to pick up on a few comments, the point I was trying to make earlier is that if the stratification by heart failure hospitalization

that we discussed in the Americas yields a point estimate similar to that in Eastern Europe, whereas that stratification in the natriuretic peptide does not, that I found perplexing, and obviously Dr. Nissen touched on that.

That said, I just want to go back to a point that one of the speakers made, and as well, I believe the speakers prior. And that is the primary analysis, as was presented to us, with all the data included, all regions, all 200-plus sites -- without any exclusion of any data, without exclusion of issues of compliance, without exclusion of issues of age, as well as any debate on issues of interaction -- yielded a positive result, if I'm not mistaken, on table 7, with a hazard ratio of 0.83 and a p-value of 0.042, not unlike what we discussed yesterday looking at additional data on heart failure hospitalization as an addition to a indication from a previously approved agent.

Thank you, Dr. Lewis.

DR. LEWIS: Thank you, Dr. Thadhani.

I have a question for Dr. Cook or Dr. Emerson. I wonder if you guys could please comment. As I understand how this study was set up, it had 80 percent power to detect a 20 percent effect, and that was with the full population.

Now, if we're being asked to consider -- and I don't disagree with Dr. Nissen's comments, by the way. But as an additional comment, we're being asked to consider just the Americas data now, so we have now half the population. And the difference between events, there was 1900 events yesterday, the difference of 115, for example, using their study as an example, and there are 522 events with the difference of 38.

Can you guys comment on how we should think about that, Dr. Emerson and Dr. Cook?

DR. EMERSON: I can offer my opinion. Again, my opinion was you should not focus on that subgroup because it's so data driven. Now again, I am focusing personally on the ejection fraction thing, and should I substitute my opinion for what was prespecified in the trial, and that's going to

be a problem.

But the power that you're going to have when you're using proportional hazards is entirely driven by the number of events you have. So if you select the strata that have the most events, then you have not lost as much power as if you select the strata that have a lower number of events. But the bigger fear is that you're selecting the strata that has the treatment effect you want, and that overwhelms any other aspect that you're doing.

Give me any clinical trial, and I can find some variable that selects out the half of the statistical information that looks most promising, and that's what we have to guard against. I understand why we might like the United States data better from the aspect both of this is the FDA and from the aspect of our healthcare delivery, not having availability of measurements we'd want and then also what the controls were.

But we still have to worry would they have come to us if it had been reversed, as we see in so many trials, where the effect is greater elsewhere

than it is in the United States, and would they have been coming back to us and finding reasons to argue against the United States data. I'm not saying they're doing that, but we always have to consider that's the possibility.

DR. LEWIS: Thank you.

Dr. Ridker?

DR. RIDKER: Yes. So I find myself really struggling back and forth on two different sides of the coin, and I want to explain why because I think there's a middle ground that might work, at least for me, and perhaps it might persuade some others.

On one side of the coin, I have tremendous sympathy for the idea that dropping 50 percent of the data, no matter how well defined and how much we all might believe the data is bad, it does make me very nervous as precedent setting issues at the FDA, for all the reasons we've heard. At the same time, I have enormous sympathy for my patients, frankly, and for the public health benefit of a drug that I probably think probably does work in certain kinds of patients.

Yesterday, we had the advantage of PARAGON and PARADIGM showing us a wide range of ejection fraction, and we discussed for quite a few hours a generalized decision to consider not HFpEF, because that's preserved ejection fraction, and again that's normal, but we somehow as a group got to something that sounded like mildly reduced ejection fraction as a potential way to go.

My colleague Scott Solomon published a paper with the TOPCAT investigators, that we didn't see today, in European Heart Journal a couple years ago, which showed a very similar figure inside TOPCAT. Now granted, the range of ejection fraction -- I just looked at the paper, and that was 44 to 85, but it kind of had the same message, which was there's an inflection point around the ejection fraction just around 50, or 55, where the benefits seem to be below that and above that. It was pretty much washed out. The important point of that paper, now that I'm re-reading it, is they didn't drop out any data at all. That paper used the entire TOPCAT trial.

So I'm sort of wondering if, in a way, our frustration about trial conduct and the understandable frustration from the investigators that they feel they have problematic data, and I have incredible sympathy for them because I think they do have problematic data. I'm feeling like maybe in this regulatory context, we might find ourselves comfortable saying let's not drop any data at all and recognize that even across the entire trial, for that ejection fraction less than, say, 50 percent, or mildly reduced, or whatever number we thought we got to yesterday, the endpoint of HHS is down across the whole trial.

So we didn't see that data presented here. I don't know if anyone has it available. And then of course the correlate to PARAGON and PARADIGM would be RALES and TOPCAT, which if I remember correctly would cover a wider range. I'm wondering if that sort of parallel -- it might help me to get to a decision here to say, okay, there's this other thing that we discussed yesterday. It kind of parallels here, and I don't have to drop any data

to get there, if that makes any sense to anybody?

DR. LEWIS: Yes, it does. Thank you, Dr. Ridker.

Dr. Merz? Dr. Merz, I think you're --

DR. BAIREY MERZ: Noel Bairey Merz. Thank you, Dr. Lewis. Yes, it just takes a minute to come up.

I would share a lot of the prior discussion. I don't think that we should drop data. I do find the secondary outcome compelling, and I agree with our NHLBI faculty that quality of life is important. These hospitalizations are expensive. It is a burden on not only the patient, but the family.

As I argued yesterday, I think that while these trials have been designed, it takes 5 years to design them, 5 years to get them funded, 10 years to digest them, and the patients move on and the epidemiology moves on. Quality of life now for PCORI is the primary outcome.

Perhaps similar to Dr. Ridker but different, I would argue that this could be approved on the

basis of that secondary outcome. I know it's probably a regulatory morass, but I think the data's there, the data's clean, and it would be a meaningful outcome and expand the use of this generic. Thank you.

DR. LEWIS: Thank you, Dr. Merz.

Dr. Gibson?

DR. GIBSON: Thank you.

DR. LEWIS: Excuse me, Dr. Gibson. Sorry. The people who don't have a second question but they just left their hand up, please put them down.

I'm sorry, Dr. Gibson. Please start.

DR. GIBSON: Sorry.

Yes, the prespecified primary endpoint was negative, however, among all the patients, even if you don't exclude Eastern Europe, there was a reduction in the cumulative incidence of heart failure. That was 394 versus 475 events. The p-value there is 0.03. The cumulative incidence of heart failure events was used in PARAGON, and this is a very important patient-centric outcome, which I think is both burdensome to patients and society;

it's quite costly.

It's unusual to reject data from countries or regions but not unprecedented. An example is the fact that the U.S. data was discounted in the PLATO trial. As I recall, there was a higher mortality in the U.S. I did find the data that patients enrolled by primary care physicians in Eastern Europe constituted a population that more closely approximated ischemic heart disease and the intended population of heart failure. The event rates were clearly much lower. Compliance was clearly much lower.

I did find the data for those patients with an EF less than 56 percent compelling. As I recall, the p-value there was less than 0.03. I did not find the p-value of 0.12 for interaction by country very compelling. The drug does have an excellent safety record, dating back to 1960.

So in my mind, for the secondary endpoint, the drug clearly does reduce the incidence of heart failure hospitalization. Again, I do find that burdensome and costly. There is no significant

harm, and it's true particularly in those with an EF of 56 percent, at least the primary endpoint. So no patients would need to be dropped and no precedent would be established for dropping large amounts of data if we stick with what is the secondary endpoint. But I would say it's buttressed by a large amount of data from the other prespecified analyses for the primary endpoint.

I do think we have to put patients first, and I don't think patients should be denied access to a drug based upon deviations in good clinical practice in one part of the world. Thank you.

DR. LEWIS: Thank you, Dr. Gibson.

Ms. Alikhaani?

MS. ALIKHAANI: I really appreciate the thoroughness of this discussion. It's been really helpful for me as a heart patient and as a consumer. I particularly value a global clinical trial, so I started out actually very hopeful about this because I'm a rare heart disease patient, and global trials are very, very important for people with rare diseases, as well as being important for

other people, other patients as well. But I also care a lot about monitoring discrepancies and trial compliance issues because I don't want things like that to interfere with the advancement of global trials and the integrity of global clinical trials.

So I'm very concerned about the missing data discussion. It makes me very uncomfortable. I don't take trial conduct issues very lightly. It's really, really important. Trial compliance is critical, and monitoring is critical, especially when they're global trials. I just want to make sure that we don't set that precedent, or the appearance of that precedent, in any way by diminishing the value of these kind of issues, and I think we've addressed them very well in this discussion all around.

I agree with Dr. Ridker and Dr. Bairey Merz, and I hope that we can move forward with this to help the patients because patients and healthcare consumers, they're really suffering from this disease. So I hope that we can go forward in the way that they suggested. I think they made,

especially Dr. Ridker, very good suggestions, and Dr. Bairey Merz. Thank you.

DR. LEWIS: Dr. Kasper? Thank you, Ms. Alikhaani.

DR. KASPER: Yes. I find myself in substantial agreement with Dr. Ridker. I, too, have been torn. Clearly, these populations were very, very, very different, and the American population looks much more like the patients I care for, minus a substantially higher number of African Americans in Baltimore, than was included in this particular trial.

I find myself also agreeing that this is likely related to ejection fraction and that the benefit is probably most likely seen in the lower ejection fraction within this range. So handling this is kind of similar to the way we handled this yesterday. It makes sense. I can't see throwing out 49 percent of the patient population, even though I think something very, very, very bad happened in Georgia and Russia. Thank you.

DR. LEWIS: Thank you, Dr. Kasper.

Dr. Emerson, your hand was up, but I think you put it down. Is that correct? In which case, I think it's Dr. Nissen.

DR. EMERSON: I did put it down, but I just wanted to point out one thing --

DR. LEWIS: Sure.

DR. EMERSON: -- and I'm not sure now is the time to do it. But I'll just note that relative to yesterday, we do have a difference, and I don't know how this bears out. But we do have cardiovascular death benefits when you look at, firstly, the American subgroup and whether that would really hold out entirely on the adjusted analysis. I don't know, but that's different from yesterday where we did not have an effect on the cardiovascular death. It was only hospitalization. So that's just something that as we generalize, we'd be generalizing to that added indication if that were appropriate.

DR. LEWIS: Thank you, Dr. Emerson.

Dr. Nissen?

DR. NISSEN: Several people, led by my

friend Paul Ridker, have suggested that we adopt an approach similar to yesterday. Let me try to point out that there are three very important differences from what happened yesterday.

Yesterday on the primary endpoint, the p-value was 0.059, so we were very close to significance for the overall trial without throwing anything out. For this study, it's 0.14. Now, that is different. Secondly, yesterday we had a trial that was conducted with very high standards of conduct. Missingness was essentially zero, almost a hundred percent follow-up, very high quality. So we don't have to worry about informative censoring. Here, we have differential lost to follow-up or withdrawn consent in the two regions, which can color the results significantly.

Then finally, yesterday we had a very strong interaction p-value for ejection fraction. The interaction p-value in the TOPCAT study for ejection fraction, using the same criteria, is not significant. So these three points make the two analyses very different. I was Willing to stretch

yesterday because all these other factors were there. We had a near-miss on p-value, we had a very high-quality study conduct, and we had a very strong interaction p-value on ejection fraction. None of those things are true for TOPCAT. Thank you.

DR. LEWIS: Thank you, Dr. Nissen.

Dr. O'Connor?

DR. O'CONNOR: Yes. Julia, thank you.

I just want to get consensus around when we're saying throwing out data. Are we talking about 50 percent or are we talking about the 149 primary events out of the total of 670 events? Which would really be representing a much lower removal of data if we talk about the removal of events. Maybe Scott can help me here.

DR. LEWIS: Thank you, Dr. O'Connor.

Dr. Cook or Dr. Emerson, do you want to comment?

Dr. Emerson?

DR. EMERSON: Yes. So here's where I have to argue both sides. In terms of the statistical

precision, if we eliminate the Russia and Georgia, are we down-weighted. We're throwing out relatively small as it reflects the precision. However, with respect to the generalizability, which is more of the patients, we'd be throwing out half the patients.

DR. LEWIS: Okay. Great.

Dr. Nissen, your hand, you just didn't put it down; is that correct, or do you have another comment? No.

Dr. Cook and Dr. Rossert, I wanted to give both of you an opportunity to comment.

DR. COOK: This is Tom Cook. I don't think I have anything else to add.

DR. LEWIS: Thank you.

Dr. Rossert?

DR. ROSSERT: Yes. Maybe I can make a few comments.

The first one, if industry was coming with a study and asking the same question, I don't think we'd have an article [indiscernible]. Having said so, I don't think we should treat this study to the

same standard, an industry-sponsored study. I think it's very valid that we're here today and asking difficult questions.

Now, I also think that the question that is most meaningful to me is whether or not to discount data from Russia and Georgia and not whether or not to rely on post doc group analysis. I would not be comfortable relying on post doc group analysis. However, based on all we've heard on the arguments, that have been compelling, made by Dr. Pitt and Dr. Pfeffer, I would be comfortable removing data from Russia and Georgia.

Considering that TOPCAT was actually a smaller study done in the Americas, look at that part of the study, of the stand-alone study, and then we could ask the question, is this study compelling enough to warrant an indication. I would add that based on the data that were presented today and have been published, my preference is the difficult question would be yes. Thank you very much for now.

DR. LEWIS: Thank you, Dr. Rossert.

If there is no further discussion on this question -- Dr. Cook, your hand is up.

DR. COOK: Yes. I've decided to make a comment. I don't know if I'm allowed to comment on the next question, which is a voting question, but the voting question --

DR. LEWIS: No, you're not.

DR. COOK: Could I just say, the voting question doesn't refer to prior evidence, whereas the voting question yesterday did. So the question here is, does TOPCAT provide sufficient evidence supporting the indication? And the difference I see between that and yesterday is I don't see the evidence within this trial alone, whereas yesterday we were allowed to bring in evidence from a previous trial.

DR. LEWIS: Dr. Cook, I'm going to ask you to hold that, if you aren't finished yet, to when we come to asking the FDA to clarify the next question.

DR. COOK: Okay.

DR. LEWIS: I'm going to pause now and

summarize. Thank you, Dr. Cook, though. I'm going to do my best to summarize what's been a fantastic discussion, which I'm sure the FDA is going to much appreciate.

I think that we have a spectrum of opinions, but overall there is certainly expressed by many people the concern about throwing out completely, half if you will, of the patients, although a far smaller number of the events, and Dr. Emerson clarified the impact on precision versus generalizability.

There was some support for looking, however, at just hospitalizations for heart failure, where without throwing out data, we find support in TOPCAT, and also for looking at the group that we talked a lot about yesterday, which is the lower ejection fraction group. Both of those things were expressed by several of our speakers.

There was also comments about the interaction value and the interaction for ejection fraction as well. And I just lost my computer screen. One second here to get back on.

I don't mean to make it too short, that summary, because I think there was a lot of detail in what everybody said, but I think -- oh, one other point that I think is worth it as a separate point is that there was an effect on CV death, and that was impressive.

There was a lot of concern about precedence and also concern about whether there was an influence of this not being a pharmaceutical company study but an NIH study. Certainly, Dr. Nissen eloquently detailed for us the missingness data issue, the issue of the p-value not even being very close, and the differences between it in a well-conducted study.

So I will stop there with my summary, and since there is no further discussion at this time of this question, I will now read the next question. It's a voting question, and Dr. Joyce Yu will provide the instructions for the voting, and I will then read the question.

Dr. Yu?

DR. YU: Yes. Thank you. This is Joyce Yu,

the DFO.

Hi. Can you hear me?

DR. LEWIS: Umm-hmm. Yes.

DR. YU: Okay. Thanks.

Question 2 is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that the voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button, that is the round circular button, in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit or send your vote. Again, you need only to select

the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the roster and each voting member will state their name and their vote into the record. You should also state the reason why you voted as you did if you want to. However, you should also address any subparts of the voting question, if any.

Are there any questions about the voting process before we begin?

(No response.)

DR. YU: Okay. I don't see any.

Dr. Lewis?

(No response.)

DR. YU: Dr. Lewis, do you want to proceed?

DR. LEWIS: I will now read the voting

question.

Does the TOPCAT trial provide sufficient evidence to support any indication?

Dr. Cook, do you want to say more about the question you had to the FDA about whether we should be considering -- even though they don't ask us that in this question, to clarify whether we should be considering the RALES trial, I guess is what you were asking.

DR. COOK: No. I was just addressing the previous question in the context of this question. I understand this question. And the way I would view the evidence in this trial from question 1 would be different depending on whether it's just about the information in TOPCAT versus everything we know about this drug in both the HFpEF and the HFrEF population. So I have no questions about this question.

DR. LEWIS: Okay. I will give the FDA a chance to comment if they want to.

DR. STOCKBRIDGE: Yes. This is Norman Stockbridge. I certainly think that you should

consider anything you think you know about spironolactone in answering this question. The difference in the wording here reflects my failure to anticipate how interested you might be in RALES as a predicate in this case, but you're certainly welcome to consider it, and anything else you think you know.

DR. LEWIS: Thank you, Dr. Stockbridge.

If there are no further questions or comments concerning the wording of the question, we will now begin the voting on question 2.

DR. YU: Okay. We will now move voting members to a voting breakout room to vote only. There should be no discussion in the breakout room.

(Voting.)

DR. YU: The voting is closed and is now complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

DR. YU: The vote results are now displayed. I will read the vote totals into the record. The chairperson will go down the list and each voting

member will state their name and their vote into the record. You can also state the reason why you voted as you did if you want to, however, you should also address any subparts of the voting question, if any.

The vote total was 8 yes; 4 nos; and 1 abstention. Thank you.

DR. LEWIS: Thank you, Dr. Yu.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification of your vote if you wish to. However, please remember to address any of the subparts of the question that correspond to your vote. We'll start with Dr. Thadhani.

DR. THADHANI: Thank you, Dr. Lewis.

My vote was yes. I believe when the NHLBI embarked on this study, they were hoping to bring an inexpensive generic therapy for an unmet medical need. On balance, I believe there's more positives than negatives, and most compelling to me were the data including all patients from all regions on

heart failure. Thank you.

DR. LEWIS: Thank you.

Ms. Alikhaani?

MS. ALIKHAANI: Yes. I voted yes. I think that it wasn't an altogether easy decision for me because of questions about the data, and I wish that there had been more ethnic diversity in the trial. But again, keeping my sights on helping patients who are living with this terrible disease, heart failure, and the quality-of-life issues that exist for patients like that, I felt that, overall, there was enough evidence that's positive enough to help patients. So that's why I voted yes.

DR. LEWIS: Thank you.

Dr. Merz?

DR. BAIREY MERZ: Thank you. I voted yes. I voted yes because I do value the secondary outcomes, and while that establishes a precedence that I think has made our colleagues concerned, I'm equally concerned about establishing a precedence that we cannot do generic trials on reasonable budgets that our federal government would do in

order to provide generic, cheap medications for the large population that we serve.

We always have to balance risk and benefits, but I see that as a balance and weighing in terms of wording [ph] type of trials and trying to make them better. Thank you.

DR. LEWIS: Thank you, Dr. Merz.

Dr. O'Connor.

DR. O'CONNOR: Chris O'Connor. I voted yes, and in doing so I considered the totality of information presented by the investigators and in the briefing document, including the RALES trial and the reduced ejection fraction patients. I think the investigators provided compelling evidence, with or without the Georgia/Russia cohort included, on the efficacy signal, on heart failure hospitalization reduction, and I think this is the augmented sweet spot of this data set. Thank you.

DR. LEWIS: Thank you, Dr. O'Connor.

Dr. Ridker?

DR. RIDKER: Yes. Paul Ridker. I voted to abstain, and I want to explain why. I actually had

to look up the formal definition of abstain, not the one about not doing something you enjoy, the other definition, which was formerly declining to vote, and I want to be very clear about why. Like many of you, I am very concerned about the precedent of dropping half the data. I think that would be wrong. Even though in this case I believe half the data is wrong, I just don't like the precedent that it would set.

As I said earlier, as I was trying to convince myself of the middle ground, I think I would be very comfortable with the secondary endpoint of HHF among people with mild and reduced, but the problem is we never saw that data today. We saw a lot of discussion about why we should be suspect of the Russia data, but I have a feeling the data that I'm looking for exists, and that there probably is a combination of the RALES and TOPCAT data stratified by ejection fraction. And if it doesn't formerly exist, it probably could easily be put together.

So for those of you who actually vote, it

says on the instructions, "yes, no, uncertain" but the voting is actually yes, no, abstain. And I would actually be in the uncertain group saying, "If that other data was made available and presented, I probably could be persuaded into a yes."

DR. LEWIS: Thank you, Dr. Ridker.

Dr. Moliterno?

DR. MOLITERNO: Yes. Thank you, Dr. Lewis.

I have to say again, thanks to all my colleagues. I enjoyed today tremendously, even more than yesterday, by the way, just because this one did take more challenge. I thought the vote was actually going to be closer personally, and I was moved by Dr. Ridker saying he felt torn earlier.

Having said that, I had to ask myself what was sufficient evidence and what was any indication, and the disagreement I had was I don't think our decision, or the FDA's decision here, asked to set a precedence. We all strive for consistency for sure, but I don't think we have to

set a precedence.

Like Dr. O'Connor, I tried to look at the totality of information, and I agree there is some evidence, and I agree that it's probably sufficient evidence. You could be a purist, but I do think, like Dr. Bairey Merz says, there is some indication, and that would probably be for the reduction in heart failure hospitalizations. Thank you.

DR. LEWIS: Thank you.

Dr. Nissen?

DR. NISSEN: I voted no, which probably won't surprise anybody from my comments earlier, and I want to make sure I'm very clear about why. I do think when we make decisions, it sets precedence, and I just would point out to my colleagues that if the pharmaceutical industry came to us with a study like this and said, "We did this study, and the p-value was 0.14, but we think a bunch of our sites weren't very good, so we're going to throw those sites out, and we're just going to look at the data on the sites that we

like," the FDA would not have even brought that before us.

I cannot hold other sponsors, including our own government, to a different standard than I would have had, over the last 20 years in FDA panels, for industry-sponsored studies. The primary endpoint here failed by a significant margin. The study was marginally powered in the first place. The large amount of missingness is very troubling, particularly when it is different in the two regions that we're trying to consider differently here. It raises the rather ominous question of informative censoring, which I don't think we have ruled out.

Now, several people have articulated that, "Well, we can look at the lower EF group," and you will recall yesterday that there was a very strong p-value for people whose EFs were below the median. Here, the interaction p-value here is 0.08; it's not significant. So by definition, at least using the standards that were applied in this trial, there is no heterogeneity based upon ejection

fraction.

In the end of the day, poor study conduct cannot be an excuse for a result that we don't like. We'd all love to have a cheap generic, widely available drug. This is a drug that is not without adverse effects. You are all aware of the Gerling paper from Canada showing what happened after some of the early spironolactone trials that showed a big increase in hospitalizations and emergency department visits for hyperkalemia and other adverse effects.

So I'm worried about letting the genie out of the bottle. I'm worried about setting a precedent that we are allowed to use the data we like and throw out the data that we don't like. I like the idea of having the uniform approach to how we review clinical trials regardless of who the sponsor is; that good science is good science. It doesn't matter who pays for the science. What matters is the quality of the data.

A final point is a lot of information was given about how in Europe they used history of

hospitalization rather than BNP as the deciding factor in whether you got into the trial or not, and we learned from the investigators, interestingly, that a lot of the sites in Europe didn't have BNP measurements available to them. Well, you know, the investigators chose those sites, and they knew exactly what they were getting into. And if they didn't have BNP, and if BNP was that important, than those sites shouldn't have been in the trial in the first place.

So for all of those reasons, I don't want to go there. I have the greatest respect for Drs. Pitt and Pfeffer, enormous respect, but I disagree. I don't think this would be a good regulatory decision, and I hope FDA doesn't go there.

DR. LEWIS: Thank you, Dr. Nissen.

So I share many of the views that Dr. Nissen just expressed. I was very torn. I almost did abstain. I do almost feel like this is an orphan disease presentation. It is obviously not an orphan disease; unfortunately, it's way too

prevalent, but there is no acceptable therapy for it. I really would love to believe that this cheap generic drug, done by wonderful colleagues of ours and the NIH, which I greatly respect, and supported by the FDA with Dr. Rose, all those things definitely were influencing me. But when I thought with my head more than my heart, I'm very concerned.

We highlighted certain aspects of this trial that showed it was not well monitored and not well conducted, but we don't know what we don't know. I mean, there may be other aspects. When you see this kind of egregious -- and I guess, Dr. Pfeffer said cancerous -- problem with the trial, there may be more problems that were just not uncovered or not apparent.

So I feel also cherry-picking one of the outcomes made me uncomfortable, an extremely important one, to keep people out of the hospital with heart failure. I think all of those things, they're just too many. As was the case for me yesterday, they're just too many exceptions to have

to make to get where my heart says would be a great place for us to go, but I can't say that my head thinks that this is a mixed, assembled body of data to do so.

I'll stop there, and I'll go to Dr. Emerson.

DR. EMERSON: This is Scott Emerson. I voted no. I did this despite the fact that I pointed out the analyses, that had they been prespecified, I would have found quite compelling. And in hindsight, had I been confronted at the time with the differential in the event rates, I certainly would have rewritten my statistical analysis plan immediately to say we'll stratify on this and I am cognizant of the difficulties in the communication between the DSMB and the investigator, some of which, in my experience, has been exacerbated by NHLBI policy, but that's ok.

But I was left at the end of the day with, if the investigators had come to me with the analysis that, a priori, made sense, I would have been far more accepting of this idea. But instead they came to me with also a zillion other analyses

that just do not meet scientific rigor at all. So now we're into this world of I can't act on that because I don't know, again, how many other things I would have seen in other situations.

So some of this is that it's got to be a well-conducted trial, so there were some problems with it, as Steve pointed out. So I'll sign on to all of Steve's opinions, and then just add in those other comments of my own. And I'll come back to some of them in question 3 and 4, but also noting that there's nothing really stopping this drug being prescribed to this patient population right now.

DR. LEWIS: Thank you, Dr. Emerson.

Dr. Gibson?

DR. GIBSON: Based upon the totality of evidence, I found the potential benefits outweigh the potential harms of the drug, the drug which has been in use for nearly 60 years. I did find that the data met the regulatory bar, being compelling, for the secondary endpoint as cumulative heart failure hospitalizations and in those with an EF

less than 56 percent. An interaction of a p of 0.08 is not persuasive in my mind to reject heterogeneity by EF, as it's so underpowered. My decision was based upon analyses that do not exclude half the patients. They include all the patients. Thank you.

DR. LEWIS: Thank you, Dr. Gibson.

Dr. Kasper?

DR. KASPER: Yes. This is Dr. Ed Kasper. I voted yes, and this I found to be a very difficult decision. I wanted to thank everyone for two incredibly interesting days. In fact, I would go so far as to say that these were two of the most interesting days I've had in the last six months. I'm very sympathetic and I find Drs. Rose, Pitt, and Pfeffer very persuasive. I also find Dr. Nissen very persuasive as well in that we certainly don't want to be setting any bad precedence here.

If there's any reason that I'm on this committee, it's because somebody thinks that I'm a thoughtful clinician, and when I put my clinician

hat on as I went into the room, I realized that I use this drug in this patient population already. So somehow I've become convinced that this drug worked, so I voted yes.

Now, after discussion of all this, if the FDA decided that there really wasn't an indication here, or that there were reasons above and beyond that where they just didn't want to go for regulatory reasons, I would be perfectly satisfied with that. My suspicion is that when the next iteration of the ACHA guidelines come out on this, and I was part of the 2013 guidelines, this will probably move from a 2B to a 2A. It's certainly not going to go to a 1. Let's put it that way. Thanks. That's it.

DR. LEWIS: Thank you, Dr. Kasper.

Ms. Chauhan?

MS. CHAUHAN: Thank you. Cynthia Chauhan.

To Dr. Kasper's point about the drug is already in use, I think that makes an important argument for this drug being approved so that the use can be monitored and physicians can be really

strongly reminded that they must, must look at potassium and the other one I'm not thinking right now.

But I want to say, we all want good trials. I enter trials all the time with the expectation and understanding that they are ethical and well conducted. We want trials where the data holds up, but we must be willing to investigate and reconsider it when it does not hold up and to support and never supplant good patient care.

These have been two very interesting days, and my learning from these two days is not in an area that I expected. It's that there's confusion about the diagnostic category of what is now called heart failure mid-range ejection fraction by putting that in with HFpEF, and that affects trial development and interpretation. The approach to including this group in HFpEF may be negatively affecting interpretation and its making. So I think it's really important that we're pulling this mid-range group out into a separate category and not lumping it with HFpEF.

Thank you, and thank you for the opportunity. I appreciate the ethical standards of the FDA. I appreciate the passion and standards of the people who conducted this trial. Thank you.

DR. LEWIS: Thank you, Ms. Chauhan.

Dr. Cook?

DR. COOK: Thomas Cook. I voted no, but it was a really close call. I very nearly abstained, and I very nearly clicked yes. In the end I voted no because none of the results that I saw were terribly compelling. The confidence intervals barely missed 1 for almost everything that I really looked seriously at, and I was concerned about the overall scientific rigor of the conduct of the study. I think we would be better served by doing at least one more study beyond this one before I would support approval for indication. That's all for me.

DR. LEWIS: Thank you, Dr. Cook.

Well, I will then attempt to summarize. I think that recognizing the unmet need and the positive effects on decreasing a very important

outcome, to be patient hospitalization for heart failure, many people voted yes. They were also influenced by the fact that this drug may already be in use. There certainly was a discussion, and I think almost a clear recommendation, for the FDA to do an analysis similar to what was done with PARADIGM and PARAGON, using RALES and TOPCAT.

I think that those who voted no have concern about both setting a precedent but also having a different set of standards for the quality of the data we would accept coming from pharma and coming from the NIH, and that is something that we shouldn't probably let influence us because our job is to look at it from wherever it comes from by a set of standards.

I think there were some general comments about the totality of the data. I think Dr. Kasper said that he felt it would not become a 1 indication with the heart society but a 2A. I think he actually had some concerns about how this will be viewed in this community.

I think that summarizes it, and we will now

move on to question 3. If an indication for spironolactone were not granted on the basis of available information, what would be necessary to augment the support for approval?

Are there any questions about the wording of the question itself for the FDA?

(No response.)

DR. LEWIS: I don't see anyone's hands up, so if there are no questions or comments concerning the wording of the question, we will now open the question for discussion.

(No response.)

DR. LEWIS: And I don't see any hands up yet, but I will just reiterate the comment that I just made, that you could augment your support for approval by using data from RALES perhaps.

I believe, Dr. Nissen, you were first, but I'm not sure. Go ahead, Dr. Nissen.

DR. NISSEN: Okay. Thank you, Julia.

First of all, I do think it's worth studying, and while I recognize that the federal agency here, NIH, doesn't have an unlimited amount

of money, I do think that there's enough information here to warrant doing the study. That study can be well focused because there at least are some prior expectations about what it should look for, to look at heart failure hospitalization; try to run the study with high quality; and enroll the right patients.

We're now in a modern era where NT-proBNP is available from almost every center that might be included, and there might be greater enthusiasm for doing this study now, that there is at least -- I would consider the data that we have in front of us from TOPCAT to be pilot data, to be preliminary data that suggests that there's possibly an effect that can be then confirmed with a follow-on study, and I think it would be worth the investment. Not everything that NHLBI is invested has worked out well. This is one where the chances of a positive study are high, and if conducted with high quality, could be done in a very efficient fashion.

DR. LEWIS: Thank you, Dr. Nissen.

Dr. O'Connor?

DR. O'CONNOR: Thank you, Julia.

Chris O'Connor. I would say that by combining, as you did, the RALES data set with the TOPCAT data set, we could get a clearer understanding of the spectrum of efficacy across the ejection fraction and better understand if the EF range between 45 to 55 is really the augmented sweet spot.

I'd also say that there is an ongoing trial. I don't know when it will end. I understand there are recruitment problems. It's a registry randomized trial being conducted out of Sweden of spironolactone in HFpEF. I think NHLBI is involved, and it's a 3,000-patient trial with clinical outcomes. So that could augment this application. Thank you.

DR. LEWIS: Thank you, Dr. O'Connor.

Dr. Emerson?

DR. EMERSON: I won't reiterate things that were just said because I agree with them, but I will just state that some guidance could get through some more careful analysis of the data

that's at hand, but I don't really think it would stand entirely on its own. But it may help the agency understand the repercussions if, as I would hope, they redefine what is HFrEF, to be a slightly higher ejection fraction, and what the implications would be for this indication as well.

DR. LEWIS: Thank you, Dr. Emerson.

Ms. Chauhan?

MS. CHAUHAN: Thank you. Cynthia Chauhan, patient representative. Since this drug is now being used off label, we have an obligation to study the drug to either support its use with appropriate monitoring or designate its use inappropriate. We cannot let the patient population possibly be abused or we need to support them, potentially being supported, in dealing with their disease. Thank you.

DR. LEWIS: Thank you, Ms. Chauhan.

Dr. Gibson?

DR. GIBSON: I agree with integrating the RALES data. That would be a great idea. And if another study was undertaken, obviously it would be

great to focus on those with mildly reduced EF, looking at total hospitalizations. But as I said yesterday, consideration could be given to a win ratio so that those patients who did not sustain events could be compared with age, and sex match people on a continuous variable, either BNP, New York Heart Association, or some other variable like that. Thank you.

DR. LEWIS: Thank you, Dr. Gibson.

Dr. Thadhani?

DR. THADHANI: Thank you, Dr. Lewis.

We were told, of course, and warned about the side effects of this agent, namely elevated creatinine and potassium. This was evident to us, it was made clear to us, and appropriate precautions have to be addressed.

As far as risk-benefit, if the agency believes there is a benefit, obviously the question is does the risk outweigh the benefit? And given that my guess would be 30 to 40 percent, at least, of the patients with this condition that have some form of chronic kidney disease, the risk-benefit

ratio would have to be looked at very carefully, if especially there are alternatives for this population. Thank you.

DR. LEWIS: Thank you, Dr. Thadhani.

Ms. Alikhaani?

MS. ALIKHAANI: Yes. Jacqueline Alikhaani, consumer representative. I would really like to see a new trial, a new and better trial addressing all of the shortcomings that we've discussed today, and also a better trial monitoring planning so that we can best protect the data integrity for all of the data, and also more ethnic diversity in a new trial. Thank you.

DR. LEWIS: Thank you.

If those of you who don't have another comment could lower your hands. Dr. Nissen, your hand is up. Dr. Emerson, your hand is up. There it goes. Dr. Emerson, your hand is up, and --

DR. EMERSON: And I still have another comment.

DR. LEWIS: -- Ms. -- oh, good. Thank you, Dr. Emerson. Go ahead.

DR. EMERSON: I just wanted to acknowledge the statements that I made. Of course, my major contribution to public health is that I don't treat patients. That having been said, when I was saying that this drug could be given, it's a diuretic, and in HFpEF, my understanding is that's an avenue of treatment that you'd have.

So that was a major element, that I was saying that you wouldn't be running up against payers ever saying what's your indication for this drug, as opposed to a brand new drug that comes with a narrow indication, that you could really run into the payers doing it. I would welcome being corrected by those cardiologists who do in fact earn a living based on their knowledge.

The other aspect that I just will note is that the sad fact of life is, is this an orphan drug? Well, it's telling that nobody who makes this generic drug wanted to go through the trouble of signing on to this idea. You won't have the marketers. You just will not have the marketers coming in and telling you -- on the other hand, I

don't know if anybody looked at the press release from Novartis yesterday, but my impression of the meeting that went down yesterday is very different than what Novartis' impression was in their press release. So that's what you're up against.

DR. LEWIS: Thank you, Dr. Emerson.

Does anyone else have a comment? Oh, I'm sorry.

Dr. Ridker?

DR. RIDKER: Yes. I actually just wanted to, more or less, put in the record something very similar today to what I said yesterday about my fundamental beliefs, and I think we've really learned this over the last two days. I just want to underscore, again, this fundamental importance of why we do randomized, double-blind, placebo-controlled trials.

I think we've seen over the last two days extraordinarily sophisticated thoughts, tremendous care by both the presenters and the commentators, and also, frankly, our FDA colleagues having some flexibility and openness about how they think about

trial data, all, from my perspective, in the context of we need to be very, very careful and, from my perspective, pushback fairly hard against those who want us to be shifting into observational data.

I just don't think the kinds of effects we saw and we're talking about here today and the kind of nuance we're talking about here today could ever come from that direction. And I just want us to be clear, again, that I think this has been an excellent example of why it's so important that we do these studies, try to make them cost-effective, and try to monitor them appropriately and, again, thank the FDA, actually, for holding these two-day meetings at all. I think it's the right thing to do.

DR. LEWIS: Thank you, Dr. Ridker, and I agree with you completely that randomized, double-blind trials are what we need to have confidence to recommend any drug. There's no such thing as a completely safe drug. Also, asking patients just to swallow one more pill and pay for

one more pill is a burden if it is of their benefit. So I echo your sentiment strongly.

We now move on to our last and fourth discussion question. If spironolactone warranted an indication, how would you describe the patients in whom such benefit applies?

Are there any questions for the FDA about the wording of this question?

(No response.)

DR. LEWIS: Okay. Then if there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

Dr. Emerson? Oh, I'm sorry. Can I pause for a second? I forgot to summarize what we all just said, and I apologize for that.

I think for discussion question number 3 for the FDA, I think it was certainly the suggestion that you look at the continuous data from RALES through TOPCAT. Dr. Emerson certainly thought that maybe there could be some more careful analysis of the current data. Looking at it in the ranges of

different left ventricular ejection fractions was also suggested, and concern about the side effects, which I share, about increased serum creatinine and potassium and being taken care of and advising those precautions, particularly for patients who are at great risks who have chronic kidney disease.

There was also certainly enthusiasm for learning from this study, and from what the study showed, to go ahead and design another study that would make good use of the data that we heard today, and I apologize.

Go ahead, Dr. Emerson --

DR. EMERSON: My only comment is --

DR. LEWIS: -- for discussion --

DR. EMERSON: This is Scott Emerson, and my only comment is that careful thought needs to be given; that some of the evidence is coming from the existing indication of spironolactone, and that in TOPCAT, certainly there was the suggestion that the effect was larger in the lower ejection fraction. So my best guess would be that the patient population that you would look at would be those

with below normal ejection fraction.

DR. LEWIS: Look at them for safety. Is that what you said, Dr. Emerson?

DR. EMERSON: No, for the indication, for the indication.

DR. LEWIS: Oh, for the indication.

DR. EMERSON: Yes. They already use spironolactone just as a diuretic. The indication is are we helping the heart failure hospitalizations and possibly cardiovascular mortality? But the composite endpoint certainly looks strongest in the subgroup with lower ejection fraction, and certainly if you were going to go with taking this data and going ahead and making an indication, I certainly think it should be limited to that group arguing borrowing from RALES and also what this data showed.

DR. LEWIS: Thank you.

Dr. O'Connor?

DR. O'CONNOR: Chris O'Connor, and I would articulate the indication and agree with Dr. Emerson, Ridker, Bairey Merz, and Moliterno,

that spironolactone would be indicated for the treatment of heart failure with mildly reduced ejection fraction, defined as EF between 45 and 55, for the reduction of heart failure hospitalization. This is based on the totality of data presented today, the RALES data, the entire briefing document, and what's in the literature, which I must admit I may have an advantage as a heart failure clinical trialist and editor of JACC: Heart Failure. Thank you.

DR. LEWIS: Thank you.

Dr. Merz?

DR. BAIREY MERZ: Noel Bairey Merz. I completely agree with that. I would simply modify it to extend up to 57 for women or 57 for everyone, for the reasons stated yesterday.

DR. LEWIS: Thank you.

Ms. Chauhan?

MS. CHAUHAN: Cynthia Chauhan, patient representative. I agree with what's been said and, once again, I think this really calls us to look at removing heart failure with mid-range ejection

fraction from heart failure with preserved ejection fraction, and making it its own very distinct diagnostic category. Thank you.

DR. LEWIS: Thank you, Ms. Chauhan.

Dr. O'Connor, do you have another comment for this discussion question or is your hand still up.

(No response.)

DR. LEWIS: Okay. Great.

So I will summarize this fourth question. I think the summary is that the group to which it would apply would be the group with ejection fraction. I think it's varied amongst the different speakers, but somewhere in the area of 40 to 45 to 55 to 57 for the indication of reducing hospitalization for heart failure primarily, although Dr. Emerson once again noted that there may be a benefit on CV death.

It was also, I think, well pointed out, and I think it's been mentioned several times, that the term "HFpEF" implying that these benefits may extend to truly normal ejection fraction would be a

mistake, and that definitely either a new name, "mid-range, mildly reduced" or a specific numerical range, as I mentioned, would be the population to which we would recommend application.

If there are no more questions, before we adjourn, are there any last comments from the FDA? I will say that I've lost Joyce Yu in even my chat, so I hope she doesn't have anything she needs to tell me. But are there any comments from the FDA?

Dr. Stockbridge?

DR. STOCKBRIDGE: Yes. This is Norman Stockbridge, and I want to express my great appreciation to the committee for a second day of a terrific set of discussions. I think this has raised some issues we hadn't really thought much about that we'll have to delve into before we do anything, if we're going to. So it's great. It's been a very rich experience, and I'm grateful to everybody who's participated in it today.

DR. LEWIS: Thank you.

Any other comments from the FDA?

(No response.)

Adjournment

DR. LEWIS: If not, I will share my thanks to our presenters today, and to the entire committee, and to the FDA for bringing us very interesting topics to discuss. I think we've all appreciated having the opportunity to think about these things the last few days and hopefully make some contribution to helping you.

We will now adjourn the meeting; two for two, adjourning a bit early. Thank you all again.

(Whereupon, at 1:37 p.m., the meeting was adjourned.)