FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE (CRDAC) MEETING

Virtual Meeting

Tuesday, December 15, 2020

9:01 a.m. to 4:09 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

Charu Gandotra, MD

Clinical Reviewer

DCN, OCHEN, OND, CDER, FDA

Jennifer Clark, PhD

Statistical Reviewer

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

(9:01 a.m.)

Call to Order

DR. LEWIS: Good morning and welcome. I would like to first remind everyone to please mute your line when you are not speaking. 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 this meeting. I will now call the December 15, 2020 meeting of the Cardiovascular and Renal Drugs Advisory Committee to order. Dr. Joyce Yu is the designated federal officer for this meeting and will begin with introductions.

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.

Ms. Alikhaani?

(No response.)

DR. YU: Ms. Alikhaani, could you please

unmute yourself? You may be muted on the platform.

MS. ALIKHAANI: Good morning. This is Jacqueline Alikhaani. I'm from Los Angeles, and I'm a heart patient, heart survivor, and citizen scientist. I'm a long-time volunteer with the American Heart Association, and I serve as an ambassador for PCORI, the Patient-Centered Outcomes Research Institute.

DR. YU: Thank you.

Dr. Bairey Merz?

DR. BAIREY MERZ: Good morning. Noel Bairey Merz. I am a clinical cardiologist and physician scientist at the Cedars-Sinai Medical Center's Smidt Heart Institute. I have a specific interest in heart failure with preserved ejection fraction, investigationally. Thank you.

DR. YU: Thank you.

Dr. Cook?

DR. COOK: This is Thomas Cook. I'm in the Department of Biostatistics and Medical Informatics at the University of Wisconsin-Madison. Thank you.

DR. YU: Thank you.

Dr. Gibson?

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

DR. YU: Thanks.

Dr. Kasper?

DR. KASPER: Good morning. My name is Ed Kasper. I'm a cardiologist with an interest in heart failure at Johns Hopkins.

DR. YU: Thanks.

Dr. Lewis?

DR. LEWIS: Julie Lewis. I am a nephrologist at Vanderbilt.

DR. YU: Great.

Dr. Moliterno?

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

DR. YU: Thanks.

Dr. Ridker?

DR. RIDKER: Yes. Good morning. I'm a

professor at Harvard Medical School, cardiologist at the Brigham and Women's Hospital, and happy to join today.

DR. YU: Thanks.

Dr. Thadhani?

DR. THADHANI: Good morning. Ravi Thadhani, chief academic officer at Mass General Brigham and nephrologist, and professor at Harvard as well. Thank you.

DR. YU: Ms. Chauhan?

MS. CHAUHAN: Good morning. I'm Cynthia Chauhan. I'm a heart failure with preserved ejection fraction patient with multiple comorbidities, including stage 4 kidney failure and pulmonary -- I forgot the word. Anyhow, I'm the patient representative, and I am in Wichita, Kansas.

DR. LEWIS: Thank you.

Dr. Emerson?

DR. EMERSON: Scott Emerson. I'm a professor emeritus of biostatistics at the University of Washington in Seattle.

DR. YU: Thanks.

Dr. Nissen?

DR. NISSEN: It's Steven Nissen, and I'm a cardiologist at the Cleveland Clinic.

DR. YU: Thank you, Dr. Nissen.

Dr. O'Connor?

(No response.)

DR. YU: Dr. O'Connor, you may be muted on the platform.

(No response.)

DR. YU: Dr. O'Connor, could you unmute your platform phone?

DR. LEWIS: It's the upper left-hand side.

DR. O'CONNOR: This is Dr. O'Connor. Can you hear me?

DR. YU: Yes.

DR. LEWIS: Yes.

DR. O'CONNOR: President of the Inova Heart and Vascular Institute and heart failure cardiologist.

DR. YU: Great. Thank you so much.

And Dr. Rossert?

DR. ROSSERT: Good morning. I'm Jim Rossert, a nephrologist and drug developer working at AstraZeneca.

DR. YU: Now we'll introduce our FDA participants.

Dr. Unger?

DR. UNGER: Good morning. I'm Ellis Unger. 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: Good morning. I'm Norman Stockbridge. I'm the director of the Division of Cardiology and Nephrology.

DR. YU: Dr. Thompson?

DR. THOMPSON: Good morning. My name is Aliza Thompson, and I'm the deputy director of the Division of Cardiology and Nephrology.

DR. YU: Thank you.

Dr. Southworth?

DR. SOUTHWORTH: Hi. This is Mary Ross Southworth. I'm the deputy director for safety in

the Division of Cardiology and Nephrology.

DR. YU: Dr. Gandotra?

DR. GANDOTRA: Good morning. I'm Charu Gandotra, clinical reviewer from the Division of Cardiology and Nephrology.

DR. YU: And Dr. Clark?

DR. CLARK: Good morning. I'm Jennifer Clark, a statistical reviewer in the Office of Biostatistics.

DR. YU: Thank you. I'll now turn it back over to Dr. Lewis.

DR. LEWIS: Thank you, Joyce.

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 or lunch. 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 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 supplemental new drug application, sNDA, 207620-S18, for the angiotensin receptor neprilysin inhibitor, Entresto, sacubitril and valsartan, tablets, submitted by Novartis Pharmaceuticals Corporation, for the proposed indication of heart failure with preserved ejection fraction.

This is a particular matters meeting during

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

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

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a

personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have with the firm at issue. 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. Thank you.

Good morning. My thanks to the committee members for their input on today's topic. I wanted to take a few minutes and make sure that you on the committee understand what flexibility you have in addressing this application. The study in question did not reject its primary null hypothesis, which was planned with an alpha level of 0.05. Nevertheless, the division strongly recommended

that the sponsor submit the application, and it contributed some recommendations for support of analyses.

You need to know that the idea of dichotomizing success of studies by p-value being less than or greater than 0.05 has no basis in law, either national or federal, or in regulations, and it is barely mentioned in guidance. The legal language refers to information that experts would find compelling.

Standards applied to rare diseases are clearly not the same as being applied to common diseases, but even among common cardiovascular diseases, the division has, with this committee's endorsement, approved several supplements on the basis of studies that did not reject the null hypotheses of their primary endpoints. These include enalapril for asymptomatic left ventricular dysfunction on the basis of the SOLVD prevention study, digoxin for heart failure in the DIG study, and carvedilol post-MI in the CAPRICORN study.

These historical cases are different from

one another and from the cases that you will consider today and tomorrow, which emphasizes the flexibility that you have here. Factors that I considered in encouraging this submission include the similarity of investigator-reported and adjudicated results. This suggested that there were events that did not need all evidentiary criteria as qualified events, but likely were nonetheless. This is an example of dichotomization of events being wasteful of information.

We recommended a blinded readjudication of investigator identified events previously rejected by the first adjudication process. In this second adjudication, the process gave some credit to incompletely documented cases, and this partial credit was incorporated in the analysis.

Subgroup analyses are always treacherous, maybe particularly so when the study does not reject its primary null hypothesis. Nonetheless, this drug has an incontrovertible effect in patients with some degree of reduced ejection fraction; and it is in the lower part of the

ejection fraction's spectrum in patients who most resembled those in the approved indication, where their treatment effect was seen in this study. This suggest that we simply do not have a useful taxonomy of the heart failure syndrome.

In summary, I would say that if this study were the sole basis for approval of a new drug, I don't believe we would be here today. I believe the case is interesting largely because you can perceive its findings as being pertinent to a population that is quite similar to the current indication, and I look forward to your discussion on this topic. Thank you.

DR. LEWIS: Thank you, Dr. Stockbridge.

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

For this reason, FDA encourages all participants, including Novartis Pharmaceuticals'

non-employee presenters, to advise the committee of any financial relationships they may have with the sponsor such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

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

We will now proceed with presentations from Novartis Pharmaceuticals Corporation.

Applicant Presentation - David Soergel

DR. SOERGEL: Thank you, Dr. Lewis, thank you, members of the committee, and Dr. Stockbridge. My name is David Soergel. I'm a pediatric heart failure and transplant cardiologist, and I lead Cardiovascular, Renal and Metabolism Drug Development at Novartis.

Today, we'll talk about heart failure with preserved ejection fraction, or HFpEF, and whether Entresto could be an option for these patients who currently don't have an approved treatment. The discussion will center on PARAGON-HF, the largest and only active controlled phase 3 clinical trial in HFpEF. Since PARAGON was designed in 2014, our understanding of HFpEF has advanced, and PARAGON moves the field even farther forward. We should consider these learnings in light of the PARAGON results.

When we first saw the data from PARAGON, the path appeared challenging since we narrowly missed the statistical significance on the primary endpoint. However, after fully evaluating the data, it was apparent that there was a true, albeit modest, treatment effect of Entresto on an important clinical outcome, hospitalization for heart failure.

The consistency of the primary endpoint with the other study endpoints and analyses further supported that the beneficial effect exhibited by

the primary was real. Further analyses showed us that individuals with lower ejection fraction and women seem to respond better to Entresto. The greater efficacy in patients with lower EF has also been seen in other trials with medicines in HFpEF.

In addition to PARAGON, evidence of Entresto's effects from other trials increased our confidence in the results from PARAGON. Chief amongst these trials is PARADIGM, which confirmed Entresto's efficacy in the adjacent patient population of heart failure with reduced ejection fraction or HFrEF.

Since Entresto's approval for HFrEF in 2015, millions of patients have been treated with Entresto. The favorable safety and tolerability profile of Entresto in HFpEF is consistent with its extensive experience with Entresto and with other agents in the RAS inhibitor class. We've had very constructive discussions with the FDA, and now we are here to seek your perspective on this totality of evidence in support of extending Entresto's use to patients with HFpEF.

Before we move to the presentations, I'd like to touch briefly on some terminology and background on heart failure and HFpEF. Heart failure occurs when the heart fails to deliver enough blood and oxygen to the peripheral tissues. Broadly speaking, two types of heart failure have been classified by the pumping ability of the left ventricle measured as the ejection fraction.

The term "HFrEF" describes patients whose hearts have markedly reduced pumping function, while the term "HFpEF" refers to everyone else, including patients with some degree of ventricular systolic and/or diastolic dysfunction.

Thus, compared to HFrEF, HFpEF patients have more varied etiologies, clinical courses, and responses to therapy. Better understanding this heterogeneity is an active area of clinical research. In fact, this research has led to the characterization of a third type of heart failure that overlaps HFrEF and HFpEF called heart failure with mildly reduced EF or mrEF.

HFpEF affects 3.25 million patients in the

U.S. or about 50 percent of patients diagnosed with heart failure. Like HFrEF, HFpEF is a serious and debilitating disease that leads to recurrent hospitalizations for worsening symptoms and substantially reduces quality of life.

A major goal of treatment is to reduce the frequency of hospitalization. Unfortunately, we have not been very successful. In fact, the proportion of patients hospitalized with HFpEF is growing and readmission is a major issue with about 40 percent of patients readmitted within one year of an initial hospitalization. Yet, despite this clear unmet need, there is no approved treatment for HFpEF.

Entresto is a unique salt complex of two active ingredients, valsartan, an angiotensin receptor blocker, and sacubitril, an inhibitor of the enzyme neprilysin. The combined actions of these two components result in beneficial effects on cardiac structure and heart failure pathophysiology. Entresto was approved in 2015 for HFrEF after PARADIGM-HF showed that Entresto

significantly reduced heart failure hospitalizations and cardiac deaths. Entresto is now registered in 115 countries, and exposure exceeds 2.6 million patient-years globally.

This slide shows the timeline of the registration program for Entresto and HFpEF. We worked closely with FDA on the design of PARAGON, agreeing to both the study endpoints and on the statistical approach. Our decision to conduct PARAGON was underpinned by the positive phase 2 results from PARAMOUNT and HFpEF and the overwhelming efficacy in HFrEF seen in PARADIGM.

At the time it was designed, PARAGON was an innovative trial, and many of these innovations have been extended into contemporary HFpEF studies. For example, instead of the traditional time-to-first-event analysis, PARAGON's primary endpoint included total hospitalizations.

This approach better reflects the clinical burden of hospitalization in HFpEF. The trial also included a variety of important secondary and prespecified exploratory analyses, like urgent

heart failure visits and effects on renal function.

We've had several engagements with the FDA to discuss the data and to evaluate the next steps for Entresto in HFpEF. These discussions led the FDA to recommend that we submit additional analyses to better understand the totality of the data to see whether the evidentiary standard could be met. We were then encouraged to submit the supplemental new drug application.

Today's presentation will focus on three trials, PARAGON, PARAMOUNT, and PARADIGM, which are the basis of Entresto's registration program in HFpEF. Beyond the registration program, there are many other clinical trials that have studied the aspects of Entresto's pharmacology and clinical effects.

Based on our view of the data, we propose an update to Entresto's indication statement that reflects the benefits seen in patients with HFpEF with lower than normal ejection fraction. The term "below normal" captures both within patient and between sex variation in the normal EF range, while

at the same time extends the treatable population beyond the adjacent HFrEF population. While this is where our deliberations have led us, we're certainly open to alternative approaches.

In summary, there is a substantial unmet medical need for a therapy for HFpEF patients, especially one that can reduce hospitalization events. Our interpretation is that evidence from PARADIGM, from PARAMOUNT, and from the adjacent HFrEF population in PARADIGM, supports a beneficial treatment effect of Entresto in patients with HFpEF, especially those with lower than normal ejection fraction.

Following its approval for the treatment of HFrEF, Entresto has been prescribed to millions of patients, and the favorable safety profile was recapitulated in HFpEF patients in PARAGON. Based on the synthesis of the data, the benefit-risk is favorable to extend the use of Entresto to patients with HFpEF with lower than normal ejection fraction.

Today we'll hear presentations on the unmet

need in HFpEF and the clinical context from Professor John McMurray from the University of Glasgow. Professor Scott Solomon from Brigham and Women's Hospital in Boston will present the PARAGON efficacy and safety data in detail. Professors McMurray and Solomon are recognized experts in the fields of heart failure and clinical trials.

In addition, Dr. Brian Claggett from Brigham and Women's Hospital also played a key role in PARAGON and attends as an expert in biostatistics. Drs. Akshay Desai and Michael Felker from the adjudication committees and several Novartis representatives are also here to address your questions.

Thank you very much for your engagement today, and we look forward to the discussion and to your questions.

Professor McMurray?

(No response.)

DR. NISSEN: John, I think you're muted. This is Steve Nissen.

DR. McMURRAY: Sorry, Steve.

Applicant Presentation - John McMurray

DR. McMURRAY: Good morning, Dr. Lewis, ladies and gentlemen, and panel members. As you can see, my name is John McMurray from the University of Glasgow in the United Kingdom. My disclosures are that I do many trials with different pharmaceutical companies, and my employer is paid by the sponsor of the studies for my participation in the clinical trials. I'm also the co-principal investigator of the PARAGON Heart Failure trial.

In this presentation, I would like to describe the clinical problem that we're here to discuss today, and this is an outline of what I want to talk about. I want to start by describing what heart failure is. I apologize. I realize many members of the committee are very familiar, indeed, with heart failure, but for those who aren't, heart failure is a clinical syndrome. In other words, it's a constellation of signs and symptoms caused by a variety of underlying cardiac problems that leads to heart dysfunction, and in

the developed world today, this is usually a problem with the heart muscle.

Heart failure is very common, affecting 1 to 2 percent of the population but a much larger proportion of older people. If you've reached the age of 40, you've got about a 1 in 5 lifetime risk of developing this syndrome of heart failure.

We think it's very important not just because it's common but because it's extremely disabling for patients who are afflicted by it. It causes a greater reduction in quality of life than almost any other chronic medical condition. It frequently leads to emergency department attendances and high rates of hospitalization, and indeed in many countries, including the United States, it is the single most common cause of hospital admission in people over the age of 65 years of age.

As a result of that, it's extremely costly. About 1 to 2 percent of healthcare expenditure is on heart failure, and most of that is as a result of heart failure hospitalization. Some types of

heart failure are also very deadly. Some types of heart failure have mortality rates of around 50 percent by 5 years, equivalent to many common forms of cancer, although as we'll see in a few moments, the mortality rate varies very much by the type of heart failure patients have.

Crucially, heart failure is a progressive syndrome. It worsens progressively over time, symptoms, signs, rates of hospital admission, and also the development of a concomitant problem, particularly renal dysfunction, which has come a bit more center stage recently in some other trials, anemia, and atrial fibrillation, as well as other cardiac arrhythmias.

I want to say something about ejection fraction because a lot of what we will talk about today relates to this metric. Left ventricular ejection fraction is a metric describing the fraction of blood that has filled the left ventricle during diastole. It's ejected during systole when the heart contracts. For the purposes of today's discussion, it's very important that we

understand what a normal ejection fraction is, and we'll probably talk a lot about that later.

Here you see a set of international guidelines, and at the bottom of this slide, you can see the mean ejection fraction. In a man, it's typically about 62 percent. In a woman, it's slightly but significantly higher at 64 percent. You can see the range in this slide as well. Maybe of more interest, this is from the U.S. This is the most recent report from the Framingham Heart Study, and you can see the distribution of ejection fraction in the healthy population, in this case with a median value of 68 percent.

With that understanding of what ejection fraction is and what a normal ejection fraction is, I want to give a very short history of heart failure as we've come to understand it and phenotype it; and that, as you will see, is largely as a result of the clinical trials that have been carried out over the past 30 to 35 years.

If we start at the far left of this timeline, you can see with the first two very

well-known clinical trials that we carried out -- the CONSENSUS trial with enalapril and the vasodilator heart failure trial, the V-HeFT trial, with hydralazine and isosorbide dinitrate, prazosin -- at that time, patients were enrolled with the clinical syndrome of heart failure. There was no requirement to measure ejection fraction. Patients were not selected for inclusion on the basis of ejection fraction.

In fact, it wasn't until 1991 with the publication of the SOLVD treatment trial, again with enalapril, that ejection fraction came to the forefront. In fact, the first time the term "heart failure with reduced ejection fraction" was ever used in the title of a publication was with the results of the SOLVD treatment trial. Though, if we fast forward a few years, there was the DIG trial, and then came the CHARM program, which we started to design in late 1999 and published in 2003.

We decided in that program, which originally had two trials in patients with heart failure with

reduced ejection fraction, to add a third trial, and we decided that we would include the remainder of patients who would be screened and would have the clinical syndrome of heart failure but would have an ejection fraction above 40 percent.

We decided that we would study candesartan compared with placebo in those patients as well. We had to think of a name to describe patients with a syndrome of heart failure but an ejection fraction above 40 percent, and we chose to describe those patients as having heart failure with preserved ejection fraction, and really thereafter, that term has remained.

There have been, as you can see, three further large trials in heart failure with preserved ejection fraction, I-PRESERVE, TOPCAT, and the trial we're here to talk about today, PARAGON heart failure. You will also notice that in each of those three studies, the inclusion ejection fraction range was 45 percent or above. And the reason these other trials moved from 40 percent to 45 percent was because of the

imprecision around measurement of ejection fraction and the importance of being certain that the patients enrolled in these more recent studies did not include patients with heart failure and reduced ejection fraction.

But things got somewhat more complicated because just around the time that we were designing PARAGON-Heart Failure, it became I think more clear in 2016, with the publication of the European Society of Cardiology Heart Failure guidelines, people had begun to recognize that patients in the lower parts of that preserved ejection fraction range were different and that these patients might be more like those with a clearly reduced ejection fraction.

As a result, a new heart failure phenotype, heart failure with mid-range ejection fraction, was described in those 2016 guidelines, and sadly after we had already enrolled most of the patients in PARAGON-Heart Failure.

So this is where we are in 2020. To use Dr. Stockbridge's words, here is the taxonomy of

heart failure syndromes, heart failure with reduced ejection fraction, which as I mentioned was really a disease that was defined by the results of a positive clinical trial, which itself was based on an arbitrary ejection fraction cutpoint.

Then our original description of heart failure with preserved ejection fraction, which was really a description of convenience, it was a term we created to describe all of those other patients. It didn't have HFrEF, and then, as I just mentioned more recently, heart failure with mid-range ejection fraction or indeed there is not a proposal but they should be renamed again.

We described this heart failure with mildly reduced ejection fraction, and again, once more, we could probably compete [indiscernible] the arbitrary ejection fraction range used to describe heart failure with mid-range ejection fraction.

However, you will note that with the description of heart failure mid-range or mildly reduced ejection fraction, of course that is redefined heart failure with preserved ejection

fraction to non-mean, an ejection fraction above 50 percent. And strictly speaking, using today's taxonomy, the trial will discuss PARAGON-Heart Failure, really, as a trial that enrolled patients with heart failure mid-range, as well as heart failure with preserved ejection fraction.

I want to look at the characteristics and outcomes in patients in these three different ejection fraction subgroups, and some of this I think will show you why the heart failure with mid-range ejection fraction category was created because of its similarities with heart failure with reduced ejection fraction.

Here is a very large combined database of, really, all of our recent HFrEF and HFpEF clinical trials, and you can see the three ejection fraction categories and some of the key clinical characteristics. But if you look at age, you can see, as with many of the characteristics, there is a gradation from left to right, from heart failure with reduced, across three mid-ranges, to heart failure with preserved ejection fraction. Patients

with more preserved ejection fraction are older.

You will also see a striking change in the proportion of women, from 22 percent in patients with heart failure with reduced ejection fraction to 57 percent of patients with heart failure with preserved ejection fraction, with mid-range, again, somewhere in the middle. You will also see here a transition in terms of comorbidities, possibly etiological comorbidities, and hypertension much more common in preserved ejection fraction and myocardial infarction considerably more common in both reduced and mid-range ejection fraction. You see some other differences noticeably in natriuretic peptide levels, which are much lower in patients with truly preserved ejection fraction.

But I think key here is myocardial infarction. Obviously in patients with reduced ejection fraction, that's often the causal injury. It's often what leads to reduced diastolic function, and you can see clearly that this is similar in heart failure with the mid-range and reduced ejection fraction and quite different from

heart failure with preserved ejection fraction.

Again, I want to emphasize the difference between men and women. In ejection fraction, the CHARM program still remains the best place, I think, to look at this because we enrolled almost 7,600 men and women right across the spectrum of ejection fraction, and you can see this shift to the right in the ejection fraction distribution in women with heart failure compared to men with heart failure.

I also want to now describe the symptoms, signs, and clinical outcomes in these three different heart failure syndromes because you will see some interesting similarities and important differences. Of course, almost by definition, all patients with heart failure, irrespective of their ejection fraction, are limited by breathlessness on exertion.

You can see in this figure that patients with interestingly mid-range and preserved ejection fraction actually more frequently describe the worst types of breathlessness, breathlessness lying

flat and breathlessness at night. They also have more edema and more other signs of congestion in patients with heart failure and a clearly reduced ejection fraction.

When it comes to quality of life, you can see that, as I mentioned, heart failure results in a very striking reduction in quality of life. This is measured in this figure using the Kansas City Cardiomyopathy Questionnaire.

There are various summary scores in that questionnaire. I'm showing you the ones that are usually reported, the maximum scores, and hundreds of scores below 100 that equates to a reduction in quality of life. Again, you can see that quality of life is reduced in all of the different heart failure ejection fraction phenotypes but, again, at least as much in patients with heart failure mid-range and preserved ejection fraction.

Now I want to look at clinical outcomes. I'm going to start with heart failure hospitalizations. Here you can see that whether we look at first hospital admission or first and

recurrent hospital admission, there's actually very little difference between the three heart failure ejection fraction phenotypes.

That is in striking contrast to what we see in relation to mortality, where there is a much more revisit mortality rate in the three ejection fraction phenotypes, patients with reduced ejection fraction, shown by the navy blue line, having by far the highest rate of cardiovascular than all-cause mortality; patients with mid-range ejection fraction, shown in red, with an intermediate mortality rate; and in patients with heart failure and preserved ejection fractions, you can see a much lower mortality rate.

You can see that these differences are greater between ejection fraction subgroups for cardiovascular mortality than for all-cause mortality. The reason for that is because in addition to mortality being lower in patients with heart failure and preserved ejection fraction, you can see that the proportion of deaths that are due to non-cardiovascular causes is also much larger in

these individuals.

Thirty-eight percent of deaths were non-cardiovascular or of unknown cause in patients with HFpEF. If you look at the patients with reduced ejection fraction, you can see that only 16 percent of deaths were non-cardiovascular of unknown cause. So there are important differences between these different ejection fraction phenotypes at least in terms of mortality.

What about the epidemiology of these syndromes in recent years? Well, the prevalence of heart failure is increasing in most and more developed countries, including the United States of America as you can see here in these data published by the American Heart Association.

Interestingly, that increase in prevalence is being primarily driven by an increase in prevalence of heart failure with mid-range and preserved ejection fraction more so than by an increase in prevalence of heart failure with reduced ejection fraction. So the growing problem is really being fueled by the people with a higher

ejection fraction.

Then of course not surprisingly, that increase in prevalence is of course leading to an increased in cost because it's leading to increased rates of heart failure hospitalization. And again, we're seeing this in all parts of the world, particularly the developed world with aging populations.

Finally, let's think about treatment, and what are the goals of treatment, and what options do we have available for patients with the different types of heart failure. Well, of course, the overarching goal of treatment is to slow that progressive worsening over time that characterizes heart failure, and in so doing, hopefully reduce the rate of deterioration, symptoms and signs, and quality of life; reduce the number of episodes of worsening that lead to emergency department visits or hospital admissions, and indeed readmissions; and then wherever possible, to reduce mortality, although as I pointed out, in patients with heart failure in preserved ejection fraction, we believe

the possibility of doing that is limited because of the low rate of cardiovascular mortality, which we believe is the modifiable cause of death in these patients.

Here are the treatments that we have available. As you can see, we have a lot for heart failure with reduced ejection fraction, but as you heard a few minutes ago, there is no approved treatment for patients with heart failure with preserved ejection fraction; and by preserved here, I mean both mid-range and preserved ejection fraction as recently redefined.

But things may be changing. At least thinking in the clinical or academic world has changed in recent years, and actually while we were completing follow-up in the PARAGON Heart Failure trial, we'd already begun to explore this new heart failure phenotype, heart failure with mid-range ejection fraction. You can see here two of the papers that came out from retrospective examination of some of our earlier trials that enrolled patients with heart failure and preserved and

mid-range ejection fraction.

I'll show you an updated figure here from these two analyses. In this slide, you see the composite outcome of cardiovascular death or heart failure hospitalization by the time to first event. These fractional polynomial analyses show you a continuous hazard ratio that is the solid green line across the spectrum of ejection fraction in the CHARM program using candesartan and in three trials in heart failure using mineralocorticoid receptor antagonist, the RALES trial, the EMPHASIS-Heart Failure trial in HFrEF, and the TOPCAT trial in HFpEF.

What you can see in both of these analyses is that there is a suggestion that these two neurohumoral blocking drugs seem to reduce morbidity and mortality in patients up to an ejection fraction well above the 40 percent threshold that we currently use to describe patients with heart failure and reduced ejection fraction. You can see with both of these agents, the benefit seems to be maintained perhaps up to an

ejection fraction of 60 percent.

To summarize and conclude, we have multiple effective therapies for patients with HFrEF, which is currently defined as an ejection fraction less than 40 percent, but we really have nothing for the remainder of patients originally defined as HFpEF, meaning and ejection fraction above 40 percent. But now that population has been segmented into heart failure with mid-range ejection fraction and the newly defined HFpEF heart failure with an ejection fraction above 50 percent.

Although these patients may have a lower mortality rate and certainly a lower cardiovascular death rate, they remain extremely symptomatic, a very poor quality of life and are frequently admitted to the hospital, and we really have nothing to offer them therapeutically. In other words, we believe that these patients with heart failure and an ejection fraction of 40 percent or above have a very important unmet treatment need.

Thank you very much. And with that, I'd like to hand over to Dr. Scott Solomon.

Applicant Presentation - Scott Solomon

DR. SOLOMON: Thank you, John.

Well, first of all, I would very much like to thank the panelists for taking the time out of your busy schedules to be here today, and I'd especially like to thank the patient members of the panel who continually remind us why we're here.

By way of disclosures, my institution has received grants for my role as co-chair of the PARAGON trial, and I've consulted for Novartis as well as other companies in the heart failure space. Over the next few minutes, I'd like to provide a little more context about the PARAGON trial, the design of the trial, and then present you the primary results of the PARAGON study.

You've already heard from Dr. Soergel today that sacubitril/valsartan is a first-in-class angiotensin receptor neprilysin inhibitor. And for those of you who are not entirely familiar with this drug, it's a crystalline compound that is composed of both the angiotensin receptor blocker valsartan and sacubitril, which is a neprilysin

inhibitor prodrug. Once ingested it comes apart into those two components.

We're all familiar with how angiotensin receptor blockers work, and valsartan in particular. They block the AT1 receptor, and sacubitril is then esterified to sacubitrilat, which is its active form, and inhibits the ubiquitous enzyme, neprilysin.

Neprilysin is responsible, among other things, for the breakdown of the biologically active natriuretic peptides, which include ANP, BNP, CNP, and several other vasoactive proteins such as adrenomedullin, bradykinin, substance P, and even angiotensin II. In fact, that angiotensin II is a substrate for neprilysin is the reason why neprilysin inhibitors need to be paired with inhibitors of the renin angiotensin system.

It's also important to note that NT-proBNP is not a substrate for neprilysin and is still a good marker of the severity of heart failure even in the setting of neprilysin inhibition. It's also worth noting that the valsartan that's present in

sacubitril/valsartan is more bioavailable than standard valsartan so that 103 milligrams of valsartan within the compound is biologically equivalent to 160 milligrams of standard valsartan.

Approximately 12 years ago, the Academic Executive Committee and the sponsor began a heart failure program with this compound that included a phase 3 trial in heart failure with reduced ejection fraction, PARADIGM, and a phase 2 trial in heart failure with preserved ejection fraction, PARAMOUNT.

Shown here are the results of the PARADIGM-Heart Failure trial with heart failure with reduced ejection fraction, and this was the largest heart failure trial yet conducted. It was presented in 2014 after it had been stopped early by the data safety monitoring board for overwhelming efficacy.

Compared with enalapril, sacubitril/valsartan reduced cardiovascular death and heart failure hospitalization and cardiovascular death alone by 20 percent, and all-cause mortality by

16 percent, all highly significant.

I show these data because PARADIGM was the adjacent patient population to what we studied in PARAGON with entry criteria that were similar in virtually every respect other than ejection fraction.

At the time we had designed PARADIGM, we also designed and conducted a phase 2 trial in HFpEF called PARAMOUNT. This study compared sacubitril/valsartan to valsartan in 301 HFpEF patients. The primary endpoint of the trial was reduction of NT-proBNP at 12 weeks. Again, it's still a good marker of the severity of heart failure because it's not a substrate for neprilysin, and this was significantly reduced by sacubitril/valsartan.

Patients were then followed in a blinded fashion for a total of 36 weeks, and during that time, sacubitril/valsartan resulted in improvement in New York Heart Association class, a marker of functional status, and left atrial size, a marker of hemodynamic benefit.

On the basis of this pilot trial and success of the PARADIGM trial, we designed PARAGON-Heart Failure. PARAGON was a randomized, double-blind, active comparator trial, testing the hypothesis that sacubitril/valsartan compared with valsartan would reduce the composite of total heart failure hospitalizations and cardiovascular death.

Of note, all of the completed and ongoing HFpEF trials, of all of them, PARAGON was the only one in which the experimental therapy was tested against an active comparator. Patients who were eligible for the trial -- and I'm going to go through the eligibility criteria in a minute -- were entered into a sequential, single-blind, run-in phase in which they first received valsartan uptitrated past target dose, and then they were switched to sacubitril/valsartan and uptitrated to half-target dose.

Patients who completed the run-in phase were then randomized to sacubitril/valsartan at a target dose of 97/103 milligrams twice daily or valsartan 160 milligrams twice daily. And this was

on top of all other background medications used to treat their comorbidities because, as we said, there were no evidence-based therapies for HFpEF, with the exception of ACE inhibitors or angiotensin receptor blockers, which patients could not be on.

The primary endpoint of the trial was a composite of confirmed first and recurrent heart failure hospitalizations and cardiovascular death, and I'll talk more about that in a second. Secondary endpoints included change in New York Heart Association functional class at 8 months; change in the Kansas City Cardiomyopathy Questionnaire clinical summary score; measure of quality of life at 8 months; time to the first occurrence of worsening renal function; and time to all-cause mortality.

In addition to these endpoints, we prespecified an exploratory expanded composite endpoint that included adjudicated urgent heart failure visits that did not result in hospitalization, and we're going to talk more about those as well.

Let me share with you some of the key considerations that went into the trial design. First, why did we choose an active comparator, especially given that there is no mandated therapy for heart failure preserved ejection fraction? Well, we found in prior trials that approximately 85 percent of patients in HFpEF studies have been on ACE inhibitors or ARBs, mostly for hypertension, kidney disease, or diabetes.

Being on one of these drugs in addition to sacubitril/valsartan would in fact be a contraindication and would potentially present a serious safety issue. For that reason, we felt that it was better to have control of RAS inhibition in both arms.

As I mentioned, 103 milligrams of valsartan and sacubitril/valsartan provide similar plasma exposure to a 160 milligrams of standard valsartan. So this design allowed us to assess the incremental effect of sacubitril on top of RAS inhibition. And as Dr. McMurray has also shown you in previous trials, especially the CHARM study, there was

evidence of some modest benefit from RAS inhibition, so we were aware that this design put us at somewhat of a disadvantage because of that.

Another really novel aspect about this design and key design consideration is that we utilized a recurrent event endpoint, which has been somewhat unusual in cardiovascular medicine, although it's commonly used in other diseases in which recurrent encounters are common, and examples of that include asthma and multiple sclerosis.

We've heard from Dr. McMurray that HFpEF is a disease that is characterized by frequent worsening heart failure events, including heart failure hospitalizations and urgent heart failure visits, and that each event is associated with a worsening of long-term prognosis. In CHARM, the risk of death increased with each additional heart failure hospitalization with a 30 percent cumulative increased risk associated with a second and third heart failure hospitalization.

It's also important to remember that a traditional time-to-first-event analysis ignores by

definition all events after that first event, so the recurrent event approach we believe more accurately reflects true burden of illness both on the patient and the healthcare system in a disease like this. The analysis was of course discussed and vetted at length with the agency prior to starting the study, and this approach has even been highlighted in the June 2019 FDA guidance, Treatment for Heart Failure Events for Drug Development.

The eligibility criteria for PARAGON were designed both to avoid overlap in the HFrEF population and to ensure certainty of the diagnosis of heart failure, something that we've been concerned about, quite frankly, because of other heart failure preserved ejection fraction trials that may have enrolled patients without heart failure.

Patients were eligible if they were 50 years of age or older with an ejection fraction of 45 percent or greater. They were required to have signs and symptoms of heart failure by New York

Heart Association Class II to IV, as well as evidence of structural heart disease, which required documentation of either left atrial enlargement or left ventricular hypertrophy by echocardiography.

They were also required to have elevation in natriuretic peptides, and the degree of that elevation was dependent on whether they had been hospitalized for heart failure within the prior 9 months and whether or not they were in atrial fibrillation at the time of enrollment. As you all know, atrial fibrillation alone can increase natriuretic peptides, so the NT-proBNP threshold was raised for patients in atrial fibrillation.

Patients were excluded if they had any prior left ventricular ejection fraction less than 40 percent; current acute decompensated heart failure; any other reasons for their signs and symptoms or a systolic blood pressure less than 110; or uncontrolled blood pressure not taking 3 or more antihypertensive medications.

The endpoints in PARAGON were adjudicated by

a clinical events committee utilizing standard criteria that were established by an academic FDA joint effort led by Karen Hicks, which included many of the people around the table today. These criteria were established originally in response to concerns about adjudication of cardiovascular endpoints in non-cardiovascular trials, but they have been used in cardiovascular trials as well.

The specific criteria for heart failure hospitalization is outlined here, and these included verification from source documents of the following: an unplanned presentation with heart failure; a hospitalization traversing a change in calendar day; at least one symptom and two signs of worsening heart failure; and qualified treatments directed at treating heart failure. And all of these had to be verified by source documentation.

An urgent heart failure visit required all of those same criteria to be met and documented, except for the actual hospitalization traversing the calendar day. But in addition, there was one additional requirement that this endpoint required

that treatment included the use of an intravenous heart failure therapy.

PARAGON was a global trial. We enrolled patients in the 848 sites in 43 countries. Shown here is the patient disposition in PARAGON: 5,746 patients entered the run-in period; approximately 9 percent came out during the valsartan run-in phase; and 7 percent during the sacubitril/ valsartan run-in phase.

Ultimately, we randomized 4,822 patients, but prior to unblinding, 26 of these had to be excluded because of severe good clinical practice violations at a single site. This left 4,796 patients for final analysis. Patients were followed for a median of 35 months, and at the end of the study, a vital status was known on all but 9 patients, and of these, 7 withdrew consent and 2 were lost to follow-up.

Shown here are the baseline characteristics of the enrolled patients in PARAGON, and these are really fairly typical for a HFpEF population. It's an elderly group of patients with a mean age of 73,

and 52 percent were women. Now, you've heard that women make up a greater proportion of patients with HFpEF than patients with HFrEF, but I have to say that we were particularly proud of the fact that we enrolled as many women in this trial as have ever been enrolled in a heart failure clinical trial.

Other demographic characteristics, including the five regions patients were from, the racial and ethnic background are shown here. The mean left ventricular ejection fraction was 57 percent, which is also typical for HFpEF, and NT-proBNP was 600 patients who came into the study in sinus rhythm and 1600 in patients in atrial fibrillation.

The majority of patients were New York Heart Association Class II. Blood pressure was well controlled. Comorbidities were actually quite common for patients with HFpEF. The vast majority of patients had hypertension. One thing that is not listed here but I know you'll be interested in is the mean estimated GFR was 63, and 50 percent of the population had an eGFR below 60. As mentioned, the majority of these patients came into this trial

on ACE inhibitors or ARBs at screening. Eighty percent were on beta blockers and 26 percent were on mineralocorticoid receptor antagonists.

Shown here are the primary results of the PARAGON study. These data were analyzed using a semi-parametric Lin, Wei, Ying and Yang, or LWYY, method, which is essentially a Cox regression equivalent for multiple events that uses a robust variance estimator to account for the correlation between events. The event rate for cardiovascular death and total heart failure hospitalizations was 14.6 per hundred patient-years in the valsartan group and 12.8 per hundred patient-years in the sacubitril/valsartan group.

There were 115 fewer events in the sacubitril/valsartan group, which yielded a rate ratio of 0.87 with an upper 95 percent confidence bound that just crossed 1 and a p-value of 0.059. The borderline nature of this result is evident when we consider that seven additional events in this arm would have produced a p-value on the other side of the 0.05 threshold. When broken down into

its components, we can see that this composite was driven primarily by heart failure hospitalizations, which were reduced by 15 percent. Cardiovascular death was numerically in the right direction but not significantly reduced.

I'm now going to show you several additional analyses that we believe are supportive of the primary endpoint showing true efficacy. As mentioned, we prespecified that urgent heart failure visits would be incorporated into the composite endpoint as an exploratory endpoint. Well, as you know, over the past five years, there's been increasing desire to treat patients with heart failure in the outpatient setting, which has been driven in part by pressure, including financial pressure, to keep patients with heart failure out of the hospital.

Urgent heart failure visits have been shown to have similar prognostic and discriminability as heart failure hospitalizations, and they've been incorporated into recent heart failure clinical trials, including the recent DAPA-HF trial. We did

not include urgent heart failure visits into the primary composite PARAGON outcome simply because when we designed PARAGON, we really had limited data on these events, and we realized that we already were using a novel endpoint. Of note, this endpoint has also been incorporated into the recent FDA guidance on endpoints for drug development of heart failure.

In PARAGON, 6 percent of our worsening heart failure events were urgent heart failure visits. Patients whose first episode of worsening heart failure was an urgent visit were similar with respect to age, comorbidities, baseline natriuretic peptide, and risk scores to those in whom the first heart failure event was a heart failure hospitalization, suggesting that the threshold for admitting a patient, rather than treating them as an outpatient, may vary by site to site but was not particularly different by patients.

As I said, this analysis yielded 95 additional events, 40 in the sacubitril/valsartan group and 55 in the valsartan group. Shown in gray

is the primary composite result already shown, and as you can see, adding these urgent heart failure events reduces the rate ratio to 0.86 with a nominal p-value of 0.04.

Shown here are the investigator-reported events that Dr. Stockbridge mentioned in his preamble. As discussed, the adjudication process had quite strict definitions for positively adjudicating heart failure hospitalizations, and thus investigators reported considerably more heart failure hospitalizations than were positively adjudicated generally because of inadequate source documentation. There were 402 additional events, 170 in the sacubitril/valsartan arm and 232 in the valsartan groups. This analysis shows a hazard ratio of 0.84 and a nominal p-value of 0.014.

Since CEC's definition for hospitalization required such strict criteria as I've previously outlined -- and this is a repeat of the slide that we saw before -- as you also heard, concern about these strict criteria favoring specificity/ oversensitivity, with the possible rejection of

true heart failure hospitalizations that did not meet the strict definition, potentially because of inadequate source documentation, prompted the agency to recommend to the sponsor that an independent panel readjudicate the hospitalizations that were reported by the investigators but not confirmed by the CEC. And you're going to hear, I think, more about this in the FDA presentation as well.

This trigger was out of concern not for the quality of the initial CEC adjudication but because of those strict definitions, and that those requirements likely reduced sensitivity for the outcome. The process that was used was one that was conceived in consultation between the sponsor and the agency.

An independent panel consisted of three blinded heart failure experts that were not involved in the original trial, and they were provided the original adjudication packets with all source documentation. Each of these individuals ascribed for each case the probability of it

representing a true heart failure hospitalization based on their clinical judgment. The probabilities were then averaged for each event and used in a multiple imputation approach to include readjudicated events in the primary analysis.

Shown here are the results of that analysis. Again, the original result in the gray box, the readjudication resulted in 231 additional heart failure hospitalizations, 105 in the sacubitril/valsartan group and 126 in the valsartan group. This reduces the primary rate ratio to 0.86 with a p-value of 0.043.

Just to put all these new analyses in context, here is a graphical summary of these several supportive analyses showing the primary endpoint on top, followed by the primary endpoint incorporating urgent heart failure visits; the investigator-reported events; the investigator-reported events incorporating urgent heart failure visits; and the analysis following addition of events from the readjudication process.

I'm now going to show you some of the

secondary endpoints, which we believe are supportive of true efficacy with metrics that are actually meaningful to patients who are living with heart failure with preserved ejection fraction. New York Heart Association class, a measure of functional status, was improved in a greater proportion of patients in the sacubitril/valsartan arm and worsened in fewer patients in the sacubitril/valsartan arm, with a 45 percent increased odds of net improvement. Kansas City Cardiomyopathy Questionnaire clinical summary score at 8 months was improved by approximately 1 point in the sacubitril/valsartan group with a greater proportion of patients achieving a 5-point improvement in this group.

Shown here is the composite renal outcome. The worsening renal function endpoint was a composite of renal death, reaching end-stage renal disease or a 50 percent or greater decline in estimated GFR relative to baseline. This was reduced by 50 percent in patients receiving sacubitril/valsartan with a nominal p-value of

0.001. Similarly but not shown here, we also saw attenuation of worsening of the slope of GFR change over time in the sacubitril/valsartan group.

Shown here are the prespecified subgroups for the primary endpoint. As you know, we generally assess subgroups in clinical trials to demonstrate consistency. In this case, however, we saw evidence of true heterogeneity, particularly in two specific subgroups that I'm going to draw your attention to here, and these were patients who were in the group with left ventricular ejection fraction at or below the median versus those in the higher ejection fraction group, and by sex, men and women.

Let me show these again a little more clearly, and we can see that women appear to benefit to a greater extent than men, and patients with a left ventricular ejection fraction at or below the median appear to derive greater benefit than those with a higher left ventricular ejection fraction.

Now, both of these subgroups' interaction p-

values were highly significant after multivariable adjustment, which incorporated all covariance and interaction terms. I will explore the left ventricular ejection fraction subgroup first, and then we're going to come back to the sex subgroup a little bit later in the presentation. When we break left ventricular ejection fraction into quartiles, we can see that the point estimates for benefit are most favorable in the two lowest quartiles, with suggestion of attenuation of benefit as ejection fraction goes up into the normal range.

Shown here are the primary composite endpoints and the expanded composite for patients just in the lower ejection fraction group, those patients at or below the median in PARAGON, which was 57 percent. And again, as I said, I will come back to the other significant subgroup in a second.

With respect to safety, I'm going to be relatively brief because we now have an enormous body of safety data with this drug. There have

been over 23,000 patients enrolled in heart failure clinical trials with sacubitril/valsartan, and in addition there have now been 2.6 million patient-years of postmarketing safety data, and I'm pleased to say that there were no surprises in the PARAGON safety data and no new safety signals.

You can see here that the number of patients with adverse events or serious adverse events and the number of patients who discontinued therapy due to adverse events were similar between groups but even numerically slightly less in the sacubitril/valsartan arms.

This particular drug is associated with certain side effects that we are obviously on the lookout for, and we did look carefully at a number of adverse events of interest, including hypotension, hyperkalemia, renal impairment, and angioedema.

Just like in PARADIGM, we saw the patients receiving sacubitril/valsartan had more episodes of hypotension, although no more discontinuation of therapy due to hypotension. However, patients

receiving sacubitril/valsartan had less elevation of serum potassium and fewer potassium related hyperkalemia related adverse events.

We also saw less elevation in serum creatinine and fewer renal impairment adverse events in patients receiving sacubitril/valsartan. The number of patients with angioedema in the trial was extremely low, numerically greater in the sacubitril/valsartan arm, but there were no instances of airway compromise.

Now, we started off by saying that this was a program of research with both the PARAGON the PARADIGM trials, and of course they were conducted in series, not in parallel; but they were similar with respect to both design and entry criteria in almost every way, with the exception of ejection fraction.

Prior to unblinding the PARAGON trial, we had prespecified that these data would be pooled, and in this slide I show you the results of this pooling. These are data that we presented last year at the American Heart Association and are

published in Circulation.

This slide shows, among other things, the powers of numbers. Had we performed these trials as a single large trial, we would have seen significant reduction in every single endpoint, including all-cause mortality. But when we looked at the data, of course we would have seen the same peculiar attenuation of benefit at the high end of ejection fraction that we've already shown you with PARAGON, with what appears to be apparent benefit throughout the ejection fraction spectrum until you get to that absolute highest level of ejection fraction that is in the range that most of us consider normal.

I'm going to show you these data in a slightly different way, continuously with ejection fraction now on the X-axis and the treatment effect, or rate ratio, on the Y-axis. And you can again see the attenuation of the treatment effect as you go up into the ejection fraction range that we would likely consider normal.

Now, let me come back to the other

interaction between men and women. As I said, women did appear to benefit to a greater extent than men. Well, interestingly, we see a similar attenuation of the treatment benefit with increasing left ventricular ejection fraction in both sexes, but the curves are shifted with women appearing to benefit to a higher ejection fraction than do men.

In summary, PARAGON built on the pharmacodynamic and morphologic benefits demonstrated in the phase 2 PARAMOUNT trial and was the largest and only active controlled phase 3 trial in HFpEF, despite narrowly missing statistical significance for the primary endpoint. We believe that the totality of the evidence supports a real, albeit modest, benefit in the overall treatment population. But this is supported by several supportive analyses I've shown, including the inclusion of urgent heart failure visits into the primary composite, the analysis of investigator-reported events, and the results of the FDA recommended readjudication

hospitalization events that were reported by the investigators but not confirmed by the CEC, often due to lack of adequate source documentation.

The secondary endpoints, which were also in favor of sacubitril/valsartan, provided additional assurance that there was a real benefit, and these endpoints I think are ones that are quite meaningful to patients with this syndrome.

We observed no new safety signals with the overall safety profile being similar to that seen in patients with heart failure with reduced ejection fraction. And finally, we observed real evidence of heterogeneity with an overall benefit that was largely driven by worsening heart failure events in patients with left ventricular ejection fraction below normal.

Thank you for your attention. I will turn back over to Professor McMurray, who will talk about clinical implications of these data.

Applicant Presentation - John McMurray

DR. McMURRAY: Thank you very much, Scott.

I'm going to try and give a clinical

perspective, as Scott said. I do want to start with reminding everybody the most important thing here, which is that for these patients with this type of heart failure, we have no approved therapies. There is a great unmet need.

Let's start with the first question, which is, is sacubitril/valsartan beneficial in patients with heart failure and preserved ejection fraction or at least in some of these patients? You've seen this prespecified analysis of the primary endpoint. When compared to valsartan, the effect of sacubitril/valsartan was not statistically significant using a conventional p-value threshold of 0.05. As Scott Solomon just said, it was borderline, and we believe that that was the case because the treatment effect size that we saw was smaller than we'd anticipated, and as a result, there was a reduction in statistical power.

You've seen these supportive analyses, including those recommended by the Food and Drug Administration, and these of course showed that inclusion of additional events narrowed the

95 percent confidence intervals and resulted in a smaller p-value. You've also seen these prespecified secondary endpoints, and we saw improvements in physician assessment of the patients, in patient-reported outcomes, and of course in renal function as well.

But I think this is really the key slide, which is about the totality of the evidence that we have because, really, the question that I think we have to ask ourselves is, were the effects of sacubitril/valsartan on the prespecified primary and secondary outcomes just the play of chance or is there real overall benefit of sacubitril/valsartan, albeit a modest benefit?

The column to the far right of this slide highlighted in the box, this shows the z-score for each of the five outcomes; that's the primary and the four secondary outcomes. This is just a method of standardizing the differences across diverse outcomes. You can see at the very bottom of that box that the aggregated z-score suggests really a very low probability that this constellation of

findings could be observed if there was no treatment effect. I think it's also important to mention that this analysis accounted for correlation amongst the endpoints that you see here.

I want to move on to talk about whether or not sacubitril/valsartan was beneficial in all of the patients or whether there was a particular benefit in subgroups of patients. Scott's already shown you these two key subgroups where we find strong evidence of a statistically significant interaction. And I have to say, normally when we see subgroup interactions, we are suspicious and treat them with some skepticism. Over the years, we've developed, I think, a set of rules to look at subgroups to how this decides whether they're credible or whether they just reflect a chance funding.

I've tried to summarize these rules on this slide, and I think we would all agree that the subgroups should be prespecified and not post hoc. Of course, those were prespecified subgroups. They

should be large subgroups with a large number of patients and events. We know that smaller subgroups with a few individuals and few events are even more unreliable and even more statistically under power.

Our subgroups were large. We had approximately equal numbers of men and women, and we divided the ejection fraction at the median. Of course, we should test for interaction, which we did. And I think more recently it's been generally agreed that we should try and adjust for multiplicity when we're testing for interaction, and we also did this, as Scott showed you.

Of maybe more interest is to examine the data for the internal architecture. You might describe that as internal consistency. And in this figure you can see that if we look at patients in the ejection fraction quartiles below 63 percent, the point estimate for the hazard ratio is consistently below 1. The point estimate is not jumping around.

In fact, we can look for more internal

consistency by including of course the PARADIGM-Heart Failure trial, where the patients had ejection fractions adjacent to those at the lower end of the range included in PARAGON-Heart Failure. And again, you can see that that hazard ratio remains consistently below 1 right across the spectrum of ejection fraction below around 60 percent.

There are some other things that we need to think about, and that includes whether or not there's any external support from other data sets; for example, are there other clinical trials that support these findings. Lastly, are they biologically believable and are they biologically plausible, so let's look at that.

Earlier, I showed you data from some of the other trials that were analyzed actually while we were conducting PARAGON-Heart Failure, those analyses from the CHARM program with candesartan and with mineralocorticoid receptor antagonist from three trials using spironolactone and canrenone [indiscernible], and I showed you that

there seemed to be this consistent benefit from these two neurohumoral modulating drugs to a higher ejection fraction than the 40 percent point that we've conventionally used to describe heart failure with reduced ejection fraction.

If we analyze the PARADIGM and PARAGON-Heart Failure trials in exactly the same way and you set these new analyses alongside the candesartan and mineralocorticoid receptor antagonists analyses, you can see, again, remarkable consistency; I would say, once more, a treatment that modulates neurohumoral systems, again demonstrating a benefit that seems to extend currently to a higher ejection fraction than 40 percent.

So we do think that there is some external evidence suggesting that drugs that affect neurohumoral systems can be a benefit to patients with heart failure, even with an ejection fraction above 40 percent and, really, that goes back to the introduction of this concept of heart failure with mid-range or mildly reduced ejection fraction, which really came about because of the growing

belief that these patients in the lower end of the HFpEF ejection fraction range seemed to look more like patients with conventional HFrEF with left ventricular systolic function; and, as I've just shown you, to respond more like those patients with HFrEF to treatments that we know work in patients with a clearly reduced ejection fraction.

The other subgroup that Scott mentioned was the analysis of women compared to men. I think we are less certain about this subgroup, but interestingly we do see another finding that appears to be consistent. As Scott showed you, sacubitril/valsartan did seem to be beneficial to a somewhat higher ejection fraction in women than in men, consistent with everything else we know about ejection fraction in women compared with men.

But actually, when we then went back and looked at the mineralocorticoid receptor antagonist trials and the CHARM program, we also saw this in qualitative interaction with all three therapies seeming to demonstrate benefit in women to a higher ejection fraction threshold than in men.

I now want to look at whether or not the benefit that we see in these patients with a lower ejection fraction is a clinically worthwhile benefit. As said, the overall benefit of sacubitril/valsartan is modest and was less than we had anticipated, but if we look at patients with an ejection fraction as or below the median value, which was 57 percent, then our interpretation might be different.

Here you see the potential events that we might prevent by treating a thousand patients for three years, and on this slide, I've got the PARADIGM-Heart Failure trial, and then you see PARAGON overall. In the bottom row in this table are the patients in PARAGON-Heart Failure with an ejection fraction at or below the median. You can see that the number of events potentially preventable in these patients with an ejection fraction in the lower parts of the range in PARAGON-Heart Failure is really quite substantial and, in fact, almost as large as in PARADIGM-Heart Failure.

You may wonder why we're seeing such a large effect in heart failure hospitalizations compared to PARADIGM. We think that reflects the competing risk of death, which of course is much higher in the HFrEF patients in PARADIGM than in the HFpEF patients in PARAGON-Heart Failure.

What about safety? Clearly, if we were to recommend using sacubitril/valsartan in patients with HFpEF, or some patients with HFpEF, we would also need to be assured of its safety profile. But again as you've seen from Scott earlier in more detail, there were no surprises. The overall safety profile of sacubitril/valsartan in PARAGON-Heart Failure was very similar to what we saw in PARAGON-Heart Failure. In fact, it was pretty similar to valsartan by itself.

So to summarize and conclude, as I showed you in my first presentation, heart failure with preserved ejection fraction is a syndrome, or many. Today we would say, as we defined it, it's actually two syndromes. But whatever it is, patients with heart failure and an ejection fraction above

40 percent have very disabling symptoms, poor quality of life, and they're frequently hospitalized. These are often older individuals. They're more often women than patients with heart failure and reduced ejection fraction. And as I've said, there is no approved treatment for patients with this type or types of heart failure.

I would say the totality of evidence from PARAGON-Heart Failure supports the conclusion that sacubitril/valsartan does have clinical benefits and indeed a favorable benefit-to-risk profile in the broad population of patients that we studied in PARAGON-Heart Failure, although in the three specified subgroup analyses that we've discussed, this benefit seemed to be more clear in patients with an ejection fraction at or below the median value of 57 percent and apparently in women as well.

I've shown you what I think is the most important supporting bit of information, which is that other drugs acting in neurohumoral pathways also seem to demonstrate a similar benefit in

patients with an ejection fraction extending above that conventional threshold of 40 percent into the lower part of the heart failure with preserved ejection fraction range.

If we accept that and if that is accepted, then I think we also have to say that the potential size of benefits in those individuals is substantial, and that is indeed with an acceptable safety profile in these patients. Thank you very much.

Applicant Presentation - David Soergel

DR. SOERGEL: Thank you very much, Professor McMurray and Dr. Solomon.

In summary then, the question for the committee is whether the totality of evidence supports the extension of Entresto's use to patients with HFpEF? Our view is that the evidence from PARAGON-HF, from the phase 2 PARAMOUNT trial, and from the adjacent population in PARADIGM does indeed support that Entresto has an important treatment benefit by reducing worsening heart failure events in HFpEF patients, especially those

with an ejection fraction below normal.

Entresto has proven to be a well tolerated treatment option for patients with HFrEF, and the safety profile has been recapitulated in the HFpEF population. This leads us to conclude that Entresto would be an important therapeutic option for these patients who currently do not have an approved treatment for this progressive and debilitating disorder.

Thank you very much, and we look forward to your questions.

Clarifying Questions

DR. LEWIS: Thank you.

We will now take clarifying questions for Novartis Pharmaceuticals. Please use the raised-hand icon to indicate that you have a question and remember to clear the icon after you have 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 questions," so we can move on to the next panel member.

Many [inaudible - audio gap]. Yours was first.

DR. NISSEN: We didn't hear you, Julia. Who do you want to go first?

DR. LEWIS: Dr. Merz.

DR. NISSEN: Okay.

You're muted.

DR. BAIREY MERZ: No. I think Dr. Merz, right? Noel.

Thank you, Dr. Lewis. I have two questions for Scott and one question for Dr. McMurray, so you can cut me off if I'm speaking too long.

For the urgent heart failure hospitalization, Scott, did that differ by region when it was readjudicated, meaning Western Europe and North America were more likely to have gone to

the strategies of not hospitalizing heart failure, particularly in the U.S., because of the recurrent penalty, the financial penalty? Did that change? Was it mostly in Eastern Europe, these repeat adjudicated events?

DR. SOERGEL: I'd ask that you clarify the question, Dr. Merz, if you don't mind? This is David Soergel from Novartis. Just to clarify, you're asking about the urgent heart failure visits readjudication or you're asking about the readjudication process itself for the urgent heart failure visits?

DR. BAIREY MERZ: Did any of that differ by region?

DR. SOERGEL: I see. Okay. Just to clarify, the urgent heart failure visits were not readjudicated. Only the heart failure hospitalizations were readjudicated at the request of the FDA.

DR. BAIREY MERZ: Okay.

DR. SOERGEL: Dr. Solomon, would you like to answer the question?

DR. SOLOMON: Well, I think the other part of the question, which is really relevant, we would have thought, as you probably do, that in the United States you would actually see more of these kinds of events because of the fact that we are penalized if a patient comes back to the hospital within 30 days of a heart failure hospitalization, but they're common actually throughout.

We could put slide 2 up. You can see here it's not just the United States. Germany, which of course is smaller and contributed fewer patients, had as many of these visits as the United States, although there are, as you can imagine, some regional differences.

DR. BAIREY MERZ: Okay. That's very helpful.

Second question, compared to TOPCAT, were these sites more vigorously monitored, particularly in Eastern Europe?

DR. SOERGEL: If I could just interject before Dr. Solomon addresses the question specifically, I think one of the things to take

away from Dr. Solomon's presentation was how rigorously conducted PARAGON was. We have a very complete set of data, as you saw, losing only 2 patients to follow-up and losing a total of 9 patients, 7 due to withdrawal of consent.

Could I ask, then, Dr. Solomon, for you to comment on the comparison with TOPCAT?

DR. SOLOMON: Sure. Well, for obvious reasons, we had just completed TOPCAT right at the time that PARAGON was being designed and then started, so this was very fresh in our mind, the issues that we had with TOPCAT, that you all know about and you'll hear more about tomorrow for sure, including the fact that many of the patients enrolled in certain parts of the world probably didn't have this syndrome we call heart failure.

We were very careful to ensure, by both the entry criteria, that patients fulfilled all of the criteria that we believed would ensure that they actually did have heart failure. That's why we required them to have evidence of structural heart disease. That was why we required them to have

elevation in natriuretic peptides.

In fact, the original design of PARAGON allowed people to get in without elevation in natriuretic peptides if they had been hospitalized for heart failure. We changed that very early in the course of the study in response to TOPCAT. That was one aspect of how we ensured that we would not get the same kind of a problem that was seen in TOPCAT.

The other was, as you know, TOPCAT was an NIH-funded study. There was essentially no budget for monitoring, at least the kind of monitoring that we normally have in the industry trials that many of us participate in, and certainly no real boots-on-the-ground monitoring. So in that respect, they're very different.

There was obviously source level documentation -- and the sponsor certainly can talk more about this if you're interested -- in this trial, and we even went a step further to have the adjudication committee look at cases of patients' hospitalizations for heart failure as their

ejection criteria to ensure that the enrollment criteria for these patients was in fact adequate and achieving the thresholds that we had set forth.

We think there's really no comparison in the way this trial was monitored compared to TOPCAT. We learned a lot of lessons with TOPCAT, and of course we had a lot of limitations given the source of funding in TOPCAT.

DR. BAIREY MERZ: Thank you.

Here's my last question for Dr. McMurray. I think on one of your implication slides, if you treated a thousand patients for three years, you prevented 122. So that would be a number needed to treat of 100 for that period of time. Do you agree with that?

DR. McMURRAY: I think the number needed to treat is actually about 9 to prevent 1 hospitalization, but I think we may have a backup slide to confirm that.

DR. BAIREY MERZ: That would be useful. Thank you.

DR. McMURRAY: Slide number 4, please.

I think the slide's up on the screen; yes, it is. Yes, in the patients with an ejection fraction as or below the median value of 57 percent of course, we're talking about the number needed to treat is 9 for either the primary outcome or heart failure hospitalization.

DR. BAIREY MERZ: Thank you. Those are my questions, Dr. Lewis.

DR. LEWIS: Thank you.

Dr. Emerson?

DR. EMERSON: Yes. I have questions, and probably slide 79 that Dr. Solomon presented would be most useful. But what I'm aiming at is trying to figure out whether we should be thinking about when we've got a treatment now for this vague syndrome that's HFpEF or whether we're merely moving the threshold for what we call the area with predominantly HFrEF.

What I'm looking for is -- I'm sorry -- 7. I apologize. This is a bizarre way to ask the question. I'm looking for the slide that looks at -- this is the one. This is a little bit a

bizarre question, but I'm trying to figure out exactly how much this syndrome of HFpEF versus HFrEF is.

What I'm going to ask is, in PARADIGM, if I went through and brought everybody's left ventricular ejection fraction documentation up to the 45 percent, and therefore also remove the idea that they were ever below 40 percent, how many of those patients would also meet the eligibility criterion for PARAGON? To my somewhat unschooled reading, it's really just this structural heart disease that makes the biggest difference. So what would be that overlap?

DR. SOERGEL: Maybe I could clarify the question, Dr. Emerson. You're asking if we took the entire PARADIGM population and then just compared the entry criteria for the PARADIGM population and applied the PARAGON criteria, would they all have qualified for PARAGON? Is that your question?

DR. EMERSON: Ignoring the ejection fraction.

DR. SOERGEL: Ignoring, yes. Professor McMurray presented this slide showing the differences in the patient characteristics in these populations that go beyond the ejection fraction, which include the different etiologies, the age, and so forth that --

DR. EMERSON: Okay. So I'll agree that that's how the effect was realized, but those weren't really as much the age as it was really required for eligibility.

DR. SOERGEL: Dr. McMurray, would you like to comment?

DR. EMERSON: Dr. McMurray's slide of 49 addressed this issue as well.

DR. McMURRAY: It's John McMurray here. Yes, I'm happy to comment, but I think what's happened -- we've got to really go back to the source as I did in my very first presentation. We simply divide heart failure out by ejection fraction at all, then we started with an ejection fraction of 35 percent as defining this syndrome that responded to certain types of treatment in the

SOLVD treatment trial. In the CHARM program, we increased that to 40 percent.

I think what we're seeing -- I'm learning -- is that systolic dysfunction, which is the fundamental problem that drugs like sacubitril/valsartan beneficially effects -- is present with ejection fractions considerably higher than we once realized, and as I pointed out, that's maybe even more so in women than men.

So it is a little bit arbitrary where you draw any dividing line, if you should draw any dividing line. But I do think there is a group of people who have a completely normal ejection fraction, and I do think they're different. I think they're different because we're clearly seeing that if your ejection fraction is 70 percent, you don't really respond to any of the treatments that we know work in heart failure.

At least with reduced ejection fraction, there's growing evidence that the pathology may be different in those patients, and there may even be different diseases hidden amongst those individuals

who have a completely normal ejection fraction; for example, cardiac amyloidosis.

So I think it is legitimate to think that there is a top point somewhere, but I think we're actually still trying to understand where the right place is to draw the line in the sand at the moment.

DR. EMERSON: And you're talking to a statistician who was not -- while I went to medical school, I did nothing clinical after that, so you've got to dumb it down a little bit for me. But the structural heart disease eligibility criterion, would that have eliminated many patients that were in PARADIGM?

DR. McMURRAY: Would that have -- no, because -- well, first of all -- you will understand this very well as a statistician -- there's a great deal of imprecision around any of the measurements that we make.

Though some of the people who were included in PARADIGM may have had a true ejection fraction that was actually above 40 percent, some of the

people who were included in PARAGON may have had a true ejection fraction that was actually below 45 percent. And as for the other abnormalities, the increase in atrial size, the increase in wall thickness, those are often common to patients with HFrEF and HFpEF as we currently distinguish those two categories.

DR. EMERSON: From my model, from what I've read in your briefing document is that the PARADIGM population is a little bit slanted towards people who have had MI and have a dead part of their heart, and that that's leading to the problem; whereas in PARAGON, what we'd be looking for in the HFpEF population is perhaps people where it's more a global myocardial problem, a very simplistic idea.

So the major thing I see here is this structural heart disease. And again, what I'm trying to find out here is if we go with this indication, to my mind, would I want HFpEF to be in that indication at all or would I just want to be able to say, "Look, we're just going on ejection

fraction and we're not really going with the idea that it's HFpEF or HFrEF."

DR. SOERGEL: If I could ask --

DR. McMURRAY: So you're -- okay. Go ahead.

DR. SOERGEL: Yes. Sorry. Maybe I could ask Dr. Solomon to comment. I think it's an important point you're raising.

Dr. Solomon, would you like to comment?

DR. SOLOMON: Yes, sure. And if I understand the question correctly, first of all, the requirement for structural heart disease in PARAGON was primarily so that we could assure ourselves that we were studying a problem with the heart, and that's really much more of an issue when ejection fraction is high than when it's low. When it's low, we do an echo, and we say, "Oh, the EF is 35 percent; there's a problem with the heart." When the ejection fraction looks pretty normal, it's much harder to look at a heart and say there's a problem there. So that was the main reason for that.

So why did we choose these? We chose left

ventricular hypertrophy because many of these patients have hypertension, and we believe that hypertension and hypertrophy contributes to the pathophysiology of this disease. We chose left atrial enlargement because that is a marker of ventricular filling pressures, and we believe that the syndrome of heart failure should be always associated with elevation in filling pressure.

So would we have seen these in PARADIGM? We didn't actually have echocardiograms in PARADIGM, but had we, we would have seen left atrial enlargement in the vast majority of those patients because it's extremely common in --

DR. EMERSON: But perhaps not as much of the left ventricular hypertrophy, but something.

DR. SOLOMON: Right.

DR. EMERSON: Thank you. That's answered my question, so thank you very much.

DR. SOLOMON: Thank you.

DR. LEWIS: Dr. Nissen?

DR. NISSEN: Thank you.

I want to talk a little bit with Scott

Solomon about the question of the precision of echocardiography and how it was measured. Was ejection fraction, for purposes of entry, measured in a central core lab or was it measured at the individual site?

DR. SOLOMON: It was measured at the individual site.

DR. NISSEN: Okay.

DR. SOLOMON: These were done on every patient. There was an echocardiographic substudy in which some patients had an echo that may not have been the same as the one that they qualified on transferred to a core lab, but that's not what you're asking.

DR. NISSEN: No, that's not what I'm asking.

Okay. So with regard to the precision of ejection fraction measurement -- you've been doing this for a long time -- what would you describe as the intraobserver variability of ejection fraction measured by echo and the short-term variability? If you measured a week apart, what standard deviation would you assign to this technique?

DR. SOLOMON: To be simple, I think probably plus or minus 5 points is defensible. It may even be higher than that in some institutions, in some labs.

We did an experiment recently where we were -- I was actually making a slide to show about heart failure with mid-range ejection fraction. We took a hundred patients who in a core lab and had an ejection fraction between 40 and 50, and we gave it back to another reader in a core lab to see where those came out, and about 30 something percent were outside of the range between 40 and 50 percent when it was redone, the same exact study in the same lab. That is even ignoring the potential biologic variability.

So I think all of us who do echocardiography know that there's some degree of imprecision there. We lived with it for many years in our lab at The Brigham. We resisted actually giving numbers. It was actually only when the oncologists demanded that they get an actual number that we started giving them. We used to say normal, mildly

reduced, moderately reduced, and severely reduced. This is a known issue, and it's inherent to the technique.

DR. NISSEN: Right. So that's where I was going.

If you were to, say, take a patient who got into PARAGON with an ejection fraction between 45 and 50 percent, let us say, then some very substantial fraction of those patients, if measured by somebody else somewhere else, would be 40, 35, maybe even low 30s percent if you think about, what, 1 and 2 standard deviations. The figure I was going to use would be about 8 percent. That's what I find in the literature, and sometimes in the literature maybe even 10 percent or greater.

So what I'm trying to get some clarity about is you have these two populations, the PARADIGM population, and we call that HFrEF, and the PARAGON population, and we call that HFpEF. But in point of fact, they are mixed populations based upon the rather large imprecision of the method that we're using for qualifying the patients, particularly

when you consider it's not being done by a core lab, and I'm sure you do it very, very precisely. I'm not so sure how well it's being done in the community.

So what I'm trying to understand here is the extent to which both of these studies are having very large overlap in the populations that they are studying.

DR. SOLOMON: Well, I don't disagree with anything you've just said. We were obviously worried about that, and part of the reason we chose 45 percent for PARAGON is we knew there would be splay, and we didn't want to contaminate the group with heart failure with reduced ejection fraction.

Now interestingly, many of the more contemporary HFpEF trials have gone down to 40 for a variety of reasons, and on the basis of what you just said, I'm sure many of them will enroll people who would have otherwise fallen within that 30 percent range. It gives a lot of credence to the idea of doing these trials together, as we did with the CHARM program, because then there's no

bias at any given site as to whether you put a person into one study or another. But I think you make a very important point.

DR. SOERGEL: Dr. Nissen, maybe I could also add. In PARAGON itself, we saw only about 5 percent of patients with an ejection fraction of 45 percent, so kind of on that cusp; 26 percent had an ejection fraction up to 50 percent, where there is, of course, going to be less overlap in the populations.

I think you're sort of pointing to the fact why we've worded the indication update the way we have, with ejection fraction below normal, sort of characterizing this uncertainty around how we define both normal ejection fraction and the imprecision of the measure.

DR. NISSEN: Yes. The reason I brought this whole point up is that I think that we've created a monster here by actually measuring ejection fraction as a percent. If you go back and look at this historically, Scott's original idea of normal, mild, moderate, and severe is probably a better

categorization.

The problem is that we've been pressed into doing this in a way that artificially dichotomizes patients into these categories that are largely -- you bring back a patient another day under different loading conditions and you can get an enormous difference. Just if their blood pressure is up, their EF is going to come out calculated a lot lower than if their blood pressure is a little bit lower.

DR. SOERGEL: And I think also, Dr. Nissen, this is exactly the advantage of having a large data set that's so high quality, as we've talked about with high-quality monitoring, qualified investigator and so forth, and consistency and completeness of data. I think this is a crucial point you're raising, but I think this is exactly why a large trial like PARAGON hopefully gets us closer to the answer.

DR. LEWIS: Dr. Nissen, is that the last of your questions?

DR. NISSEN: Yes. That's the last of my

questions. I just wanted to explore the ejection fraction question. I've gotten some appropriate answers, so that helps me.

DR. LEWIS: Great.

Dr. O'Connor?

DR. O'CONNOR: Thank you. Can you hear me?

DR. LEWIS: Yes.

DR. O'CONNOR: This is a question for Dr. Solomon. I wanted to know whether two aspects of the trial conduct regarding the CEC adjudication and the DSMC interim analysis may have blurred the efficacy signal of the overall trial.

If you bring up slide 50 or 62, I think you've nicely outlined that the trial leadership adopted the Hicks criteria for the CEC charter, which is part of the New England Journal supplement, recognizing, as a co-author on that, that this charter can handcuff members of a CEC in their adjudication process. So let me give you an example, particularly in HFpEF where there's a large population of patients who have obesity and may not be able to distinguish the physical sign

criteria that you have outlined.

If a patient came into the hospital in this trial with progressive shortness of breath; was admitted to the hospital with an elevated natriuretic peptide level but because of obesity could not determine the other signs of congestion or there was not source documentation for that; but was diagnosed with heart failure; treated with IV furosemide for 5 days; and discharged with a discharge diagnosis of heart failure but only met one of the physical signs, that patient would have been deemed by the CEC as not having heart failure.

Is that correct?

DR. SOLOMON: Yes, and I'll make some comments, Chris, but I'll also hand over to Akshay Desai, who chaired the adjudication committee, because he can probably provide even more clarity about individual types of cases.

But your comment about being handcuffed is one that's very important. As you know, when these criteria were designed -- and I was part of that group as well, as were many of the people, as I

said, around the table -- they were mostly designed to maximize specificity, not sensitivity.

Our concern, of course, is that in the setting of a heart failure trial, where the investigators are all heart failure doctors, when one of those doctors tells us that the patient is admitted for heart failure and that everything is not as clearly documented or, as you say, there's a reason why a sign or symptom may be absent, then in many respects, we are second-guessing that investigator who has decided to admit that patient for heart failure; and that might be good in certain clinical trial circumstances, but it might not be good in other clinical trial circumstances.

Akshay, would you be able to talk a little bit about the specifics of when you felt that the CEC may have been handcuffed because of either lack of source documentation or lack of clarity with respect to symptoms?

DR. DESAI: Yes. This is Akshay Desai. Can everyone hear me?

DR. O'CONNOR: Yes.

DR. DESAI: Thanks, Dr. O'Connor, for the question. I think you're absolutely right, that there were circumstances, both due to lack of detail within the source documentation and occasionally due to confounding of some of the symptom presentation by comorbidities in which the CEC would have liked to have adjudicated heart failure but could not find sufficient support to meet the elements of the charter definition, which was drawn from the SCTI document.

So I think there were examples of cases sometimes where we had scant documentation, and we would query the sites to provide additional supporting evidence to meet the trial definition and could not get it, and therefore, in some cases reluctantly, failed to adjudicate heart failure; and then in other circumstances where there was a lot of discussion based on symptoms that may have been related to comorbidities such as obesity, or COPD, or other diagnoses, where it wasn't clear that it was evidence of heart failure, and we had trouble therefore meeting the letter of the

definition.

So I would say that we erred on the side of specificity, oversensitivity, and tried to meet the study definition on each of its elements in order to adjudicate heart failure.

DR. LEWIS: Thank you.

DR. O'CONNOR: So doing so, I just want to understand from the data safety monitoring board interim analysis, when two-thirds of the adjudicated events were evaluated, did the DMC communicate to the steering committee in any fashion -- because of what looks like it was about a 50 percent reduction in the efficacy on heart failure hospitalizations possibly due to this adjudication anomaly -- that the trial should either increase enrollment -- maybe enrollment was done -- but more importantly extend follow-up to accrue more events, given the landing of this plane at p-value 0.06?

DR. SOERGEL: Dr. Solomon, would you like to comment?

DR. SOLOMON: Yes, sure, and Marty Lefkowitz

can weigh in if there's something that I'm misremembering. But, no, the DSMB did not make any recommendations at that time other than to say continue the trial as planned. When we go back and look at what the DSMB was looking at during this trial, it was actually a positive trial for them throughout the entire time that they were reviewing it. It was only the last several months, again because of the borderline nature, that the p-value went above 0.05.

DR. O'CONNOR: Thank you, Dr. Lewis and Dr. Solomon.

DR. LEWIS: Thank you.

MS. Chauhan?

MS. CHAUHAN: Thank you. This is Cynthia Chauhan, patient representative. I think my question is for Dr. McMurray, but I'm not sure. I understand thinking about the different types of heart failure in terms of ejection fraction, but I also know that HFpEF is a very complex systemic disease as opposed to HFrEF, and more and more work is being done on phenotyping HFpEF.

So when you look at it from that point of view and you look at the use of Entresto, have you looked at the phenotypes for different response to this drug, given that the response appears to be primarily in the mid-range population?

DR. McMURRAY: Thank you very much for that question. It's John McMurray here. I suppose in a way the best phenotyping that we understand in heart failures is phenotyping by ejection fraction, which is why we focused on that to some extent . We have looked at the effect, obviously, according to other comorbidities, according to renal function, according to various biomarkers, and essentially see a consistent picture. I know there are other approaches to phenotyping, for example, using artificial intelligence and so on, but we've not done that.

But I agree with you, this is a complex condition. It is probably multiple conditions. We've only scratched the surface of that today by talking about now the trichotomization of ejection fraction, but there's probably much more to

understand about these patients.

MS. CHAUHAN: Thank you. And the other thing that I wonder about as I look at this, I think we all know that HFpEF is often misdiagnosed or undiagnosed, and when approval would get out into the communities, how do you see working with the community physicians to help them understand appropriate use as opposed to just throwing a drug at something?

DR. McMURRAY: That's an --

DR. SOERGEL: I think I could answer Ms. Chauhan really quickly on that one.

MS. CHAUHAN: Sure.

DR. SOERGEL: This is, actually, why we're here today. We think it's important to provide prescribers with information about Entresto's potential effects in HFpEF patients, and this will allow us to provide the appropriate materials so that treatment can be directed more appropriately. I think with respect to how the academic and medical community would take up the medicine, maybe I'll hand that off to Dr. McMurray.

DR. McMURRAY: I'm so sorry.

DR. LEWIS: I'm going to --

DR. McMURRAY: I was going to say --

DR. LEWIS: Go ahead. We're a little bit past time, so if you could be brief.

DR. McMURRAY: Okay. I'll be very quick.

We obviously spent a lot of time thinking about that when we designed PARAGON-Heart Failure. You heard there were problems with TOPCAT with similar questions, to be honest, but in other trials we did call out preserved. So in this trial, we tried very hard, on the basis of requiring structural heart disease on an echocardiogram -- elevated biomarkers, elevated natriuretic peptides -- to be sure as possible that these patients who had symptoms and signs had those because their heart wasn't working properly. And to me, translating the approach we used in the trial into clinical practice would be the best way to implement this evidence.

MS. CHAUHAN: Thank you.

DR. LEWIS: Okay. I have Dr. Gibson,

myself, Dr. Thadhani, Dr. Kasper, and Dr. Nissen with questions remaining. I believe we'll have time to come back to them later, but now we will take a 10-minute break. Please remember that there should be no chatting or discussion of the meeting topic with anyone during the break. We will resume at 11:27 Eastern time. Thank you.

(Whereupon, at 11:18 a.m., a recess was taken.)

DR. LEWIS: We will now proceed with FDA presentations.

FDA Presentation - Charu Gandotra

DR. GANDOTRA: Good morning, advisory committee, panel members, FDA colleagues, applicant participants, and all attendees. I am Dr. Charu Gandotra, clinical reviewer from the Division of Cardiology and Nephrology, Office of New Drugs, CDER, FDA. We are here today to present Entresto for the proposed indication of heart failure with preserved ejection fraction to the Cardiovascular and Renal Drugs Advisory Committee. This will be a joint clinical and statistical team presentation.

This slide acknowledges the FDA review team. As presented earlier today, sacubitril/valsartan is approved to treat patients with heart failure with reduced ejection fraction defined as left ventricular ejection fraction, LVEF, of equal to or less than 40 percent.

The applicant is seeking a new indication stated as: to reduce worsening heart failure defined by the applicant as total heart failure hospitalizations and urgent heart failure visits in patients with chronic heart failure and preserved ejection fraction with LVEF below normal. The applicant has defined heart failure with preserved ejection fraction, HFpEF, as heart failure with LVEF equal to or greater than 45 percent.

The study supporting the proposed indication is PARAGON-Heart Failure, details of which were presented earlier today. PARAGON-Heart Failure did not meet its prespecified success criterion for the primary endpoint, however, several supportive efficacy analyses suggest a consistent treatment effect. The Division of Cardiology and Nephrology

solicits advice from the advisory committee on whether available data support benefit of sacubitril/valsartan for treatment of patients with symptomatic heart failure with LVEF equal to or greater than 45 percent.

HFpEF is an ill-defined syndrome that is associated with increased risk of morbidity mostly due to the recurrent hospitalization for heart failure and mortality. It is increasing in prevalence with no approved therapies. Hence, HFpEF represents a significant unmet need.

The primary efficacy endpoint of the PARAGON-Heart Failure trial was an adjudicated composite of total hospitalization for heart failure that included first hospitalization and recurring hospitalizations in cardiovascular death. The division agreed to the prespecified threshold of a one-sided p-value of less than 0.024 in the final analysis to reject the null hypothesis. However, PARAGON-Heart Failure demonstrated a rate ratio of 0.87; a 95 percent confidence interval of 0.75 to 1.01; a one-sided p-value of 0.029; and a

two-sided p-value of 0.06. Thus, the study failed to reject the null hypothesis.

Prospectively planned exploratory analysis using an expanded composite endpoint that combined the primary efficacy endpoint of total hospitalization for heart failure and cardiovascular death with urgent heart failure visits was conducted. This expanded endpoint was defined as "worsening heart failure." Urgent heart failure visits were heart failure events defined similarly to hospitalization for heart failure, except that no overnight hospitalization was required for treatment.

We believe that an urgent heart failure visit is an important event reflecting morbidity associated with heart failure. The distinction between urgent heart failure and hospitalization for heart failure may predominantly reflect local clinical practice with respect to management of heart failure and possibly heart failure severity at the time of presentation. The expanded efficacy endpoint analysis yielded a nominally significant

result favoring sacubitril/valsartan with a rate ratio of 0.86; a 95 percent confidence interval of 0.75 to 0.99; and a two-sided p-value of 0.04.

The first two rows of this table summarizes the event rate and effect size for the primary endpoint and the prespecified exploratory expanded composite endpoint. Further, the applicant conducted a sensitivity analysis utilizing investigator-reported instead of adjudicated events for the primary composite endpoint. The shaded row in this table displays the result of investigator-reported primary composite endpoint. This analysis added events to the primary endpoint and resulted in a rate ratio of 0.84 with a p-value of 0.01.

Furthermore, the division has an interest in graded adjudication whereby adjudicators are not forced to provide a binary yes or no decision for each event as is commonly done and was followed in PARAGON-Heart Failure, but instead to determine a consensus probability.

Hence, after discussion of the PARAGON-Heart Failure top-line results, the FDA recommended a

blinded, independent readjudication of investigator-reported hospitalization for heart failure events that had been eliminated in the initial adjudication process. The idea was to re-categorize negatively adjudicated events where there was some probability of a true hospitalization for heart failure event.

Possibly, some true hospitalization for heart failure events may have been negatively adjudicated primarily due to a lack of documentation of data elements needed to meet the adjudication criteria for a hospitalization event. The readjudication committee members were allowed to use their clinical judgment to assign probabilities of hospitalization for heart failure to these investigator-reported hospitalization for heart failure events. These probabilities were used to obtain an average probability for each event. A multiple imputation approach was then used to integrate the readjudication events in the primary endpoint analysis.

The highlighted rows in this table show the

results after incorporation of readjudicated hospitalization for heart failure event to the primary and expanded composite endpoints. The readjudicated endpoint analysis resulted in an effect size similar to the prespecified adjudicated analysis, but with a smaller p-value.

I will now invite my colleague Dr. Jennifer Clark from the Office of Biostatistics to discuss these results in more detail.

FDA Presentation - Jennifer Clark

DR. CLARK: Thank you. Good morning, members of the committee. I'm Dr. Jennifer Clark from the Division of Biometrics II in the Office of Biostatistics. I'll be going through the efficacy data, specifically focusing on heart failure and CV death events for the PARAGON study. Each of these events could belong to one or two categories, which included being adjudicated, investigator reported, or negatively adjudicated.

Heart failure events that were negatively adjudicated were later sent for readjudication as has been previously described. In general, there

seemed to be good follow-up with patients through the end of the study. For those who did not complete, it was primarily due to death, which was balanced between the two arms.

Instead of using just the first event data, as is usually done in time-to-event analyses, recurrent events analyses were prespecified, which looks at all the endpoint events that a patient experienced during the study period. The recurrent events methods used for the analyses are shown here and differed by the type of endpoint.

Endpoints that included CV death as part of the composite were analyzed using a semi-parametric proportional rates model. Other non-death endpoints used a joint gamma frailty model to account for competing risk of CV death. The CV death endpoint was analyzed with a standard Cox time-to-event regression model.

Given how borderline the results for the different categories of the primary endpoint analysis were, we broke down the event category distribution to see how many events were either

only adjudicated, which means that the event was reported by sources other than the investigator; both adjudicated and investigator reported; or investigator reported only, which means the event was negatively adjudicated. The events that we will show are based on the recurrent events analysis, which means it includes all events that patients experienced, not just the first events.

In doing this breakdown, we looked at the data for hospitalization for heart failure, cardiovascular death, and urgent heart failure visit events. These event categories are based on the category for which the event was adjudicated into. There were 30 events, which were investigator reported as a different category from which they were adjudicated.

Of these 3 events, 8 heart failure hospitalizations in the sacubitril/valsartan arm and 18 in the valsartan arm were adjudicated as heart failure hospitalizations but reported as urgent heart failure visits. Similarly, one event in the sacubitril/valsartan arm and 3 in the

valsartan arm were adjudicated as urgent heart failure visits but were reported as heart failure hospitalizations.

For the event breakdown, these 30 events are considered to be adjudicated only. While this will not change results seen in the adjudicated analyses, some of our analyses for the investigator-reported endpoints may differ slightly from the applicant's. Leaving these events out did not have any substantial impacts on the investigator-reported analysis results.

When looking at all heart failure hospitalization events, not just first events, we see that there were 22 that were adjudicated only for the sacubitril/valsartan arm compared to 28 in the valsartan arm. Looking at the second column, it's apparent that most events were both adjudicated and investigator reported, with 668 events in the sacubitril/valsartan arm and 769 in the valsartan arm.

The third column of negatively adjudicated events has 247 in the sacubitril/valsartan arm and

315 in the valsartan arm. In comparing the first and third columns, we see there were many more negatively adjudicated events than there were adjudicated-only events in both arms. This leads to a much higher event rate for the investigator-reported endpoint. This difference adds over 500 additional events in total for the investigator-reported events analysis when compared to its adjudicated counterpart.

There were far fewer cardiovascular deaths than heart failure hospitalizations. Most events were both adjudicated and investigator reported, with 135 events in the sacubitril/valsartan arm and 139 in the valsartan arm. However, unlike heart failure hospitalization, there were more events that were adjudicated-only than negatively adjudicated. When comparing event rates between the two arms in all categories, cardiovascular death appears to be fairly balanced with little trend.

Urgent heart failure visits contributed the least number of events of these three event types.

It also had a different pattern with most of these events being negatively adjudicated. While there aren't many urgent heart failure visits, there does seem to be some trends favoring the sacubitril/valsartan arm. We will explore these trends next, comparing the efficacy event through the different endpoints.

All adjudicated heart failure hospitalizations are grouped together in the blue squares on the table. Comparing these events in the figure, we see that there is a noticeable trend with valsartan having more total heart failure hospitalizations.

All adjudicated cardiovascular death events are now circled in blue in the table. The black diamonds in the plot, which you can see over here and here, also represent these events. Adjudicated cardiovascular death appears fairly evenly split between the arms.

When we combine all of the adjudicated heart failure hospitalization and cardiovascular death events, then we have all the events that make up

the prespecified primary composite endpoint. These events are in the blue box in the table, which corresponds to the blue dots in the figure, which are here and here. When combining these two categories, we see a trend in this endpoint that is reflective of what was seen in heart failure hospitalization events.

The light blue boxes include all adjudicated events from the primary composite endpoint, as well as adjudicated urgent heart failure visits. Adjudicated heart failure visits are in the open black triangles in the plots you can see here and here. These events have a small trend favoring sacubitril/valsartan. This extends into the expanded composite endpoint, which can be seen here in the light blue circles, over here and over here.

The favorable trend for sacubitril/valsartan seen in the primary composite is also seen here, but with slightly more events. The red box contains all of the investigator-reported events that correspond to the primary composite endpoint. The gray triangle, which you can see here and here,

represents all investigator-reported heart failure hospitalization events. The gray diamonds, here and here, represent all investigator-reported cardiovascular death events. Combining these two events corresponds to the red dots you're seeing here and here.

Again, we see very little difference in the number of cardiovascular deaths and there are fewer here than were adjudicated. The trends favoring the sacubitril/valsartan arm for this composite are due to investigator-reported hospitalizations for heart failure. The red dots in the figure make it apparent that there were more of these investigator-reported events than adjudicated events due to there being more heart failure hospitalization events.

The last peach-colored box adds in investigator-reported urgent heart failure visits to the composite. Open gray triangles, which you can see over here and here, represent the investigator-reported urgent heart failure visits. Recall that the pattern for this event

proportionately had the most negatively adjudicated events, so there are many more investigator-reported events than there were adjudicated events.

Adding this into the composite endpoint, which is represented by the peach dot in the figure, which is here and here, gives the biggest jump in events when compared to either its adjudicated counterpart, represented by the light blue dots over here and here, or the investigator-reported primary composite, represented by the red dots, here and here. We'll also notice that the investigator-reported expanded composite endpoints, over here and here, also has the greatest number of events of all the endpoints examined in the efficacy analysis.

In looking at this dot plot, it's meant to give a visual comparative analysis between all the composite endpoints and their event components. One of the big take-home messages from this comparison is that the main factor behind the difference in event rates between the two arms is

due to differences seen in the number of heart failure hospitalizations.

The urgent heart failure visits event rate has a similar trend but with few events. This is seen in both the adjudicated and investigator-reported endpoints. While the investigator-reported endpoints typically have more events in both the study arms, the ratios of events are fairly similar when compared to the adjudicated endpoints.

There were 566 negatively adjudicated investigator-reported hospitalizations for heart failure events that were sent for readjudication. Of these, four had previously been adjudicated as urgent heart failure visits, so these were removed for our readjudication analysis.

The distribution for the average readjudication probabilities for each of the events is shown here with probabilities ranging from 0 to 1. While zero was the mode for the readjudicated events, most of the events were given a non-zero probability of being a heart failure

hospitalization.

These readjudicated events could be viewed as a bridge between the adjudicated and investigator-reported events. Results based on the adjudicated endpoint events are shown in blue in the forest plots, and you can see over here. Results for the investigator-reported events analysis are shown in red down at the bottom here.

We ran analyses adding in events with different thresholds for the readjudicated event probabilities. The second line in the forest plots, which you can see over here, includes only events that were both adjudicated and investigator reported. There were 668 events in the sacubitril/valsartan arm and 769 in the valsartan arm that met these criteria. All other results in the forest plots are adding in readjudicated events based on different probability thresholds.

The first threshold includes all events that were given an average readjudicated probability of 1. These additional events were added to those that were both adjudicated and investigator

reported, so now there are 679 events in the sacubitril/valsartan arm and 775 in the valsartan arm.

If you wanted to use a different probability threshold to include all heart failure hospitalization events that were assigned at least an average readjudicated probability of 75 percent or more, then those results are seen over here at the 0.75 mark on the vertical axis. Results based on average readjudicated event probabilities above 25 percent tend to be more like the adjudicated analysis results.

Rather than just including whole events into the analysis based on probability thresholds, we used multiple imputations to include the 562 negatively adjudicated events into a sort of weighted analysis. In order to do this, we imputed 1,000 data sets. The probability that the event was included in each data set was based on the average readjudicated probability. Results from these multiple imputations were then combined using Rubin's rule. This type of analysis adds

approximately 104 hospitalization events to the sacubitril/valsartan arm and 124 hospitalization events to the valsartan arm.

The results from this analysis are shown here in the middle rows. Point estimates are the same as what was seen in the adjudicated analysis results, which are shown in the top rows, however, there are more events added to this analysis.

We can see this reflected in the confidence intervals and nominal p-values. It's important to note that the prespecified adjudicated primary endpoint shown in the first row is sitting above the protocol specified threshold, so the ultimate conclusion is that we failed to reject the null hypothesis for the PARAGON study.

In reviewing this study, we ran many analyses to better understand the data, however, it is essential to remain cautious when running data explorations. Running such analyses is reasonable to better understand and characterize the results. However, any results which were run outside the prespecified multiplicity adjusted results do not

hold the same rigor to provide the same weight of evidence that the prespecified analyses offer.

Any statistical significance was lost in this study with the prespecified primary composite endpoints. While certain analysis results may look quite compelling on their own, we must be careful to avoid cherry-picking results from the study based on small p-values.

The statistical results for the study are fairly straightforward. The study failed to provide the expected level of evidence against the prespecified null hypothesis of a null or a worsening treatment effect, so it failed to reject the null hypothesis. This failure to reject the null hypothesis is not evidence that sacubitril/valsartan does not have any effect, but this study does not have the level of evidence needed to establish statistical significance for the observed treatment effect.

I'll now turn this back to Dr. Gandotra who will discuss some of the subgroup analyses. Thank you.

FDA Presentation - Charu Gandotra

DR. GANDOTRA: Thank you, Dr. Clark.

As we have heard from the applicant, subgroup analyses suggest a heterogeneity of treatment effect in two main subgroups by sex and LVEF for the adjudicated primary efficacy endpoint. These results are circled in red on this forest plot. It appears that females and patients with LVEF equal to or less than the median of 57 percent have a stronger trend in the rate ratio in favor of sacubitril/valsartan compared to males and patients with LVEF greater than 57 percent, respectively.

In the next eight slides, we will further explore the treatment effect in these two subgroups starting with LVEF. Note that these subgroup analyses results should be construed as hypothesis-generating and not as definitive evidence for or against a treatment effect within particular subgroups. In the PARADIGM trial, the demonstrated efficacy of sacubitril/valsartan versus enalapril in patients with heart failure, with LVEF equal to or less than 40 percent, such

heterogeneity of treatment effect was not observed. The median LVEF in PARADIGM-Heart Failure was 35 percent.

This table shows the distribution of patients and primary efficacy endpoint event rate in the two subgroups and sub-subgroups. The breakdown of patients between these subgroups and sub-subgroups was fairly even. The largest sub-subgroups were males with LVEF below the median and females with LVEF above the median. The overall event rates were similar between all sub-subgroups except females with LVEF above median who experienced the lowest event rate.

In PARAGON-Heart Failure, screening LVEF values were measured by echocardiography. The American Society of Echocardiography defines normal LVEF range as 52 to 72 percent in males and 54 to 74 percent in females. This bar graph displays the distribution of patients in PARAGON-Heart Failure by LVEF categories and treatment arms. Note that 46 percent of the PARAGON-Heart Failure population had an LVEF equal to or less than 55 percent,

which, based on the American Society of Echocardiography definition of normal LVEF, includes all patients with a below normal LVEF in PARAGON-Heart Failure.

This figure submitted by the applicant displays the estimated treatment effect of sacubitril/valsartan compared to valsartan against LVEF at screening as a continuous variable. The rate ratio for the adjudicated primary endpoint is less than 0.8 in patients with LVEF between 45 to 55 percent. It is between 0.8 and 1 in patients with LVEF between 55 and 65 percent and more than 1 in patients with LVEF greater than 65 percent, which is only 15 percent of the PARAGON-Heart Failure population.

While these analyses suggest that patients at the lower end of the LVEF spectrum studied in PARAGON-Heart Failure have a greater treatment effect and there is a biologic plausibility for such a finding, the likelihood of this being a chance finding cannot be completely excluded. If overall trial results had been statistically

significant, the relationship between LVEF and treatment effect would have been interpreted with more confidence.

We further explored the event rate for adjudicated primary composite endpoint in the two subgroups by treatment arm. The results are displayed in this table. The first row shows that the event rate was lowest in females on sacubitril/valsartan shown in red, whereas the event rates in the other three subgroups were fairly similar. The second row shows that the event rate was highest in patients with LVEF equal to or below median in valsartan arm shown in red, whereas event rates in the other three subgroups were fairly similar.

Possible interpretations of these findings can be, number 1, in the sacubitril/valsartan arm, given that the event rate is similar in both LVEF subgroups, one may infer that patients responded similarly to sacubitril/valsartan regardless of HFpEF; number 2, in the valsartan arm, event rate is higher in patients with lower LVEF compared to

patients with higher LVEF.

If patients with LVEF less than the median are considered more similar to patients with HFrEF than HFpEF, then one will expect that an angiotensin receptor blocker will be more efficacious in patients with LVEF less than, compared to greater than, the median LVEF of 57 percent. These data suggest heterogeneity of response by LVEF to valsartan, not to sacubitril/valsartan.

The third row in this table shows event rates in these sub-subgroups. In male patients with lower LVEF, event rates were similar between the two treatment arms. In male patients with higher LVEF, the event rate is lower in the valsartan arm. In female patients with lower LVEF, the event rate is lowest in the sacubitril/valsartan arm and highest in the valsartan arm compared to any other groups, leading to the lowest rate ratio. In female patients with higher LVEF, the event rate is slightly lower in sacubitril/valsartan arm compared to the valsartan

arm.

These data suggest that male patients, regardless of LVEF, do not respond to sacubitril/valsartan. We find these results to be inconclusive. We believe that the support for efficacy of sacubitril/valsartan from the PARAGON-Heart Failure trial depends, to some extent, on whether heart failure is one disease that encompasses both reduced and normal ejection fraction; or whether it is two distinct diseases, HFrEF and HFpEF; or more than two diseases, HFrEF or failure with mid-range ejection fraction and HFpEF with multiple etiologies.

Arguments against approval of sacubitril/valsartan for treatment of patients with HFpEF are as follows. PARAGON-Heart Failure failed to reject the null hypothesis for the prospectively planned primary efficacy endpoint. If HFpEF is truly distinct from HFrEF, then a single trial that fails to reject the null hypothesis does not provide substantial evidence of efficacy to support approval.

Furthermore, the subgroup analyses suggest a heterogeneity of treatment effect in two important subgroups but no conclusions can be drawn from available data. In the valsartan arm, the primary endpoint event rate is higher in patients with LVEF equal to or less than 57 percent compared to LVEF greater than 57 percent, which is unexpected and may perhaps be contributing to the observed treatment effect.

Considerations favoring approval are as follows. Various prespecified sensitivity and post hoc analyses suggest efficacy of sacubitril/valsartan compared to valsartan in reducing heart failure events in the overall patient population of heart failure with LVEF equal to or greater than 45 percent.

If we consider that the pathophysiology of heart failure is somewhat overlapping between patients with LVEF equal to or less than 40 percent and greater than or equal to 45 percent, then the findings of efficacy of sacubitril/valsartan in PARADIGM-Heart Failure lends support to the

efficacy findings in PARAGON-Heart Failure. The safety profile of sacubitril/valsartan is similar in PARAGON-Heart Failure and PARADIGM-Heart Failure.

Finally, patients with heart failure with LVEF equal to or greater than 45 percent represent a significant unmet need with no approved therapy. The overall benefit-risk considerations may support approval of sacubitril/valsartan to treat patients with heart failure with LVEF equal to or greater than 45 percent. Thank you for your attention.

Clarifying Questions

DR. LEWIS: We will now proceed with clarifying questions for the FDA. Dr. Gibson and Dr. Thadhani, you had your hands up from before. If you still have a question for the FDA, please put your hand up, but if it was intended for the sponsor, please put it down.

Please use the raised-hand icon to indicate that you have a question, and remember to clear the icon if you've asked your question. When acknowledged, please remember to state your name

for the record before you speak and direct your questions 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 with a question with, "That is all for my questions," so we can move on to the next panel member.

Dr. Gibson, do you have a question?

DR. GIBSON: Yes, I do have one question for the FDA, but also, I guess in another time, a question for the sponsor.

The question for the FDA was, yes, we see a positive interaction term for EF; yes, we see a positive interaction term for gender. But I'm interested in the interaction between these two. In other words, did you explore whether there was a second-order interaction such that gender modifies the relationship between EF and the treatment effect?

I mean, looking at the two by two table, it

appears that way. For me, it would make a difference in understanding if this is a true modification of the results by EF by gender. So that is my question. Thank you.

DR. GANDOTRA: Thank you, Dr. Gibson, for your question.

DR. CLARK: Hi. It's -- go ahead.

DR. GANDOTRA: We did explore the possibility of confounding. On slide 36, we have some descriptive statistics that displayed the percent, the distribution of patients in these sub-subgroups, but I will defer further clarification to Dr. Clark.

DR. CLARK: We looked at the sub-subgroups as was seen in the subgroup slides. There would be an interaction with a small p-value for that, but it is not something that we explored too vigorously. We wanted to look more at the modification within each of the sub-subgroups and what the clinical interpretation of that could potentially be.

DR. GIBSON: Yes, so they each modify the

treatment effect, but gender may modify the impact of the treatment effect and vice versa.

Is that what you're saying?

DR. CLARK: Yes, that's correct. It looks like there could be potentially something there, but we decided to look at this as more hypothesis-generating than anything that is definitive.

DR. GIBSON: Sure. Alright. Thank you for answering my question. I have no further questions for the FDA.

DR. LEWIS: Thank you.

Dr. Nissen?

DR. NISSEN: Yes. Thank you. I have two questions. One is I'd like to get the FDA's reaction to a concern about recurrent event analyses. In recurrent event analysis, a small number of patients having very many recurrent events would have a huge weight on the outcome, would it not, such that you could have a therapy where the overall effect on the large population was modest; but because a handful of people had a

lot of events, each patient isn't weighted the same. A few patients are weighted very heavily.

I'd like the statisticians and others to react to that concern about using recurrent event analysis.

DR. CLARK: This is Jennifer Clark with the FDA again. That is something that we looked into in terms of the methodology. We ran different sensitivity analyses to see how the recurrent events analyses are affected, the results, and we looked at the distribution of events, the number of events experienced by different patients, and you can see that in our briefing package.

Most patients experienced zero or one event, but you can see we also compared this to the first event analyses, which you have a hazard ratio of around 0.9, I believe. So there was some impact, but it was reasonable. And based on the methodology, it was behaving as we would expect it to behave, so we didn't see anything wrong with the data in terms of that.

DR. NISSEN: Okay.

My second question, maybe this is a rhetorical question and maybe it's not. FDA statisticians, do you have the view that there is really a major difference between a p-value of 0.059 and 0.4? Is it really all that different? That's probably a rhetorical question, but I'd like your reaction to this idea that there's something magical about the 0.05 value.

DR. CLARK: I guess in our briefing document, we sort of called the results more borderline because you have to draw these thresholds and you do have to prespecify them. And while there might not be much difference, you can kind of see in the readjudicated analysis results, adding more events, it didn't change the point estimates at all, but your p-values are affected by that.

So, yes. It's just a matter of how many events you have in your analyses that is really what's going to affect your p-values and your test results, and that was something we were trying to emphasize in our presentation by showing the number

of events.

DR. NISSEN: I got that message.

DR. EMERSON: Dr. Lewis, this is Scott Emerson. May I comment on that question?

DR. NISSEN: Please, Scott.

(Laughter.)

DR. EMERSON: It's so rare statisticians are asked to respond.

DR. LEWIS: I agree. I agree, Scott. Go ahead, as we spoke about in practice. Go ahead.

DR. EMERSON: The p-value was measuring the chance that you're going to approve distilled water, something that you know doesn't work and what percentage of the time that will happen. Of course, the power is the probability that if a treatment truly works, we look at it.

We're also interested in the positive predictive value; that is to say given that we approve a drug, what's the chance that it works? And the statistical power and the type 1 error map between the prior probability that a treatment works and the posterior probability; that is to say

if you test all drugs and 10 percent of them really works, then after we find the significant results, what's the positive predictive value?

In a simple model, you can look at the power divided by the type 1 error. That means if you look at the 0.05 versus 0.059, that is a 22 percent increase in your type 1 error. In order to have the same positive predictive value when you use 0.09 versus when you use 0.05, you would need to increase your power by a relative 22 percent, which is impossible from 90 percent to over 100 percent.

So we care more about slight differences in the type 1 error than we care about slight differences in the power. And I'll just remark that most things we do that inflate the type 1 error do not inflate the power by very much. So maybe instead of 85 percent power -- I don't have a way to compute this, but I'm going to say maybe we have 86 percent power if we agree to use level 0.06 the way we did it, inflating it. So you lose something in the positive predictive value.

Perhaps we don't care too much when we think

the drug works. If the LVEF is close to 0.45, maybe we're so much considering that that's probably really a HFrEF patient that we're pretty sure it works. But when you're up at the other end, where we've been entirely unsuccessful over the years in finding a treatment, the prior probability that the treatment works is probably quite low, and by inflating our type 1 error, we've greatly increased our -- well, greatly decreased our positive predictive value. So that's my long-winded answer.

DR. NISSEN: A fabulous answer, Scott. Thank you.

DR. LEWIS: Dr. Ridker?

DR. RIDKER: Yes, thank you.

Let me preface my specific clarifying question by the fact that I appreciate we have a very sophisticated committee and a very sophisticated FDA; in fact, in this particular case, a very sophisticated set of investigators. And many of the issues that Dr. Stockbridge noted in his opening statements to us is really what this

is all about, and I appreciate the flexibility being shown here by both investigators and the FDA to think a little bit beyond just the p-value, just the confidence interval, and try to focus on what's really best for the patients in front of us.

That being said, we can bring up slide 43. I think it makes this the most easy way to ask the question because we're talking here about a variety of important clinical trial issues. Having both been an investigator and on these committees for many, many years, I think this is the first time I've seen the FDA present a subgroup of a subgroup.

I understand why it's being done here, but I guess the clarifying question is simply -- Dr. Stockbridge noted that there have been some times in the past when the FDA did move beyond the primary endpoint to approve a drug for various issues, and I think that was correct and good -- I just want to know is there a precedent for a subgroup of a subgroup? And I can't quite tell what the argument being made in slide 43 was here.

DR. GANDOTRA: So as I mentioned, these are purely exploratory. We were trying to further understand the heterogeneity of treatment effect that we observed in these subgroups. These numbers, they're inconclusive, but we were looking at this closer to see if we can get to some better understanding of why we're seeing this heterogeneity.

(Crosstalk.)

DR. GIBSON: I will interject, that in the prasugrel experience, the FDA looked at low body weight, the older patient, and those without prior stroke TIA, three subgroups, in redirecting the labeling based upon subgroups within subgroups of subgroups as well. So there is some precedent from my recollection.

DR. RIDKER: My memory is that had to do with differing side effects in different groups. I don't think we're talking about -- what we're getting at here is this slide has a suggestion that women -- and I congratulate the investigators who had more than 50 percent women, which is

terrific -- clearly benefit in this reanalysis, and I think that's great. But we've seen other analyses, both from the FDA and from the sponsor, showing that on this continuous ejection fraction scale, the men also seemed to benefit. And that's where I'm just trying to figure out where you're asking us to focus our attention, I guess.

DR. GANDOTRA: So when you look at the data on a continuous scale, it does suggest that males derive some benefit; albeit, it is lower than females. When you look at LVEF, it's the same thing. Patients who have lower LVEF appear to be deriving more benefit. The data in these tables are dichotomized, so they don't show the complete picture, but it's just another way to compare the findings in these subgroups.

DR. RIDKER: Okay. Thank you. I appreciate that.

DR. LEWIS: Dr. Ridker, are you done?

DR. RIDKER: Yes, thank you.

DR. LEWIS: Okay.

Dr. Gibson, did you have a question?

DR. GIBSON: I did have one more question, and I was wondering if the FDA looked at this issue. We often view hospitalization as a binary event, but some hospitalizations may be more severe and last longer. The patient-centric outcome is how long was I out of the hospital and alive? In moving towards embracing continuous variables rather than dichotomania, was their analysis done looking at numbers of days alive out of the hospital without urgent clinic visits or hospitalization? Thank you.

DR. GANDOTRA: Yes, days alive and out of hospital due to hospitalization for heart failure were looked at, and the difference is about 7 days favoring sacubitril/valsartan.

DR. GIBSON: And was that statistically significant?

DR. GANDOTRA: I would reserve statistical comments here. This was one of the many exploratory analyses that were done in this trial.

DR. GIBSON: So was it nominally significant?

DR. GANDOTRA: I believe not, but I can defer to the applicant for clarification.

DR. GIBSON: Okay. Thank you.

DR. LEWIS: Okay. Thank you, Dr. Gibson.

I have a couple questions, and maybe I guess they're all questions. First off, I wanted to clarify that, indeed, nominally the study drug lost on first event analysis, and also that obviously the dichotomy versus doing a more weighted response to any event has nothing to do with adjudication except those are separate concepts that could be done either by an adjudication committee or by local investigators.

However, the local investigators didn't know they were being adjudicated afterwards, and I don't know that the FDA has any information or I could find any in the literature about what would happen between the concurrent if they did not know that they were going to be followed up by a sophisticated adjudicated committee.

Also, do we have any data on whether the PIs at the local sites were actually caring for the

patients during these hospitalizations or that they were even at the hospital that the PI was at, or whether they were working with the same sort of discharge summary information available to the adjudicators?

Do you guys want me to do those over again for you one by one?

(No response.)

DR. LEWIS: Did the FDA hear me?

DR. GANDOTRA: From the FDA --

DR. LEWIS: Okay. Go ahead. This is for the FDA, yes.

DR. GANDOTRA: We do not have data to inform us how the investigators would report if they did not know whether the new events were going to be adjudicated or not know if that was going to happen. There is plenty data. When you look retrospectively at trials that had central adjudication, the treatment effect did not change very much if they looked at investigator-reported versus adjudicated events.

So to answer your questions, we do not have

that kind of data to answer if they would behave differently. And I will defer this to the applicant if they have any additional clarification on this.

DR. LEWIS: I will let you go ahead and answer the other questions, then we can come back to the sponsor later for that question. Did you have any data on whether the PIs were caring for the patients or was even at their hospital when they characterized the events, and could you confirm that nominally it lost on the first event analysis?

DR. GANDOTRA: No, I do not. The first event analysis was not the primary endpoint here. It was the total hospitalization for heart failure. So we were not expecting a significant p-value here.

DR. LEWIS: Okay. I think that it actually nominally lost, if I recall from both the briefing documents, but we can maybe clarify that later.

Dr. Emerson, do you have the question or was it answered?

DR. EMERSON: That was in order to make the comment, so I lower my hand.

DR. LEWIS: Okay. Great.

Dr. Merz?

DR. BAIREY MERZ: Yes. In follow-up to the prior questions, specifically Dr. Gibson, did you look at the New York Heart classification as well as the Kansas City Heart Failure Questionnaire for these similar types of interactions for ejection fraction and gender, as we have been presented in the primary outcome? Specifically, did they track together? Also, these symptomatic characterizations, did they track with the outcome?

(No response.)

DR. NISSEN: I think somebody is muted who's speaking.

DR. LEWIS: Yes. The FDA, we cannot hear you. But it's the FDA, so it shouldn't be muted.

Can everybody hear me?

DR. BAIREY MERZ: Yes.

DR. GANDOTRA: Yes. I believe this question is for Dr. Gibson.

DR. BAIREY MERZ: No. The question is for the FDA.

DR. LEWIS: No, no, no.

DR. BAIREY MERZ: I'm sorry. You demonstrated interactions, which are more important than sub-subgroups, for both gender and left ventricular ejection fraction greater than or equal to 57. Did the Kansas City Heart Failure Questionnaire and the New York Heart Association classification demonstrate similar interactions? Did the symptoms track with the outcomes and hospitalization?

DR. GANDOTRA: So first point, the change in KCCQ and NYHA class, we did not think that those changes were clinically meaningful; that's one. Second, we questioned the interpretability of the p-value that's associated with these secondary analyses when the primary endpoint was statistically -- was not significant. There were subgroup analyses done, and they are not consistent with the overall subgroup findings for the primary efficacy endpoint.

DR. BAIREY MERZ: Thank you. But interaction analyses can be done even though the primary results are not statistically significant by randomization, and sometimes those interaction analyses are informative.

DR. LEWIS: Does the FDA want to comment on that?

DR. GANDOTRA: Thank you. We did not conduct such interaction analyses.

DR. BAIREY MERZ: I'll just leave the comment, I think that that would be informative. Thank you.

DR. LEWIS: Thank you, Dr. Merz.

I want to remind everybody, even though I call on you, to also state your name before speaking.

Ms. Chauhan?

MS. CHAUHAN: Thank you. Cynthia Chauhan. I realize my language base is different from many of yours, So if this has been discussed and I missed it, I apologize.

I understand that in mid-range heart

failure, you see a usable place for this. What I don't understand and I don't think I've heard is when you look at the range of HFpEF, did you look at where the negative side effects -- where the adverse events fell? Did they fall more in the above-50 range, more in the below-50 range, or just across the board?

DR. GANDOTRA: This is Charu Gandotra. Thank you for your question. Overall, the adverse effect profile is similar between patients who have reduced ejection fraction versus patients that were enrolled in PARAGON-Heart Failure. We did not further divide the data into subgroups to see if there were differences by median LVEF in PARAGON-Heart Failure. So they're fairly similar if you had an ejection fraction less than 40 percent versus greater than 45 percent. Thank you.

MS. CHAUHAN: My concern with this is if you expand this medication to all HFpEF patients but it only is significantly useful in those with ejection fractions below 50, are you expanding the exposure to side effects, without equal opportunity for

benefit, to those with normal range ejection fraction?

DR. GANDOTRA: That's a good point. When we look at the overall benefit-risk ratio here, the benefit of potentially preventing hospitalization for heart failure versus a potential adverse effect profile of decrease in blood pressure, increase in potassium, side effects can be monitored and mitigated. In the overall picture, the benefit might be more here than the potential risk.

MS. CHAUHAN: So even for those that are above 50 percent, or above 50?

DR. GANDOTRA: Only 25 percent of the PARAGON-Heart Failure population had an ejection fraction of less than 50 percent, and if you look at 55 percent cutoff, its only 46 percent of the population. So we are really going into sub-subgroups when we look at an LVEF of 50 percent.

MS. CHAUHAN: Okay. Thank you.

DR. LEWIS: Dr. O'Connor?

DR. O'CONNOR: Yes. Chris --

DR. LEWIS: And please state your name.

DR. O'CONNOR: -- O'Connor here.

DR. LEWIS: Thanks.

DR. O'CONNOR: A question for the FDA scientists on slide 43. It seemed that you had raised concerned about the 16.4 events per hundred patient-years in the valsartan group for the LVEF less than equal to 57. Could you restate your concerns? Because I don't see a concern there. We know that patients with lower ejection fractions have higher event rates, and in the treatment in sacubitril/valsartan, it's lower, but that suggests the treatment efficacy.

DR. GANDOTRA: Right. And as I mentioned before, these are purely exploratory to understand this better.

One of the concerns here was that patients who have an LVEF equal to or less than 57 percent have patients who potentially are more similar to patients who have reduced ejection fraction. So they should have responded better to an ARB versus

patients who have an LVEF of greater than 50 percent, where this was not an improved therapy for these patients. But your point is well taken, but this may be just because the event rate is higher in patients who have a lower LVEF. So point well taken. Thank you.

DR. O'CONNOR: Thank you, and thank you, Dr. Lewis.

DR. LEWIS: Dr. Gibson, did you have another question? Because your hand is up.

DR. GIBSON: I'm so sorry. I forgot to put my hand down.

DR. LEWIS: Okay. Dr. Thadhani?

DR. THADHANI: Yes. Good morning. Thank you, Dr. Lewis.

A question for the agency. First of all, thank you for the thorough analysis. In slide 35, the agency highlights that in PARADIGM there's no heterogeneity of treatment effect when it was examined by sex or median LVEF.

I'm curious from the agency's standpoint how we as reviewers should take that comment in light

of some encouragement, I would say, not just by the agency but also of course by the sponsor, too, and perhaps look at PARADIGM and PARAGON as more similar than dissimilar, given those striking differences in the sex findings. Thank you.

DR. GANDOTRA: Thank you. This is Charu Gandotra again. The reason why we bring this up is that we are trying to understand is there truly a different response by sex to sacubitril/valsartan. In PARADIGM-Heart Failure, both men and women derived benefit with sacubitril/valsartan, whereas when we look at PARAGON-Heart Failure, data appeared to suggest that men maybe derived very little or no benefit with sacubitril/valsartan.

So is there a biologic possibility for such a differential response if your EF is different? It does not seem likely but a point to be considered as we're trying to figure out if these subgroup differences are real or not.

The other point that was brought up earlier today, PARAGON-Heart Failure looked at recurrent hospitalization events, so the number of patients

who contributed to the difference in treatment effect is small. Now, could that lead to these big differences in rate ratios in these two subgroups is another question, but a low concentration, I might add.

DR. THADHANI: Thank you.

DR. LEWIS: Okay. If it's ok with the panel, what I'd like to do, if there are no further questions for the FDA, I have a list of people who had outstanding questions to the sponsor, and the first was Dr. Gibson. If you still have questions for the sponsor, it would be helpful if you went ahead and put your hand up. And I have myself, Dr. Thadhani, Dr. Kasper, and Dr. Nissen, if that's correct.

Dr. Gibson?

DR. GIBSON: Yes. My question was, again, as I asked the FDA before, the total number of days out of the hospital free of death, it sounds like it was reduced by 7 days. Does the sponsor know if that's the correct number and was there a nominal p-value associated with that? Thank you.

DR. SOERGEL: Thanks, Dr. Gibson. Yes, we do have those data.

Dr. Lefkowitz, do you want to comment on this?

DR. LEFKOWITZ: Sure.

Hi. This is Marty Lefkowitz from Novartis clinical. The answer is that it was not nominally significant. But I do want to point out that days alive out of the hospital relates to total hospitalizations as well, as opposed to just heart failure hospitalizations. Obviously, we particularly chose recurrent events because we thought it was a better metric because of the variability in discharge across the globe.

DR. GIBSON: But days out of the hospital and free from heart failure hospitalization, do you know that number?

DR. LEFKOWITZ: Yes. No, I'm sorry. The 7 days is days alive out of heart failure hospitalization. That's the 7 days, and that was not nominally significant.

DR. GIBSON: But that is for all

hospitalizations; that's not for heart failure hospitalizations.

DR. LEFKOWITZ: Actually, I would need to check that specifically. I would need to check that.

DR. LEWIS: Okay. Go ahead and check it, and you either can come back to us during this question period or after our lunch break.

I have the next questions. I wonder if the sponsor could help us understand why CV death was included in the primary outcome since you had well-established evidence that CV deaths were less common in the HFpEF group. Also, with this thought that you think this is going to be beneficial throughout the ejection fraction range, could you tell us a little bit about why you reduced -- in PARADIGM, you amended the protocol to only allow people in with an ejection fraction less than 35 percent.

DR. SOERGEL: Thanks, Dr. Lewis. Obviously, CV death is an important event and is a typical component of the composite primary endpoints for

cardiovascular outcomes trials.

Let me ask Dr. Solomon perhaps to comment on the rationale for including it in PARADIGM specifically.

DR. SOLOMON: Yes. First of all, you're absolutely right that CV deaths are less common in patients with heart failure preserved ejection fraction. And as Dr. McMurray's also alluded to, because the proportion of deaths that our cardiovascular is lower in heart failure with preserved ejection fraction, we believe that the total number of deaths will be less modifiable.

But we do include these because, number one, they're competing risks, and if there were indeed a potential benefit of CV deaths -- and it's conceivable there would be if we had enough power -- we know that we would have had to do a much, much larger trial to have done that because cardiovascular death, we had about 400 overall in this study. We had a hazard ratio that obviously was 0.95. We had in the original calculations anticipated potentially 0.9, but that would have

even required 2500 events and we only had about 400, but we had to include it for the issue of competing risks.

The other question, if I might answer, regarding PARADIGM, why did we amend the protocol, the primary reason the protocol was amended -- and it was amended well into the trial when we already had many thousands of patients who were in the 35 to 40 percent range -- at that time, the EMPHASIS-Heart Failure trial had been reported, and we were concerned that based on those results, there would be a marked increase in the use of mineralocorticoid receptor antagonists, which would lead to a reduction in the event rate; and one way to address that was to amend the protocol so that we ended up with patients with a lower overall ejection fraction in the trial. But depending on whether you include 35 exactly in or not, there were still as many as 2,000 patients in the PARADIGM-Heart Failure trial between the range of 35 to 40 percent.

DR. LEWIS: Thank you. Those are all my

questions.

Dr. Gandotra, do you have a comment or an answer?

DR. GANDOTRA: I just wanted to share the number about number of days alive out of the hospital in PARAGON-Heart Failure.

Days alive out of the hospital during the randomized treatment period, adjusting for follow-up time, was 7.14, and this is the difference between sacubitril/valsartan versus valsartan. The confidence interval here is minus 5.86 to 20.15, and if you look at days alive out of heart failure hospitalization during randomized treatment period, adjusting for follow-up time, the number is 6.49 with a confidence interval of minus 6.36 to 19.38.

I just wanted to clarify that. Thank you.

DR. GIBSON: Thank you.

DR. LEWIS: Thank you very much.

Dr. Thadhani?

DR. THADHANI: Thank you, Dr. Lewis. A question for the sponsor. This is a question for

David, I believe, as well as for Scott, possibly. On slide 68, the sponsor, or I believe Scott, presented quite impressive data when the effect on the renal outcomes for the patient population were highlighted, with a quite impressive point estimate and confidence interval.

The question I had was as follows. Number one, while there may not have been a reason to do so, I was curious if the sponsor has looked at whether the readjudication events either changed the point estimate, made it stronger or weaker, if the same outcome was looked at.

The reason I ask that question is, again, we go back to the compare or contrast with PARADIGM. And in PARADIGM -- which I believe, as was presented, had virtually inclusion/exclusion criteria, especially with renal function other than, of course, with the ejection fraction -- there did not appear to be any dramatic effect on renal function. So if the sponsor or Dr. Solomon can comment on that, that would be helpful. Thank you.

DR. SOERGEL: Yes. I'll comment. It's David Soergel of Novartis. Thanks for the question. Yes, this was, I think, a very interesting finding coming out of PARAGON, this finding on the composite renal endpoint, And it actually is similar to the effect that we saw in PARADIGM. So I'll ask Dr. Lefkowitz maybe to talk through the data.

DR. LEFKOWITZ: Yes. Hi, Dave. This is Marty Lefkowitz again. In reality, findings between PARAGON and PARADIGM are actually quite similar. In PARADIGM, I have to say that I think that may have been the first study where a renal endpoint was used as the secondary endpoint in a heart failure trial. But in any case, first of all, the reduction in eGFR in both studies were very similar, between 0.5 to 0.5 mL per year.

In terms of the composite renal endpoint -- and let's bring slide 2 up, then -- this is the renal composite in PARAGON that you've seen, that Dr. Solomon has shown. The same endpoint applied in PARADIGM, you can see the

hazard ratio at the bottom. I just want to say that in PARADIGM, we prespecified a somewhat different endpoint, but we didn't hit statistical significance. The endpoint in PARADIGM, instead of the 50 percent decline, we used an endpoint that was actually used in the S study, which had to do with the 30 mL decline because we didn't think we'd have enough power to see it.

So this is a retrospective analysis in PARADIGM. As you can see at the bottom of this slide, we also showed a decrease in this more classic composite endpoint, and the decrease in eGFR was actually quite similar between the studies. And just to comment further, we've seen this decrease in eGFR between sacubitril/valsartan comparators in several other heart failure studies, so we do think it's a consistent finding.

DR. THADHANI: Great. Thank you. So the retrospective analysis, when you do apples to apples comparison, they appear to be similar. Thank you.

DR. LEWIS: Dr. Kasper?

(No response.)

DR. LEWIS: Dr. Kasper, do you still have a question for the sponsor?

(No response.)

DR. LEWIS: You're muted, Dr. Kasper.

DR. KASPER: Sorry. At this point, I have no further questions. Thank you.

DR. LEWIS: Thank you.

Dr. Nissen?

DR. NISSEN: I have no further questions.

DR. LEWIS: Thank you, Dr. Nissen.

Ms. Chauhan?

MS. CHAUHAN: Thank you. This is Cynthia Chauhan, patient rep. This is for the sponsor, and if these questions are not appropriate, just tell me.

If the FDA approves, what are your postmarketing plans? And if it does not approve, what are your plans going forward?

DR. SOERGEL: Those are great questions, Ms. Chauhan. I think it's difficult to project forward that far, but right now we're fully

committed to continuing to do research in heart failure and try to bring new therapies to patients. With respect to Entresto, I think we'll see how the conversation goes today. Obviously, based on the presentation that you've seen, we feel confident about the data that we're showing, but at the end of the day, we're open to the advice from the committee. So I hope that answers your question.

MS. CHAUHAN: Sort of. The thing I worry about is the postmarketing plans because so many physicians who take care of these patients are not knowledgeable about either the disease or the interventions.

DR. SOERGEL: Well, yes. I think it's a great point. I think if Entresto were to be approved, having an effective therapy I think would possibly give practitioners even more of a drive to make a diagnosis and to be able to deliver an effective therapy. I think it's a strong rationale for including the data in the product insert and being able to describe the treatment effects to practitioners, and hopefully finally deliver

something for this unmet need.

MS. CHAUHAN: Thank you.

DR. LEWIS: Dr. Gibson, do you have another question for the sponsor?

DR. GIBSON: Yes. So anytime there is missingness, we worry about informative censoring. Here you had very good ascertainment of vital status in all patients, except, say, nine. But we're not talking about missingness of patients here; we're talking about missingness of source documentation for the CEC process.

I was reassured that the relative risk reduction was constant in the readjudicated sample versus the original, but I guess one question that comes up is, was the characteristics of the patients who had missing information or missing source documents similar between the two groups? Was there no evidence of a process whereby there could be some informative censoring, and was the risk of the patients who had missingness of their documents similar to the risk of the patients who did not have missingness of their documents? Thank

you.

DR. SOERGEL: Those are interesting questions. I think that, starting from the top if I understand the question properly, the question is, given the stringency of the documentation requirements for the CEC, is it possible that the lack of documentation might reflect something different in the patient populations with respect to those individuals who are positively adjudicated versus those who were negatively adjudicated?

Do I have that correct?

DR. GIBSON: That was, is there a difference between the treatment arm and the control arm with respect to the amount of missingness and to the risk of patients who had missingness?

DR. SOERGEL: Yes. Maybe the place to start here is if you look at the CEC adjudicated patients, individuals who were positively adjudicated, and you look at the effect size in that population, and you compare it to the individuals who were reported by the investigator -- so didn't depend on the amount of

documentation necessarily that were collected on those patients -- the effect sizes are almost the same.

So we see a very consistent level of effect of sacubitril/valsartan in the population irrespective of that question, I would think.

DR. GIBSON: Okay. Thank you. Yes. No, it does suggest that they were non-random in distribution, but thank you.

DR. LEWIS: Okay. I think that does complete all the questions for the FDA and the sponsor.

Would it burden any of the committee members if we broke for lunch now and come back in, say, 40 minutes at 1:30 and begin? I'm told by Dr. Yu we can begin the open public hearing session at 1:30. That will give us a little more time for discussion or we may end early.

DR. MOLITERNO: David Moliterno. I'd support that motion.

DR. THADHANI: I back up that motion. Dr. Thadhani.

DR. LEWIS: Okey-doke. So we will reconvene at 1:30 p.m. with the open public session. We will now break for lunch. Panel members, please remember that there should be no chatting or discussion of the meeting topic with anyone during the lunch break. Thank you.

(Whereupon, at 12:53 p.m., a lunch recess was taken.)

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

(1:30 p.m.)

DR. LEWIS: It is now 1:30. Prior to starting the open public hearing session, Novartis has indicated to us during the break that they had a couple of follow-up slides about, I think, the time-to-first-event subject.

Is everybody back, and is Novartis ready to show us their slides?

DR. SOERGEL: We are. Thanks, Dr. Lewis.

This question came to the FDA about how we should interpret the time-to-first-event endpoint in relation to the recurrent event endpoint. As we've talked about, the rationale for recurrent events in heart failure preserved ejection fraction is that the disease is characterized by these recurrent hospitalizations and, of course, they're clinically impactful.

I'll ask Dr. Claggett to speak to the statistical rationale for using recurrent events versus time to first, and this hopefully will address your question.

(No response.)

DR. SOERGEL: Dr. Claggett, are you on mute?

DR. CLAGGETT: Hi. Can you hear me now?

DR. LEWIS: We can.

DR. CLAGGETT: Okay. Great. Sorry if you may not have heard me.

This is Brian Claggett, Brigham and Women's Hospital. Hopefully, we've made the clinical argument to the importance of counting all events and not just the first events as has been historically done in cardiovascular trials. I think the clinical rationale is the most important component of that decision, but there is also an interesting statistical angle, which, as we've learned over the course of exploring these recurring events approach, is that we have identified that the Cox model that we traditionally use actually has a technical issue in settings of high heterogeneity.

So you can imagine an international trial with HFpEF patients being extremely heterogeneous and that the Cox model will systematically

underestimate the treatment effect, so the numerical results you get with that seems to be an incomplete picture of what the true treatment effect is. This is actually known. You can see it in the sample size section of the study protocol, where we indicated that we anticipated a smaller observed time-to-first-event effect compared to the current events effect, and we've shown this in simulations and in other previous studies.

So essentially, if we view the time-to-first-event estimates as a good way of underestimating or getting something that is a 30 to 40 percent underestimate of the true treatment effect, then I think that's how I would interpret that time-to-first-event result.

DR. SOERGEL: Does that answer your question, Dr. Lewis?

DR. LEWIS: Do you have other comments, sponsor, on this? I heard you might have a slide or two to show us.

DR. SOERGEL: We do. This is in reference to Dr. Nissen's question with respect to the effect

being driven by a few number of patients. We'd like to offer a bit more color on that as well. I'll hand it over to Dr. Lefkowitz, and then to Guenther Mueller-Velten to discuss that.

DR. LEFKOWITZ: Okay. Thank you. What I'll do is just briefly review for you just the patients with the various number of events just to set the background. We did carefully look at whether this was driven by a few outliers, and my colleague, Dr. Mueller-Velten, will review that analysis, and I think you'll see that that wasn't the case.

If we take slide 3 up, this specifically shows the number of patients with these unique number of events. By that I mean there were 671 patients of the 1083 who only had one event, and as you can see, 234 had two events and so on. For example, there were only 14 patients in the study who had 7 or more events. Overall, recurrent events accounted for 43 percent of the total events in the study, and looking at other heart failure studies, that's, I think, pretty characteristic.

If you bring slide 2 up, this then shows you

the number of events by treatment group, the first event, second event, et cetera. And here you can see, if you look on the column, the fourth column, the difference. So whether it was the first, second, third, or fourth event, sacubitril/valsartan consistently reduced those number of events regardless of the number of events.

Now, I'll ask my colleague, Dr. Mueller-Velten to specifically respond to Dr. Nissen's questions about the outliers driving the events.

(No response.)

DR. LEWIS: Did you check your mic?

DR. MUELLER-VELTEN: Okay. Can you hear me now?

DR. LEWIS: Yes.

DR. MUELLER-VELTEN: Okay.

This is Guenther Mueller-Velten, Novartis biostatistics. We performed some supplementary analyses that showed that even high event achievers contributed to the magnitude of the treatment

effect, as they should. The relative contribution is limited and they do not dominate the treatment effect.

This slide shows descriptively how the overall treatment difference of the primary endpoint events in PARAGON was achieved. We had 115 fewer events in the Entresto arm, and more than 50 percent of those prevented events were first or second events. Then we had the tapering contribution of subsequent events through this treatment difference.

As Dr. Lefkowitz said, only 14 patients had more than 6 events and 9 patients had more than 7 events. We noted in the analysis -- but I should mention also that the maximum study duration was 56 months, so it's not excessively many hospitalizations. But we did an analysis -- and can I have slide 1 up -- where we tried to characterize what is the contribution of a high event number to the overall treatment effect.

For example, if you look at this, K equals 1 row, there we show that if we ignore all events

after the seventh in the analysis, we would lose approximately 1.5 percentage points of the treatment effect, going from 0.87 to 0.885. The interpretation of that is that the eighth and subsequent events contribute 1.5 percentage points to the treatment effect, which is a relative contribution of 13 percent.

In summary, the estimate of rate ratio we think appropriately reflects the magnitude of the reduction in the rate of primary endpoint events in the PARAGON study population, and the effect size is not dominated by a few patients. Thank you.

DR. SOERGEL: Thank you, Dr. Lewis. That was it for us.

DR. LEWIS: Dr. Nissen, do you have a comment or does that satisfy your questions?

DR. NISSEN: Yes. Could you put that last slide up a second? It actually shows what I was concerned about so that if you limit the analysis to four or fewer events per patient, the rate ratio is about 0.9; then if you add all those subsequent events, it then drops to 0.87.

So there is some magnification of the apparent effect by including all those additional events. If you were to go back and show us the rate ratio for time to first event, it's going to be somewhere in the range of around 0.9. So it's not a trivial effect. It's not an enormous effect, but it's certainly not a trivial effect.

I don't know if Scott Emerson or any of the statisticians want to comment.

DR. EMERSON: If I might?

DR. LEWIS: Scott?

DR. EMERSON: Yes. Thank you.

DR. LEWIS: You may.

DR. EMERSON: This is a hard issue. At one level, in terms of the true public health impact, decreasing all hospitalizations matters, certainly in terms of cost. But in terms of how many patients benefit, then I'll just note that, roughly, 20 to 40 events are at each level. So there's an excess of 30 patients who had one event, excessive. Then 28 patients having two, that's 56 events. And then similarly, if you go through and

multiply the number of events down, that deficit, at each level.

So I'm in the same boat, yes and no. There is always an interest in saying how many patients have we benefited, but I do think that the mean number of hospitalizations has some meaning, certainly on a public health impact, and perhaps it's weighted a little bit towards the patients with most severe disease, if you will.

DR. LEWIS: Dr. Ridker, did you have a question?

DR. RIDKER: Well, it's a comment on the same issue. I'm looking at my briefing book from the FDA on page 36 -- it's their table 10 -- to address this issue. It's a yin and yang issue because at one side there, they have the first event for the primary composite. The hazard ratio is 0.92. The confidence interval is 0.81 to 1.03. On the other hand, as you go down the list of all the components, they're all on the correct side of 1, and they all range somewhere between 0.92 to 0.88.

So it's not like it's moving very much, and it seems to be quite consistent across these issues. Even if you undid the rather brilliant thing the investigators did to have a composite endpoint, just simply run with the first one, you're still getting a magnitude effect on first event that's in the same ballpark as the overall trial.

I actually agree. I think the societal benefit here is substantial because it is about how many times someone gets hospitalized and the societal benefits of that. So I think it's quite an interesting analysis, and it's probably part of what we're all being asked to think about. I find it reassuring that the first event analysis has hazard ratios that are basically in exactly the same range.

DR. EMERSON: This is Scott. May I ask one more comment? And this is just to remark upon that the hazard ratio as measured by the time to the first analysis is a completely different summary measure than the hazard ratio based on recurrent

analysis or the mean number of events and things like that. So I'm not certain that I would call one more biased than the other. Certainly, there are differences in how the distributions behave, but I personally have no problem with the recurrent event analysis.

Open Public Hearing

DR. LEWIS: Okay. Thank you. I want to thank both the sponsor for sharing that information with us and our panel members for discussing it.

I believe our open public hearing speakers are here and on, so 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 it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of

your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your 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 speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, your audio is connected now.

DR. ZELDES: Great. Can you hear me?

DR. LEWIS: I can hear you. Thank you.

DR. ZELDES: Great. Thank you.

Good afternoon. Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Nina Zeldes, 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 conflict of interest.

Today the committee is asked to consider a proposed new indication for Entresto to reduce

heart failure in patients with chronic heart failure and preserved ejection fraction with LVEF below normal. As you have read in the briefing materials, the trial failed to reach the prespecified primary endpoint. While FDA consideration for approval is not unprecedented in such cases, as the FDA memo points out, it is unusual.

It is important that in the clinical trial there was no difference between treatment arms with respect to CV death risks. These endpoints only reached significance in post hoc analyses. It seems that some of the post hoc analyses were recommended by the FDA. However, post hoc analyses are meant to be exploratory and intended to follow up when a finding is in fact significant in order to better understand the findings and guide future research.

Another major concern is the lack of diversity in the sample. Only 2 percent of patients were black, 52 that took Entresto and 50 in the control group. A recent meta-analysis found

heart failure can be higher among black patients, with one study indicating heart failure rates almost twice as high among black patients. This is of particular concern since FDA and other experts have previously noted that there can be racial differences in the efficacy of cure rates for heart disease.

In addition, many of the study sites were in Europe and only 12 percent of study sites were in North America. The healthcare systems vary widely between these regions, which may affect whether these results generalize for the population in the United States, which is the major focus of the FDA.

Racial disparities in cardiac treatment and outcome are well documented and racial disparities in health care have been in the major media all year. We are not merely being politically correct when we state that more black patients are needed in clinical trials. It is a scientific and ethical responsibility to include adequate numbers of black patients when studying treatments that black patients are likely to use.

For example, other cardiac research has shown that ACE inhibitors are less effective at reducing both systolic and diastolic blood pressure among black patients compared with white patients. Interest needs to be further studied in order to show whether it is equally effective for back patients.

Unfortunately, we can't assume that postmarket research of Entresto will do a better job of recruiting black patients. We know from earlier studies that the incentive to recruit more black patients is during the premarket research, not postmarket. FDA should not approve this new indication until an adequate number of black patients have been studied and the results are conclusive for all patients.

Although the prevalence of hospitalization for heart failure is increasing in the U.S., we ask you to urge the FDA to delay approval for the new indication of Entresto until a substantial number of black patients have been studied to determine if the benefits outweigh the risks for them. Thank

you.

DR. LEWIS: Thank you, speaker number 1.

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

MR. SCHALL: Thank you. I'm John Schall, chief executive officer of Caregiver Action Network. Caregiver Action Network is the nation's leading family caregiver organization working to improve the quality of life for the more than 90 million Americans who care for loved ones with chronic conditions, disabilities, disease, or the frailties of old age. Novartis is one of over 40 companies that support CAN's nonprofit mission to educate and support family caregivers.

I'm here today to speak in support of FDA approval of Entresto for the treatment of HFpEF. I want to talk about the tremendous need for a therapy for HFpEF from the perspective of the family caregiver because HFpEF is a disease where the dyad of the patient and family caregiver

working together is even more critical than it is with other disease conditions.

There are several serious problems and challenges that patients and families face now. First, HFpEF is extremely difficult to diagnose, sometimes even taking years to reach a diagnosis. It's difficult to diagnose because it looks so much like other illnesses such as COPD, anemia, disorder breathing, or other conditions. As one family caregiver said, quote, "The disease is a chameleon. It masquerades as everything else."

This is an extremely difficult period for the patient and the family caregiver as they experience seriously concerning symptoms without a diagnosis of the problem. Secondly, when the diagnosis does finally come, patients and family caregivers are faced with the reality that there really are no treatments currently available. The relief of finally having a diagnosis is replaced with the grim realization that there isn't much the doctors can do about it. In fact, the treatment of the patient's comorbidities often overshadow the

actual HFpEF when it comes to treatment because the comorbid conditions are much more straightforward to address.

HFpEF itself gets deprioritized in treatment, even though it is the driver of the symptoms. This results in a policy pharmacy situation for the patient and creates a tremendous medication management challenge for the family caregiver. According to our surveys, in most cases it is the family caregiver rather than the patient's themselves who manage the medications.

Lastly, as hard as it may be to accept, many healthcare professionals actually do not always believe that the patient has HFpEF. Some doctors, some emergency room physicians, and others may have limited knowledge of HFpEF and instead focus on addressing and treating particular symptoms, which may or not be appropriate for treating a HFpEF patient.

HFpEF patients often must go to the hospital, but it's not always a positive experience. Family caregivers have told us that

they actually do all they can to avoid visiting emergency rooms for this very reason. That's why finally having a treatment for HFpEF is so important for patients and their families. To have a valid therapy such as Entresto will give hope to patients and family caregivers that this systemic disease can be addressed in an effective manner. Indeed, it will not only help treat the disease, but the very fact that there is a treatment available may make doctors less reluctant to diagnose the condition and may make emergency room and other healthcare professionals more aware of HFpEF.

At last, we would have a treatment that addresses the underlying systemic disease rather than only addressing individual symptoms and comorbidities. For these reasons, we strongly support the approval of Entresto. Thank you.

DR. LEWIS: Thank you. Thank you very much.

Speaker number 3, your audio is now connected. Will speaker number 3 begin and introduce yourself? Please state your name and any

organization you are representing for the record.

DR. MEYERS-MARQUARDT: Good afternoon. I have no conflict of interest with Novartis or Entresto. My name is Dr. Meyers-Marquardt. I'm an adult nurse practitioner and certified heart failure nurse with more than 10 years of experience on heart failure management. I represent more than 2,300 professional nurses, members of the American Association of Heart Failure Nurses, focused on uniting professionals, patients, and caregivers in the support and advancement of heart failure practice, education, and research to ultimately promote optimal heart failure patient care.

In the U.S., heart failure is newly diagnosed in over 650,000 people annually, half of which are heart failure with preserved ejection fraction or HFpEF. Those over 40 years of age have a 20 percent lifetime risk of developing heart failure. Regardless of ejection fraction, the majority of these with heart failure have some component of systolic and diastolic dysfunction, suggesting treatment for one type of heart failure

may have similar impact on the other.

Studies have identified baseline NT-proBNP as a strong predictor of heart failure hospitalizations and cardiovascular death. As previously stated, 50 percent of all those diagnosed with heart failure will have HFpEF, and this is disproportionately identified in women. Hypertension is the most frequently associated comorbidity, but obesity, coronary artery disease, atrial fibrillation, and hyperlipidemia are also associated with HFpEF, thus making the treatment more challenging. As those with heart failure progress to the ACC/AHA heart failure stages, their five-year survival lessens. Deterioration of NYHA functional class independently predicts increase in mortality.

HFpEF management is perplexing as it has few effective pharmacologic treatments and limited management guidelines, unlike heart failure with a reduced ejection fraction. Even with guidelines, studies on HFrEF discovered less than 20 percent were on guideline-directed medical therapy despite

eligibility.

There are a few studies focusing on HFpEF. PARAMOUNT is a small study comparing sacubitril/valsartan with valsartan. It found sacubitril/valsartan reduced NT-proBNP left atrial size and improved NYHA class. Worsening of these values correlate with worsening progress in those with HFpEF. A decrease in atrial size may be related to reduced remodeling as seen with HFrEF.

PARALLAX compared optimal and individualized therapy with sacubitril/valsartan. Sacubitril/valsartan showed significant reduction in NT-proBNP after 12 weeks, improved quality of life at 4, a lessened decline in renal function, and a 50 percent decrease in heart failure hospitalizations.

PARAGON-HF was the largest clinical trial in HFpEF to date, 4,796 individuals. Sacubitril/valsartan decreased NT-proBNP regardless of sex or LV ejection fraction. Rates of decreasing renal function and serious hypokalemia were lowered. Deterioration and quality of life

score was less. Men had positive changes in their NYHA class and women with higher LVEF continued to experience treatment benefit. Patients with HFpEF from my clinical practice, together with other colleagues, verbalized many personal benefits on sacubitril/valsartan as seen in this slide. Family members and caregivers had similar comments as to the improvements seen, and their statements reflect an improvement in quality of life.

My conclusions of these studies and clinical experience of managing those with HFpEF are it's a challenging disease to manage due to limited guidelines and effective pharmacological therapies. This disease impacts women more frequently. Quality of life is central to patients, families, and caregivers. Heart failure hospitalizations decrease quality of life, increase mortality, and is associated with increased levels of NT-proBNP.

Agents positively impacting these factors such as demonstrated by sacubitril/valsartan or Entresto are a valuable addition to the pharmacologic armamentarium of those with HFpEF,

and we support its approval. I appreciate your time and attention. Thank you.

Questions to the Committee and Discussion

DR. LEWIS: Thank you very much.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

We will proceed with the questions to the committee and panel discussions. I would like to remind 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 will read the first discussion question.

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

Are there any issues or questions about the

wording of the question?

Dr. Cook, please state your name and your question.

DR. COOK: This is Thomas Cook. Yes, I have a number of comments. I'm going to play the naysayer here, I think. My version of the role of the investigator is to convince me, the skeptic, that in fact his proposed therapy is beneficial in the way that he claims it is. So I want to point out ways in which I find the primary analysis that has been done to be problematic.

The primary issue is that we have an issue of competing risk, which has been raised before, but none of the analyses presented actually formally addressed the issue of competing risk, and in fact one can show mathematically that the competing risk problem is unsolvable, what we statisticians would call non-identifiability; that is, it's impossible in the context of competing risk to independently assess the treatment effect on non-fatal events in the presence of mortality.

The analyses were done in one of two ways,

and I suspect that both of these have come into play in these analyses. If you look at the figures on slide 56 of the sponsor presentation, you see the mean cumulative events per 100 patients on the vertical axis and then time on the horizontal axis. You see that the blue curve, Entresto, is lower than the gray curve.

Now, this analysis was done using the Ghosh and Lin approach as claimed in the sponsor briefing document. What Ghosh and Lin do with respect to mortality is they effectively impute people who died of zero events during the rest of their follow-up. That means that someone who died early in this analysis would be assessed as having no recurrent healthcare events beyond that.

So it's conceivable that some component of decrease that we see between the gray line and the blue line with day 2 early mortality in the experimental arm, which decreases the corresponding subsequent risk of rehospitalization. That's one way in which mortality is dealt with, and it's impossible to know whether that's happening.

The second way in which mortality is dealt with is by treating it as a censoring mechanism, and when you treat mortality as a censoring mechanism, especially in this recurrent event analysis, you're typically imputing hospitalization beyond the time of death; that is, if you censor someone, their expectation is they will continue to be experiencing events of interest beyond the time that you stop observing them. So to the extent that these analyses incorporate censoring at the time of death, there's this implicit imputation that's subsequent to rehospitalization. I do not have any idea what the impact of that is, and also that was seen.

Therefore, I'm not convinced that the differences that we see between groups is due to a decrease in hospitalization rates and could be due to interactions between hospitalizations and mortality. And I'm going to stop there. I think those are my primary comments. I think there's a departmental [indiscernible] flaw in the whole idea of using these recurrent event analyses in heart

failure.

Oh, I would make one additional comment. I think it was Dr. Solomon who mentioned that these kinds of analyses are used in asthma and MS, but those diseases, as I understand it, are not subject to the same kind of mortality rate that we're seeing here; therefore the competing risk issue is not present in those contexts. That's the end of my comments. Thank you.

DR. LEWIS: Thank you, Dr. Cook.

I guess I'm going to assume that no one has any questions about the specific wording of the question, and we are, as Dr. Cook began, proceeding with the discussion the question. But if you do have a question about the specific wording and we missed that, please just begin your question that way.

Dr. Emerson, I believe your hand was next.

DR. EMERSON: And mine was about the wording of the question, but I can address it at the same time, and that is the question of "an" indication, and that is that I do have problems with the

wording of the indication that is being asked for, so I will be addressing the idea that there is some indication that I could go with.

My comments on this are, first, that we're asking, to my mind -- well, and I guess to theirs as well -- an expansion of an indication, and I'm always nervous about that. In my classes, I always take the extreme example of a hypothetical clinical trial of oral contraceptives versus placebo and for birth control. I point out that after a year of unprotected intercourse, the placebo arm might have 43 percent of subjects pregnant and the oral contraceptives might have 3 percent pregnant. That difference is easily detected in the relatively small clinical trial.

Of course if I restricted my enrollment only to women, it would be a difference between 88 percent roughly and 6 percent, say, even easier to detect. But if you allow expansion of indication where it's really only one subgroup that's benefiting, you can prove anything if you get a large enough sample size, and I think we need

to worry about that here, particularly.

So my problem with the indication is it's not clear to me that we are really demonstrating anything in the HFpEF patients due to the overlap between HFpEF and HFrEF by some latent disease quantity. I do applaud the sponsor for trying to separate them a little bit to make certain that the patients that they enrolled in PARAGON had different ejection fraction levels than did their PARADIGM study, but the idea of dichotomizing at any particular threshold is a useful thing to do for science and for statistics sometimes, but we really believe it's more continuous than that.

So it really does look like any effects that we see on hospitalizations is in a group that could easily be thought to be just the best of the HFrEF patients. We have no proof of that particularly, but I'm very, very nervous about the idea that in the sponsor's slide 36 that Dr. McMurray presented, where they made a big thing of showing the 9 or 10 different classes of treatments we have for HFrEF and then we have nothing for HFpEF, and that we

might give an indication where we use the word "HFpEF" but really say it has to be low ejection fraction, we're giving them the ability to say, "Oh, finally we have something that's treating HFpEF," and it's not necessarily. I'm not at all convinced of that. I'm not convinced that they've shown that.

So my indication that I want to speak to the rest is we're really just talking about moving the threshold for what is HFrEF, and moving it higher.

I've already spoken to the idea of what's the p-value that I'm talking about that we have and, overall, probably the 0.06 p-value, given the sequential analysis versus the desire that they have on the 0.048, is of issue. It changes what the positive predictive value is. However, the plausibility, the plausibility that that threshold below 40 percent ejection fraction is not an absolute says that, yes, I can easily believe, on patients who have an ejection fraction above 40 percent but still low, that the treatment probably works, in which case I'm less concerned in

that group.

I'm less concerned in saying we're redefining HFrEF to be just low ejection fraction, but the second that we started moving into all of the patients, I think the fact that there hasn't been any treatments identified argues that our ideas are perfectly good hypotheses to test, but as it turns out, they don't work, and therefore we have to figure that the prevalence of our good ideas is low.

So again, thinking of an indication that goes to the redefinition of HFrEF, the ideas that we have -- and I'm very sympathetic to Dr. Cook's comments about saying how we're handling cardiovascular mortality versus how we're handling events, just the hospitalization. I personally think that these recurrent events, counting the death as an event is to be preferred over just treating it as another missing at random and censoring the patients exactly then. So all of his complaints are absolutely valid, but some of the alternatives that we might consider are even worse.

Then the other thing that I am just a little bit nervous about is the idea of the mechanism, hospitalizations. We've got to worry about are we changing physician behavior vis-a-vis other signs and symptoms of the disease, particularly say hypertension, just in terms of who they hospitalize and who they don't. But again, as I spoke to earlier, I think going with the mean number of hospitalizations is worthwhile and disappointing that it doesn't show up in the days.

So overall, I'm for giving an indication that does not say HFpEF but does say low ejection fraction. And I'll just note that I am probably willing, personally, just to absorb the observed effect modification between men and women, recognizing that some of the data that was shown by the continuous measures of risk in the modeling there is something that is promising.

Then lastly, I've come to in the background that we're considering all of this versus what's potentially an active control. Certainly valsartan is active in the HFrEF from previous studies, and I

really don't know how much we've considered that we're looking at that in HFpEF and are we just objecting to some element of getting noninferiority against valsartan by itself in the highest ejection fraction, whereas we're getting some improvement in the groups that have low ejection fraction. Those are my comments.

(No response.)

DR. NISSEN: Julia, you're muted.

DR. LEWIS: Thanks. Thank you.

Thank you, Dr. Emerson.

Ms. Chauhan?

MS. CHAUHAN: Thank you. I apologize for the background noise. Today's the day they clean my house.

I share the concerns the last speaker talked about, but the other thing that I wanted to bring up is what the first public speaker talked about because that's a concern I share.

What about the black population? They're at very high risk for this problem but they are very low in participation in the trial. How do you put

that together to make sure that this population is well served if this is approved? Thank you.

DR. LEWIS: Thank you, Ms. Chauhan.

Dr. Nissen?

DR. NISSEN: Okay. Well, my views are similar in many ways to what Scott Emerson was talking about. Let me see if I can articulate this.

First of all, we've managed to dichotomize heart failure into HFpEF and HFrEF, and that's reflected in PARADIGM and PARAGON. We've done so, unfortunately, with a very imprecise measure, namely ejection fraction. So I do think there is a lot of overlap between the PARADIGM population and the PARAGON population.

What the post hoc analyses tell me is that the more the PARAGON population looks like PARADIGM, the more the benefit. And those post hoc analyses directly address, Norman, your question, is that if you look at all the analyses, no matter how you cut it, regardless of gender or anything else, the lower the ejection fraction, the more

appearance of benefit that you see in PARAGON.

So Scott laid it out pretty clearly. There's not really evidence that, truly, HFpEF benefits, but the post hoc analyses suggest that perhaps the cutpoints that were used in PARADIGM were too conservative and that there might be some wiggle room here to expand the indication so that people whose ejection fractions are below normal, but not as low as they were in PARADIGM, could potentially benefit.

Now, this is very risky, of course, because whenever you're slicing and dicing and looking at post hoc analyses, you're at great risk for making mistakes. But I think the consistency of the evidence when you look at the two trials, as you get below what we would call a normal ejection fraction within all the limitations of this terribly imprecise measure, the lower you get, the more likely you are to benefit.

The question that I'm asking, based upon these post hoc analyses, is can we provide a public health benefit by expanding the indication to

include people that are not below 40 percent? Now, where you draw that line is really hard, but I was convinced by the post hoc analyses that something's going on there. You want to call it mid-range ejection fraction; call it whatever you like. But the idea that these patients all appear in these simple buckets is just scientifically wrong. It is a continuum, and there is a lot of overlap, or at least certainly some overlap, being PARAGON and PARADIGM.

(No response.)

MALE VOICE: I think you're muted again, Julia.

DR. LEWIS: Dr. Nissen, are you done?

(No response.)

DR. LEWIS: I guess you are.

Dr. O'Connor?

DR. O'CONNOR: Thank you, Julia.

I want to make a couple comments regarding the previous comments of my colleagues. First of all, I think there's complete consistency of the findings around the prespecified hypothesis in the

post hoc analyses, and I think whether we're at 0.06 or 0.46, I think we have to move away from a p-value determining whether we have success or not. I would ask the statisticians if the investigator-called endpoints was the primary adjudication events, would we be here today?

Then when you take that one step further, as I've commented earlier, there was an artifact of the adjudication process by the CEC in which they threw out 400 events, many of which were heart failure because of source documentation and inability to confirm a second physical finding on these very strict Hicks criteria. And that's why the sensitivity analysis with the additional independent panel, as well as the investigator calls, all consistently fall in the range of a positive p-value if you want to live and die by a p-value. But Dr. Cook said 0.06 makes him nervous; 0.046 would make him better. Well, that to me is worrisome.

Number two, there's a lot of discussion by the statisticians on whether HFpEF is a real entity

or not. There's certainly a large body of literature by clinicians and clinical investigators to support that the biology does change as you reach higher EFs in heart failure; and in fact, there's a plausible explanation that there may be an enrichment cardiac amyloid in males with EFs greater than 55 that are resistant to this type of therapy, so that's a plausible explanation.

But if you look at figure 9 in the briefing document, I want to argue with Dr. Nissen that, to me, it does look like between the ejection fraction of 45 and 55. This is on the CEC confirmed primary endpoint. It looks like that curve is relatively flat, so it's not a steep linear relationship that you're articulating. Yes, lower, there's more effect, but there does look like there is an entity in the mid-rEF range, and what we call this clinical condition I think is a nuanced argument. I think we have to appreciate that there is a signal from this large data set, and we shouldn't live and die by a p-value of 0.06. Thank you.

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

Ms. Alikhaani? Ms. Alikhaani, did you withdraw your question? Okay.

MS. ALIKHAANI: Yes. I am concerned about how the different categories of heart failure are being defined, the percentiles for that, and also the fact that there's this crossover factor also. With these kinds of discrepancies, it's just not clear to me how those categories are defined. I don't understand how we can be totally sure of the relevance and accuracy of the trial outcomes with this issue, and then how do we totally define the effectiveness from the trial outcomes based on these kind of issues?

Also, I just think there's a great lack of diversity in the clinical trials, not a significant amount of diversity. This is an ongoing problem with so many clinical trials, and we've got to start addressing these issues. We have to do a better job of outreach, education, and awareness building to diverse and traditionally underserved segments of our communities, especially communities of color that are experiencing ongoing, on an

ongoing basis, the greatest disparities in care.

Heart disease kills more people and disables more people in the black community than any other community, and then of course with other people, too, all the way down the line. But we have to do something about this great disparity that is just going on and on and on, and we have to start now. It can't always be next time we'll do that. We need to do it now. There's an immediate need for this. So these are these are my concerns at this point of the discussion.

DR. LEWIS: Thank you, Ms. Alikhaani.

I know, Dr. Nissen, you dropped your phone, but may I let Dr. Merz go, and then we'll go to you?

Dr. Merz?

DR. NISSEN: Go ahead.

DR. LEWIS: Thank you, Dr. Nissen.

DR. BAIREY MERZ: Thank you. It's Dr. Bairey Merz. I would make three points, and then, once again, talk about interaction.

I think the totality of evidence here is

actually strong for a very mild benefit in morbidity, and then fill in the blank, in patients with. I think this is an example of demographic population shifts while we're planning trials. We have the aging epidemic, the obesity epidemic, the diabesity, metabolism epidemic, and this has caught us and our science with the new realization that something imprecise -- I agree with Dr. Nissen -- can so easily help us as treating clinicians understand what the underlying root problem is. Look at the HFpEF literature; there's anywhere from 5 to 20-plus genetic phenotypes, so we clearly don't understand HFpEF.

Then the last thing I would say, I'm supportive of strong evidence of totality for this, whatever we want to call it, mid-range or the healthy part of HFrEF. My interaction comment, again, is we have known about sex differences in this crude marker ejection fraction, but done very well and repetitively with things like cardiac MRI, where for example in Dallas Heart, a median LVEF is 75 percent in women and 70 percent in men. And

pick a study, any other study; that 5 percent difference is almost always there in rigorous studies such that this physiologic difference, which is inherent in certain childhood, is going to preferentially show that women will benefit in this, call it what you want, mid-range, healthy part of HFrEF. Thank you.

DR. LEWIS: Thank you, Merz.

Dr. Nissen?

DR. NISSEN: Yes, just one quick comment. FDA also asked which parts of the post hoc analyses do not contribute. I found that all of the readjudication analyses and different ways of looking at this, the investigator-reported readjudication, they don't influence my thinking very much, if at all.

If you really look at those analyses, the relative risk, the rate ratio, is unchanged. You add or take away events and you shift the p-value a little bit, but you don't change the overall interpretation of the studies. So it's a rather interesting effort, but I don't think it's

contributory toward our understanding of how to interpret the data. Thank you very much.

DR. LEWIS: Thank you, Dr. Nissen.

Dr. Ridker?

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

I wanted to make a brief comment. I too am persuaded that the combination of PARADIGM and PARAGON suggests that there clearly is, in my mind, a group of patients in this in-between space that benefit, and I think our patients would benefit from being able to use this combination drug for that purpose. But I also think the words matter more than we're giving them credence here.

I happen to be an echocardiographer. I know there are other echocardiographers on this call as well. Whether we think it's imprecise or not, and it clearly is, it's also the best we have, and it clearly is the way the drug will get used because out in the real world, this is the fundamental way the ejection fraction is measured.

I would say to you that I do have some sympathy to the idea that "preserved ejection

fraction" to me sounds normal, so maybe that's not the word we want. I don't like "lower limits of normal" because I don't really know what that is. I must say I don't really like "mid-range" either because I think the clinical community is not as up to date as is the heart failure community. But "mildly reduced," I as an echocardiographer know exactly what that is.

I think someone said this earlier. In the old days, we used to say mild, moderate, or severe, and that clearly is they're all three abnormal. I could support the language here of "mildly reduced" and think that Would be the middle ground that would find us, in expansion of this label, to a place I'm comfortable with, without going somewhere that I think the data become quite murky.

Mid-range for me just sounds -- I don't know what it really means outside the context of the heart failure research community, but mildly reduced is something that's quite replicated in even the community-based echocardiography world. I just want people to think about that.

DR. LEWIS: Thank you, Dr. Ridker. Are you done? That was your last comment?

DR. RIDKER: Yes. I'm sorry. That was the end of my comments. Thank you. Yes, that's the end.

DR. LEWIS: Okay.

I guess I have a question for my cardiology colleagues and a comment. My first question for my cardiology colleagues is there are many drugs that have been proven to work and reduce ejection fraction, yet none in preserved ejection fraction.

What about the data that's been put before us today makes you want to make this be the first one that crosses over both? And if we were to grant the same, if you will, concessions or saying post hoc analyses to some of those other studies that showed a benefit reduced but not preserved, would we have more than one drug to consider for this indication?

Chris, I think you raised your hand in response to my question to the cardiologists.

DR. O'CONNOR: You said Chris O'Connor?

DR. LEWIS: Yes.

DR. O'CONNOR: Yes. Hi. Thank you.

It's an excellent question, Julia. And I think one of the things that we have to be reminded of is that if you actually looked at the analysis in CHARM with candesartan with a similar endpoint -- obviously post hoc because that wasn't prespecified in their preserve trial -- there was a signal of advantage versus placebo that's on the order of what we see here.

So I think we need to remind the group that ARB probably has a signal of benefit in this mildly reduced ejection fraction. I like the way Paul stated that. So we're really looking at a drug that's going against an active comparator that probably has some benefit in mildly reduced ejection fraction. But to specifically answer your questions, there is a small signal in the ARB candesartan, and I think there's probably a signal yet to be determined with the MRA class. Thank you.

DR. LEWIS: Okay.

I'm not sure. Dr. Gibson, did you raise your hand in response to my question?

DR. GIBSON: I didn't. I actually was going to respond to the first question.

DR. LEWIS: To my first question.

DR. GIBSON: Well, no, the first question --

DR. LEWIS: Oh, the actual question. Yes. Then hold on one second.

DR. GIBSON: Okay.

DR. LEWIS: Okay. The only other one would be -- go ahead. My only other comment would be that I guess CKD patients often are put in this category of having HFpEF, although I notice their absence on most of the slides. I will say that determining the volume overload, usually an edematous CKD patient with COPD with an exacerbation of heart failure is something I think is maybe more challenging than my cardiology colleagues think and may benefit from perhaps a non-dichotomized adjudication process.

So that's my last comment. I think

Dr. Thadhani is next.

DR. THADHANI: Thank you, Dr. Lewis.

I want to echo your comment about CKD, but also just come back to a very important point, of course, that Ms. Alikhaani brought up, and that is the lack of enrollment of diverse individuals in PARAGON. I would certainly agree with that, and the urge and the desire to change that I think is everybody's responsibility.

We obviously have been encouraged to look at PARADIGM and PARAGON in combination. I'm somewhat comforted, although not completely satisfied, that at least in PARADIGM, there were about 400 patients included, and I suspect the subgroup analysis there in that population demonstrated benefit. In combination with PARAGON, then, there were over 500 patients; certainly, again, helpful in the right direction in terms of representation in these kinds of studies but certainly not adequate.

I guess the only other comment I'll make, as Dr. Lewis knows all too well, is when we look at otherwise patients with chronic kidney disease and

ask which patient populations are overly represented, they tend to be those of black and brown skin. So I'm somewhat, again, comforted by the fact that those individuals without significantly reduced ejection fractions but with CKD, which are quite common, that present with heart failure may certainly benefit.

Thank you, Dr. Lewis.

DR. LEWIS: Thank you, Dr. Thadhani.

Dr. Moliterno?

DR. MOLITERNO: Thank you, Dr. Lewis. I mainly raised my hand so I could see if you'd say my name properly.

DR. LEWIS: Oh, God.

DR. MOLITERNO: No, just kidding. Thanks.

DR. LEWIS: Okay, you're right.

DR. MOLITERNO: I've been super impressed throughout the entire day today with how exact and insightful all the comments were from all my colleagues, and that's why I've been quiet. I think this series of topics and conversations have so much nuance to it. I think had the PARADIGM

study had patients with an EF of 41 percent, would we have thought differently; or had PARAGON had patients with an EF above 40 percent as opposed to above 45 percent, if the conversation would be different; or if we accepted a p-value, a priori, of 0.06. So it's been interesting.

One thing we didn't talk about is the zillion statistical analyses that have been done, but yet not correction for them or consideration for them, and that should be in the back of our minds about whatever adjustments are needed.

I liked your comments recently, and I think patients almost never have heart failure as a stand-alone diagnosis. It's unusual to have just, say, a mitochondrial disorder in the myocardium. Almost always they've got either ischemic heart disease or they've got long-standing high blood pressure, and I think that's what we're seeing, is as the patient has more preserved ejection fraction, chances are they're older.

They're more likely a female. They more likely have 70-year-old kidneys, and 70-year-old

pulmonary lymphatics, and 70-year-old everything else that causes that combination of 70-year-old parts and pieces of parts to give them symptoms consistent with heart failure, more so than, say, somebody with an ejection fraction that's markedly depressed, where that's going to be a greater contributor to their symptoms, and therefore receive more benefit from drugs such as we're discussing today.

So I don't have anything novel to say. I just wanted to say thanks, everyone, for just really fantastic comments. Thank you.

DR. LEWIS: Thank you.

Dr. Gibson?

DR. GIBSON: Great. Thank you. I want to say I'm quite supportive of the efforts of graded adjudication of events, although the process was applied retrospectively here. I adjudicate a lot of events, and the issue of what to do with events, where the event meets the criteria by I guess what I call the spirit of the law but the source documents are missing, no event happened by the,

quote, "letter of the law." This has always really, really bothered me.

This often happens when a patient presents to an outside hospital and access to the original source documents might be very poor. Though what you often have is an outside physician may state in a narrative that the patient had certain lab findings or EKG findings, but the actual source documents from that hospital may be missing and can't be retrieved for a wide variety of reasons, some of which are various privacy rules.

So the criteria for an event to be adjudicated as having occurred may be met based upon the account, in this instance, an outside doc, but the actual supporting documents may be missing and no event is said to have occurred. So if not source documented, it didn't happen.

I do agree that it is wasteful and inefficient to discard all these efficacy events because of missing documentation, but as a matter of process, I'm quite concerned about safety events. We may be discarding safety events just

because of a missing document, and that could breach the systemic underreporting of true numbers of safety events.

We've heard a lot of people say that the CEC process yields greater precision through the use of rigorous definitions as compared with local site investigator assessment. The use of the rigorous definitions is intended, at least in part, to minimize bias, but the missingness of the documents is very likely missing at random, and the complete elimination of an event that was not well documented really, I think here, is an example where it really only serves to reduce the sample size.

But I did find it compelling that the relative risk reduction was constant, but when you use graded adjudication, you did up the sample size, and as a result, the p-value was changed a little bit, but the magnitude of the event reduction was not changed. And I agree with Dr. Nissen that that was reassuring that you're not altering the magnitude of the relative risk

reduction, you're just altering the certainty around that.

So I'm not sure exclusion of events because of missing documents makes things more precise or results in precision. I might call it pseudo precision. I think we've erred a bit on the side of pseudo precision. I think you've all heard absence of evidence is not evidence of absence, and I do find this graded process important. I hope that it will be used more frequently, and I would hope the FDA would issue guidance for its future use in this regard.

I did find the prespecified secondary endpoints, and the non-prespecified analysis, and renal progression data all very compelling. All were quite consistent. Thank you.

DR. LEWIS: Thank you, Dr. Gibson.

Are there any other comments for this discussion? Dr. Gibson, your hand is still up. I don't know if you just didn't put it down yet.

DR. GIBSON: I just didn't put it down. Sorry. Thanks.

DR. LEWIS: It's ok.

Alright. If there is no further discussion, I think I'll try and summarize it. I think both Dr. Cook and Emerson, statisticians on our panel, had some concerns. Dr. Cook's concern was about the competing risk of death's effect on recurrent heart failure and the interactions between death and recurrent heart failure.

Dr. Emerson had multiple concerns, one, that expanding the indication of a population, you can almost prove anything, and that in this particular matter, the overlap may not be proving anything new because of the overlap between HFpEF and HFrEF. He also had a concern that really moving the p-value from 0.06 to 0.048 was not impactful. The question was the plausibility of it, and I think his take was that it probably included close to 40 percent. He agreed with Dr. Cook and was disappointed that the reduction in heart failure was not supported by a significant reduction in the days of hospitalization.

I think several of our speakers and I both

echo it, and I'm deeply appreciative that they noted it. This is in the United States a disease that affects the black population, the African American population, and here we had a very low representation of that population.

There was also concern about, in general, the subject matter of dichotomizing HFrEF and HFpEF, and they are probably very likely a continuum. PARADIGM and PARAGON could be viewed as working over that continuum. Many of the post hoc analyses would support that and the risks are fairly low.

So from a public health benefit point of view, something in the mid-range that doesn't go above, I guess, the median or truly doesn't go up to a truly normal HFpEF would be a consideration. I think a lot of people had a real concern about using the term "HFpEF" as the indication as opposed to perhaps another term, whether it be "mild HCF" or "mid-range."

The adjudication process itself was also discussed and there were concerns about data that's

wasted. I think there was a lot of support. I'll just anecdotally say when we adjudicate acute renal failure, we do do it in a graded fashion based on the evidence, and I think there was a lot of support for allowing adjudication committees or perhaps investigators to have a choice other than yes or no. Particularly, not discarding safety events was noted as well.

I think that was a good summary. If someone wants to add to that summary, please feel free to do so, put up your hand and you can do so; otherwise, we will move on to the voting question.

(No response.)

DR. LEWIS: I will read the voting question.

Does PARAGON-HF, perhaps supported by previous studies, provide sufficient evidence to support ANY indication? In this case for the voting question, we are only going to discuss any issues with the wording of the question that you want to address to the FDA to clarify. If anyone wants the wording clarified, please raise their hand.

(No response.)

DR. LEWIS: If there is no discussion, voting members -- question 2 is a voting question -- will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record, which I have, and all questions and discussion regarding the words of the vote in question are complete, which appears to be -- I have two hands up, and I assume that's about the wording of the question.

Dr. Cook? I'm not sure who went first, so if it's ok, I'll just randomly pick one.

Dr. Cook?

DR. COOK: Yes. My question is, does this mean any indication whatsoever can be used or does this mean, does it exist at least one indication?

DR. LEWIS: Does the FDA want to comment on the intent of your question?

DR. STOCKBRIDGE: Yes. This is Norman Stockbridge. I'm trying to get at, without provoking further discussion, exactly what the

indication would be, whether we think this study, PARAGON, results in an extended claim beyond what they've already got.

DR. COOK: Okay. Thank you, Dr. Stockbridge.

Ms. Chauhan?

MS. CHAUHAN: Cynthia Chauhan. My question was similar. By using the word "any" are you freeing the FDA, or Novartis, to say anything they want, or by using the word "any" are you saying you will restrict it to specific ones?

DR. STOCKBRIDGE: You're going to get a chance to comment in the follow-up question how you would describe any benefit you think there is.

MS. CHAUHAN: Okay. So if we say yes, we're not giving blanket permission.

DR. STOCKBRIDGE: Correct.

MS. CHAUHAN: Okay. Thank you.

DR. LEWIS: Okay. If there's no further discussion, Dr. Joyce Yu will provide the instructions for the voting.

DR. YU: Thank you, Dr. Lewis.

This is Joyce, the DFO. 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, which you have but you can do again, 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. Next, the chairperson will go down the roster 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.

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

(No response.)

DR. LEWIS: Okay. I will read the question one more time.

Does PARAGON-HF, perhaps supported by previous studies, provide sufficient evidence to support any indication? And I think we've already addressed any questions about the wording.

Dr. Yu, are you going to move us?

DR. YU: Yes, if we're ready, we will now

move the voting members into the voting breakout room to vote only. There should be no discussion in the voting 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: Hello, everyone. This is Joyce, the DFO. 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 is 12 yeses, 1 no, and zero abstentions.

Dr. Lewis?

DR. LEWIS: Okay. Thank you.

Dr. O'Connor?

DR. O'CONNOR: Yes?

DR. LEWIS: Thank you. 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 for 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. O'Connor.

DR. O'CONNOR: Christopher O'Connor. Yes. Thank you.

DR. LEWIS: Dr. Merz?

DR. BAIREY MERZ: Noel Bairey Merz. Yes, because of the totality of the evidence and also new information regarding normal thresholds. Thank you.

DR. LEWIS: Dr. Ridker?

DR. RIDKER: Yes. It's Paul Ridker. I voted yes, and I'm sure we'll talk about it later, but I'm favoring those with reduced ejection fraction.

DR. LEWIS: Ms. Chauhan?

MS. CHAUHAN: Thank you. Cynthia Chauhan. I voted yes. It was a very difficult decision. I chose to vote yes based on Dr. Stockbridge's explanation that as I understood it, this opens us up to discussion of a more focused talk about how to use it or whether to use it. Thank you.

DR. LEWIS: Thanks.

Dr. Moliterno?

DR. NISSEN: Moliterno.

DR. MOLITERNO: There you go.

David Moliterno. I voted yes, as others have stated, because of the totality of information from new data presented and the biologic plausibility of the hypothesis. Thank you.

DR. LEWIS: Dr. Nissen?

DR. NISSEN: I'm glad I have a name that's easy to pronounce.

(Laughter.)

DR. NISSEN: I voted yes. We're going to have more discussion about it, but we didn't discuss it in great detail. But the rate ratio of 0.78 in the group that had the below-median

ejection fractions compared with 0.99 in the group that was above median, I felt to be fairly compelling in the context of what we learned from PARADIGM. So like Paul Ridker, I do see the potential for an indication for those people. How we define this is going to be very important, but how we define the group that would benefit will be an important discussion.

DR. LEWIS: Ms. Alikhaani?

MS. ALIKHAANI: Yes. I voted yes, even though I was very concerned and very disappointed about the lack of significant diversity in the trials. We have to do better than that. We can do better, we know better, and we can get it done, and I look forward to more discussions and opportunities to talk more about that.

This is an area where we have patients who are suffering. It's a great unmet need, and I just want to make sure that patients have every opportunity possible to have their health care improved and have a good quality of life. This is really, really critical. I have family members who

have heart failure. I know it's a very difficult disease.

So that's the reason I voted no, and I also was impressed by the fact that it's something that really helps women, and that's another major underserved community in many ways in healthcare. So those are important factors to consider.

DR. LEWIS: Thank you.

Dr. Gibson?

DR. GIBSON: Yes. Dr. Gibson here. Based upon the unmet need, the lack of any currently indicated treatments, the totality of evidence from the present study and those that preceded it, the retrospective analyses, I found that the potential benefits outweighed the potential harms of the drug.

I agree with Dr. Stockbridge that p less than 0.05 has no basis in law, national or federal, and I did find that the data met the regulatory bar of being compelling, and I look forward to our discussion of the proposed label group that is somewhere between PARADIGM and PARAGON, maybe

something called paramiddle [ph]. Thank you.

(Laughter.)

DR. LEWIS: Dr. Cook?

DR. COOK: This is Thomas Cook and I voted yes. Despite my revelations about the interpretation of the analysis we've given, it shows more likely than not, in light of PARADIGM, that there is evidence of some benefit here in some subjects. Thank you.

DR. LEWIS: Dr. Emerson?

DR. EMERSON: Scott Emerson. I voted yes. The lack of meeting the prespecified threshold in the overall analysis but missing it by just a little was enough to have me regard that the biologically plausible and strong results in the low ejection fraction group is quite compelling.

DR. LEWIS: Dr. Thadhani?

DR. THADHANI: Thank you, Dr. Lewis.

I voted yes based on, number one, certainly the totality of the data and, number two, the unmet need for vulnerable populations as has been discussed. Number three, the fragility of the

p-value, as Dr. Solomon highlighted, only 7 patients would have changed that and we perhaps would not be having a discussion; and, hence, the focus on the totality and the consistency of the data regardless of subgroups that we've looked at. Then finally, very importantly for me, as I'm sure for others, is the safety profile of the agent and, in fact, potential benefits, especially in populations like those with kidney disease.

Thank you, Dr. Lewis.

DR. LEWIS: Thank you.

Dr. Kasper?

DR. KASPER: Ed Kasper. Thank you, Dr. Lewis. I voted yes, and see an indication for those with mild abnormal ejection fraction in order to decrease hospitalization for heart failure. Thank you.

DR. LEWIS: Thank you.

I'm next. I voted no; lone girl or lone man. I think my concerns I expressed during the discussion, but the lack of precedent for drugs that work in severe reduced failure versus

well preserved. This study didn't study mildly reduced or middle-range. It studied everybody above a certain level, so that would actually include people with truly normal EF. I'm not sure a drug that has a side effect of hypotension in some of those patients couldn't cause harm, so I'll be interested in our further discussion of the other questions.

I will now summarize the panel's discussion. I think, with the exception of me, everybody was impressed with the totality of evidence. Everybody agreed that the p-value of 0.05 wasn't written in stone. The new data and analysis in post hoc as well as prespecified persuaded people. And of course I think we heard a strong voice about the unmet need in this population who suffer greatly and for whom there is currently no things to offer.

DR. NISSEN: If I may comment, I don't know about other people, but for me, the unmet medical need had absolutely nothing to do with my vote. We can have the largest unmet medical need in the world, and if the therapy doesn't work, it's not

beneficial. So that didn't play any role in my vote, just for what it's worth.

DR. EMERSON: This is Scott Emerson. I echo that. What I was going to say is sometimes it's learning to say no and to first do no harm.

DR. LEWIS: I agree with you completely. I think that often when we're facing orphan diseases, we're facing the same thing. There's a desperate need, but if you give them something that either doesn't help or hurt, you haven't actually done them a favor, so I don't disagree.

Ms. Chauhan, do you have another comment? Your hand is up.

MS. CHAUHAN: Yes. I strongly support what these gentlemen were saying. I am a patient with heart failure with preserved ejection fraction, but I don't want to rush blindly just because something looks good for other people. Thank you.

DR. LEWIS: Great. Thank you. And again, I was summarizing what I heard, but thank you guys for adding to that summary.

We're now scheduled to take a 15-minute

break, and I think we have time to proceed since we are actually running a little bit ahead of time and that we have also a lot of agreement and opinion. Panel members, please remember that there should be no chatting or discussion of the meeting topic with anyone during the break. We will resume at about 3:28.

DR. NISSEN: That's 20 minutes from now.

DR. LEWIS: No. Sorry. That's right; not quite so long, 3:23, 3:20. How about 3:20?

DR. NISSEN: 3:20 sounds good. Let's rock and roll.

DR. LEWIS: Okay, 3:20. See you all back at 3:20.

(Whereupon, at 3:09 p.m., a recess was taken.)

DR. LEWIS: It's 3:20. I hope we're all back. I am now going to read the third discussion question, and it will be displayed.

If an indication for Entresto were not granted on the basis of available information, what would be necessary to augment the support for

approval? Are there any questions or issues about the wording of the question to the FDA?

Ms. Chauhan, I think your hand is up from before or do you have a question about the wording of this question?

MS. CHAUHAN: I'm sorry. I thought I had put it down. No, the wording is clear.

DR. LEWIS: No problem.

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: I guess I could begin the discussion since I was the one who voted no. I sound maybe strict, but it concerns me that for a disease that there is currently no drug that's shown a benefit, that we are leaping with lots of bounds to several things. I agree a p-value of 0.06 is not really different than a p-value maybe of 0.048, however, we're applying that in this situation.

I agree that there is some evidence, for

sure, from the PARADIGM trial that supports a PARAGON trial, and that evidence like that could be supportive of a claim even when you don't have two studies with p 0.05 or whatever the unofficial at some time rule was, however, again it's another thing for here. Using not the prespecified analyses but a post hoc analyses is also fine but, again, it's another thing that was added on to what we were doing here.

So I guess if I said what we should we do, then I think we should do what maybe this information tells us would be the way to look at this question, which is take people in the mid-range, below and above 40, and do the study with that group of people. I think I would highly support not using dichotomized adjudication methods, although I think I would still support adjudication, and I'll stop there.

Ms. Chauhan, I think you were next.

(No response.)

DR. LEWIS: Ms. Chauhan, do you want to comment?

(No response.)

DR. LEWIS: You are on mute, so you need to unmute. And you're muted on the Adobe Connect, so go up to the Adobe Connect to unmute.

Could you guys unmute her, please?

MS. CHAUHAN: Hello?

DR. LEWIS: Yes, we've got you.

MS. CHAUHAN: Okay. Thank you.

This is Cynthia Chauhan, patient representative. I agree with your comments largely. I think what's necessary is a new trial in HFpEF and HF mid-range. I also think in that trial we really need to work hard to make the population of the trial representative of the affected population. That means not only including minorities but those of us with HFpEF usually have significant comorbidities, including renal failure and pulmonary hypertension, amongst others. Those populations also need to be included in an arm to discriminate how that affects the potential effect of the drug, so future trials I think are what are needed. Thank you.

DR. LEWIS: Thank you.

Dr. Ridker?

DR. RIDKER: Yes. I obviously voted already that I thought that there is an indication that Entresto, it gets in this. But taking the question literally, if it was not granted, I agree with what you said that there would need to be another study, and I would call it probably in that reduced ejection fraction category. But just like the previous speaker, I would strongly encourage, either way, that this next study be done with, again, very substantial minority recruitment.

I would point out that I presented in front of this committee in 2008. That's a long time ago. That was our JUPITER trial, and we had 16 percent black and 14 percent Hispanic/Latin, and that was a trial that ran between 2001 and 2008. So it is doable. It takes commitment. It takes a desire to want to know the answer, and I would just encourage any sponsor going forward to heed that issue, and I'm done.

DR. LEWIS: Thank you.

Dr. Emerson?

DR. EMERSON: This is just echoing what you said, Dr. Lewis. It's hard for me to imagine that the patients with normal ejection fractions are going to suddenly change and show something, so I would be focusing on the mild and lower. To me, one of the things that we wish we had, that we'll talk about, I guess, on the next question, is the difficulty of the indication in the ejection fraction that's less than 40, where we do have mortality endpoints, cardiovascular endpoints, rather than just the hospitalization, yet we don't have that here; so focusing on that lower group, maybe even making it more continuous down through the range to see where we might pick up mortality endpoints.

DR. LEWIS: Great. Thank you.

Dr. O'Connor?

DR. O'CONNOR: Chris O'Connor. I'd just complement what Dr. Emerson said. There's really not an indication for mortality, cardiovascular mortality, and if there was a need to augment the

support for approval for that indication, another trial would need to be done, and it would be best done in that lower range of mid-rEF ejection fraction. Thank you.

DR. LEWIS: Dr. O'Connor? Oh, that was Dr. O'Connor.

Ms. Alikhaani?

MS. ALIKHAANI: Yes. I agree with the prior comment, another trial with diversity in all the areas that have been mentioned. I think it's a good opportunity to make it the best that it can be.

DR. LEWIS: Thank you.

Dr. Nissen?

DR. NISSEN: Yes. First of all, if an indication is not granted, studying what we've all called sort of this mid-range, but I would extend it up to about 55 percent ejection fraction and down to 40, and I would broaden the endpoints. You learned something important about the effect on the kidney, so I see no reason why a broad composite that included renal adverse events could not be

included in such a study.

I would just point out, and I suspect Dr. Lewis would agree, that the morbidity and mortality associated with end-stage renal disease is really substantial in this population, and showing a benefit when it's part of the prespecified composite outcome would be really important for patients to know and for physicians to know in order to best treat these patients. So I'd make it a broader composite.

DR. LEWIS: Thank you, Dr. Nissen, and I certainly would echo that end-stage renal disease is an awful outcome, particularly in this population.

I'm sorry. I don't know whether Dr. Merz was before Kasper.

DR. BAIREY MERZ: Yes.

DR. LEWIS: Okay. Dr. Merz?

DR. BAIREY MERZ: Noel Bairey Merz. I would second these good suggestions for a new trial, and I would amplify had there been 64 percent women rather than 52, with all applause to the group,

they probably would have met the primary endpoint, and that higher prevalence is the prevalence of women in this condition if we're still going to call it HFpEF.

Also, though, before that, I looked back. The New England Journal article does have quality-of-life improvement that was statistically significant in the New York Heart Association classification, and I would consider a quality-of-life indication. These patients are miserable. They often fear their symptoms and their inability for their activities of daily living much more than anything we can do to them in the hospital. Thank you.

DR. LEWIS: Thank you.

Dr. Kasper?

DR. KASPER: Thank you, Dr. Lewis.

I would differ slightly with what people are saying in that I think this field is moving away from LVEF as the sole genotype, or phenotyper for lack of a better word, and towards other things, whether they be molecular biomarker or whatever.

We're kind of caught in a middle ground. We're not there yet, but we're clearly unhappy With ejection fraction as being the be-all and end-all. I'm not sure I would repeat another large expensive trial using EF as the arbitrator and that I would look to design something completely different that's heading off in a different direction of phenotyping. Thanks.

DR. LEWIS: Thank you, Dr. Kasper.

I believe Dr. Emerson is next. And may I ask the panelists who have had their questions answered to please put their hand down unless they have another question.

DR. EMERSON: You were speaking to me right then. I'm sorry.

DR. LEWIS: No, I was acknowledging you. I assume you still have a question, but there were a lot of other hands up.

DR. EMERSON: No. That was an error.

DR. LEWIS: Oh, you're an error, too. Okay. Alright.

Dr. Gibson and Ms. Chauhan, you both have

your hands up. I'm going to guess you still have questions or comments.

Dr. Gibson?

(No response.)

DR. LEWIS: Dr. Gibson?

(No response.)

DR. LEWIS: Ms. Chauhan, do you have another comment?

MS. CHAUHAN: Yes, I do. This is Cynthia Chauhan.

DR. LEWIS: Great.

MS. CHAUHAN: I'm just responding. I think it was Dr. Emerson who said the trial should not include those of us who have a HFpEF above the 50 range. The reason I would like for all of us to be included is so that we don't get some kind of creeping authorization not based in reality.

If we're included and it shows nothing in us, then that takes care of that. If it does show something, we can move on from there. But I don't happen to believe that these diseases are a spectrum of gradation. I believe that HFpEF and

HFrEF are very different. They both affect the heart but how they do that is very different. So that's why I think the whole HFpEF population should be included. Thank you.

DR. LEWIS: Thank you, Ms. Chauhan.

Dr. Gibson?

DR. GIBSON: Yes, I agree. Rather than repeating another large trial, I might urge the sponsor to focus on and enrich for women perhaps in that mid-reduction EF range. It might be interesting to switch over, if the regulators agree, to something like a win ratio approach.

If the patient had cardiovascular death, or hospitalization, or urgent visits that count, obviously. But if they didn't have an event, then they could compete with another age X match person in the other arm on a continuous variable like NT-proBNP, or New York Heart Association class, or renal progression. So there might be a way, given that this is confirmatory, to bring in some biomarkers to allow them to compete on those variables to really reduce the sample size

dramatically.

DR. LEWIS: Okay. Thank you, Dr. Gibson.

Are there any further comments in regards to this question? If not, I'll try to summarize our comments.

(No response.)

DR. LEWIS: Okay. So if there were to be another study, I think that the group is mostly favoring enriching it for some aspect that's going to increase events or is a population of interest, whether that be the mid-range people who are between the 40 and 57 percent, women, or interestingly using another marker that may better represent the heterogeneity of this group or why they're so different than the HFrEF group, and a variety of biomarkers were suggested.

Adding renal failure as an outcome, since there was certainly, although small numbers, a strong signal there, was also mentioned. The thought of looking at people who don't have an actual event but looking at a surrogate marker in those people and matching them with the control

group versus the study group, was also suggested.

I think that overall summarizes it, and I think the minutes will pick up the things that I didn't catch, so I will now read the final and fourth question.

If Entresto warranted an indication, how would you describe the patients in whom such benefit applied? Are there any questions to the FDA about the wording of the question or the issues that are being asked about?

Dr. Nissen, do you have a question about the wording?

DR. NISSEN: No, I don't have a question about the wording. I was going to respond to the question, so when you're ready.

DR. LEWIS: Yes. If there are no questions or comments concerning the wording of the question, we'll now open the question to discussion and, Dr. Nissen, you're first.

DR. NISSEN: Okay. I was working on a sheet of paper sort of trying to write an indication, so let me give it a try. What I said was,

"Sacubitril/valsartan is indicated to prevent heart failure hospitalization in patients with an ejection fraction less than the lower limit of normal despite treatment with guideline-directed heart failure therapies." Then I put in parentheses "for at least X months," although that last phrase may or may not be included. But basically the concept is, if you're below the lower limit of normal, despite treatment with guideline-directed therapies, that you are likely to benefit on hospitalization.

DR. LEWIS: Thank you, Dr. Nissen.

Dr. O'Connor?

DR. O'CONNOR: Chris O'Connor. I would agree with what Dr. Nissen said but maybe word it slightly differently, that sacubitril/valsartan is indicated for the reduction of heart failure hospitalization in patients with mildly reduced ejection fraction as defined by EF greater than 45 through 55, and then one of the echocardiographic structural -- that wouldn't be in the sentence, and then the eligibility criteria; so mildly reduced

ejection fraction, EF 45 to 55. Thank you.

DR. LEWIS: Dr. Emerson?

DR. EMERSON: I was really hoping that somebody else would solve by conundrum for me first. But I'll just say that I was also trying to incorporate the existing indication. So it's the idea of how do we say that in the mildly reduced, it's worsening heart failure as defined by hospitalizations and the like, and in the more extreme reduced ejection fraction that it has the mortality endpoints. But I'm going to leave that to the FDA ultimately to have to wordsmith that.

DR. LEWIS: Okay. Dr. Merz?

DR. BAIREY MERZ: I agree with Dr. Nissen's statement and would modify it to be up to 57 percent to acknowledge the higher threshold for women that are predominant in this group. Thank you.

DR. LEWIS: It looks like Dr. Gibson.

DR. GIBSON: Yes, I agree with Dr. Merz. I would extend it up to 57 percent. I think that's important to capture as many women as possible who

may derive benefit.

DR. LEWIS: Ms. Chauhan?

MS. CHAUHAN: Cynthia Chauhan. I agree with extending it to 57 percent to capture the women. I think the indication should very strongly state the limitation of the use to people below 57 percent.

DR. LEWIS: Thank you.

Dr. Ridker?

DR. RIDKER: Yes. So I'm going to mildly push back against my esteemed colleagues on this. I would stick with mildly reduced and not go to 57, and an echocardiographer. There's tremendous echo creep in how people read studies when they know something might or might not happen on that basis, and I think mildly reduced is where the sweet spot is between what we know is true in PARADIGM and what we believe and suspect is true in PARAGON.

But 57, it's normal for a lot of people, and echocardiographers, very often there's a schism between the number and the thing. So I would do mildly reduce. The FDA has already taken a proactive step here, and I think that that would be

a way to find a middle ground that would work for me.

DR. LEWIS: Thank you. Dr. Ridker.

Dr. Thadhani?

(No response.)

DR. LEWIS: Dr. Thadhani, you're muted on the Adobe Connect.

DR. THADHANI: Sorry. Thank you, Dr. Lewis. Apologies.

Ravi Thadhani. I certainly agree with my colleagues and leave it to the cardiologists to distinguish mildly reduced versus 57 percent. The only other comment I will make is the issue of an extension of a claim versus a separate claim just given the differences in cardiovascular mortality between the two studies, which were quite different. Thank you.

DR. LEWIS: I think Dr. Merz wants to respond, so, Dr. Kasper, I'm going to let her jump ahead of you.

Go ahead, Dr. Merz.

DR. BAIREY MERZ: I do. Noel Bairey Merz.

I think the issue of course is the treating clinician needs thresholds and, obviously, an ejection fraction of 57 percent in an otherwise healthy and well person who has not been hospitalized for heart failure, and has no left atrial enlargement and has no elevation in BNP or NT-proBNP, would not be a candidate. I would be worried about a mild reduction and that that actually would be even harder to understand as treating physicians. Thank you.

DR. LEWIS: Dr. Kasper?

DR. KASPER: Yes. I have to say I'm with Dr. Ridker on his mildly abnormal LVEF island. Thanks.

DR. LEWIS: Thank you.

Dr. Moliterno?

DR. MOLITERNO: Thank you, Dr. Stevens [sic].

David Moliterno. Yes, I agree with not putting 57 percent. I think it gives the false impression of the precision of echocardiography. I think we all agree that there's a plus or minus 5

window. My inclination would be to say below normal. If you force me to come up with a number, it would probably be 55; 57 just happens to be the median in the study, but there are many other studies where the median is a bit lower, so I probably wouldn't push that.

We already know that we've got plenty of therapies. Agreed, none are approved for this indication, but even when they are approved in therapies, somewhere earlier in the presentation it was highlighted, again, that a minority of patients receive appropriate guideline-directed medical therapy, so I'd try not to make it too onerous or difficult, but just say "not normal ejection fraction with heart failure." Thank you.

DR. LEWIS: Thank you.

Dr. Nissen?

DR. NISSEN: Yes. I really want to argue against the term "mildly." It's vague, its imprecise, it can be interpreted however anybody wants to interpret it. The reason I wrote it to suggest below the lower limit of normal is that

while it's not an exact number, at least it has some precision around it. Mildly leaves it in the eye of the beholder, and I just don't think from a regulatory point of view that it makes sense to use a term that is that vague.

DR. LEWIS: I'm going to take the liberty of asking you a follow-up question. Would you add any BNP guidelines for that?

DR. NISSEN: I wouldn't. But the way I wrote it, of course, I didn't state what I should have stated, which is that these are people who have active heart failure with symptoms. I mean, that was implicit. I just didn't put it into the statement.

So if you're symptomatic with a syndrome that's consistent with heart failure and you have an ejection fraction below the lower limits of normal, I believe it's in the public interest for you to get sacubitril/valsartan. Unless you're below 40, you're probably not going to prevent death, but you will prevent hospitalizations, and you may well prevent advancement of renal disease.

So there's a real public interest in defining that group carefully, but you have to have symptoms. I don't know that BNP is the way to go.

DR. LEWIS: Thank you.

Dr. O'Connor?

DR. O'CONNOR: I just wanted to come back to guidance around some range and maybe mildly reduce. Maybe it's take the "mild" out and say "reduce." But I think, as Dr. Moliterno said and Dr. Ridker, that if there is 5, we heard 8-point potential error, we certainly don't want a significant portion of patients with EF of 60 or greater receiving this therapy, although we know that in the women it does show efficacy.

Most of the patients are cared for by primary care physicians with HFpEF, so they're going to need guidance. Echo labs have different ranges of normal. You can have a normal here of 55, you could have 60, you could have 50. So I think giving guidance around 45 to 55 would be the sweet spot. Thank you.

DR. LEWIS: Thank you.

Dr. O'Connor?

DR. O'CONNOR: No, that was me. That was me.

DR. LEWIS: Sorry about that.

Dr. Ridker?

DR. RIDKER: Yes. Maybe what I'm struggling with here and the reason I like reduce is because the investigators went after preserved ejection fraction, and I admire them for having done so, and I think that Dr. McMurray in his introduction gave us the beautiful history of how this all evolved and the words we're struggling with. But preserved to me is normal, and what we're discovering here is that this investigative group between PARAGON and PARADIGM have figured out that there's this in between that to me is not normal, but I think the drug works. That's what we're trying to solve here.

So to me it may just mean that HFpEF hasn't been solved, and I'm just nervous that anything that sounds normal is beyond where I suspect the FDA wants to go since they're already being

open-minded about allowing us to think about a trial that canonically was neutral. But the New England Journal published it as neutral because it is HFpEF, whereas I think this is correct; that we found that they did a good job finding this intermediate group. So that's where we're trying to land, I think.

DR. LEWIS: Dr. Thadhani?

DR. THADHANI: Sorry. I did not put my hand down. Apologies. No question. Thank you, Dr. Lewis.

DR. LEWIS: No problem.

I think I'm next, and I will put my hand down. I'll just say that I think this shows us the challenge of trying to write and leave the FDA an indication when you're kind of going outside the boundaries of what the trial actually did and kind of cherry-picking your subgroups that you think are giving you the partial signal you saw. So I think it is really quite a challenge and I appreciate all the panel members who are trying to help out with it.

Dr. Kasper, you were next, but I saw your hand just went down.

DR. KASPER: Yes, but I was just going to point out something that we all already know, which is that the American Society of Echocardiography has very clear-cut definitions of what normal, what's mild, moderate, and severe, and it's defined by gender. So we should try to be consistent with that, I think.

DR. LEWIS: Thank you.

Ms. Chauhan?

(No response.)

DR. LEWIS: Ms. Chauhan?

MS. CHAUHAN: Sorry. Can you hear me now? Hello?

DR. LEWIS: I can.

MS. CHAUHAN: Okay. Cynthia Chauhan.

DR. LEWIS: Yes, we can hear you.

MS. CHAUHAN: One of the things I worry about goes back to a couple of things you have said, and that has to do with if this were approved without another trial, are we opening any kind of

floodgate for other researchers to go back and see this as an invitation to try to, for want of a better term, backdoor their way into some approvals? I'm thinking about some of the things you've all said earlier about the other two trials.

I just wonder what people's thoughts are about that. Am I being too conservative or do you think that's a valid concern?

DR. LEWIS: Dr. Nissen?

Thank you, Ms. Chauhan.

DR. NISSEN: Your concern does not fall on deaf ears. As FDA and as Norm Stockbridge pointed out, we have occasionally done something like this, and it's interesting. I was involved in several of them, including -- Norm, you may remember -- the reanalysis of CAPRICORN.

It should be done carefully, conservatively, and only when it really is compelling that the public interest supports it. But the idea that when you have a clinical trial and you fail the primary endpoint, that you can then go and data mine until you find something that you like, and

then submit for an indication, what we're doing here with these recommendations is we're not opening the door to that. We should not open the door to that. That's not good public policy.

MS. CHAUHAN: No.

DR. NISSEN: But what FDA did here is they wanted us to look at more than one trial. You've got PARADIGM as well as PARAGON. They wanted us to look at the breadth and totality of the data and the fact that there were some rather extraordinarily strong interaction terms here that suggested heterogeneity and response. That isn't the case most of the time, and as long as we're careful here, this does not set a precedent that we can't live with.

MS. CHAUHAN: Thank you.

DR. LEWIS: Thank you, Dr. Nissen.

Are there any other comments or discussion for this question?

(No response.)

DR. LEWIS: If not, I'm going to actually, before we adjourn, ask for last comments from the

FDA. And one of the things I want to ask them is -- we do have some time -- did you want us to address in a more broad sense, irrespective of this trial, adjudication versus no adjudication and dichotomy versus getting more out of the events by possible, probable, or however it is it's done?

Dr. Stockbridge?

DR. STOCKBRIDGE: This is Norman Stockbridge. I think we've had a reasonable discussion of that. There seems to be a fair endorsement of that, especially, I might say, if it's done prospectively, so that's good. But if people have other comments on that topic, that's fine, too. I've been going to heart failure meetings for a while advocating for this.

DR. LEWIS: So I'll open it to the panel.

Does anyone want to make any further comments on whether you would feel comfortable without adjudication and instead just going with what the investigators say the event was or wasn't? I do think there seemed to be quite a uniformity on that we could maybe get more information from

events in a couple different ways by not dichotomizing and also getting information for people who don't have events.

Dr. Nissen, I think your hand was up first.

DR. NISSEN: You know, there are pros and cons to this, and I think we've got to be very careful here. And it really is this question of sensitivity versus specificity. I think that it is appropriate for regulators to be conservative, meaning to favor specificity over sensitivity. I have no doubt that sensitivity is higher if you use just the raw reported events, but it also means that there's potentially a magnification of benefit that would lead to approvals of something that might be more marginal. So I'm not so sure that I want to give up on adjudication.

Now, I think we need to do a better job of adjudicating, which means that we need methodologies like you used here to have a graded response where we can set the thresholds and look at that very carefully. But I also know, having done this -- we've done this in over 100,000 events

in our place -- that there are some pretty bizarre events that are submitted by investigators, where when you look at it, you're left scratching your head saying, "What were they thinking?"

DR. LEWIS: Thank you.

Dr. O'Connor?

DR. O'CONNOR: Yes. Chris O'Connor. I would agree with what Dr. Nissen said, that the adjudication process is a good process. It helps hold up the integrity. You often from the committee can find areas where there could be some data integrity issues. They might be determined first by an endpoint committee, source documentation, and variability can be brought to light early on for corrected purposes.

The Hicks criteria I think was too strict, but I think we've learned that, and there's been published modifications with that criteria. But I think what Dr. Stockbridge did and has pointed out really advances the field in adjudication, which hasn't advanced at all in heart failure in 20 years. So I really think this is terrific to put

probabilities on these endpoints, and I think the investigator should do it and the endpoint committee should do it. Thank you.

DR. LEWIS: Dr. Ridker?

DR. RIDKER: Thank you, Dr. Lewis. I actually wanted to take this opportunity to comment a little more broadly on this issue that I think is near and dear to most of us right now and very relevant to Dr. Stockbridge's opening comments and his recent question to us.

I think that what is going on today, and I think what probably is going on tomorrow when we meet again, is very important because all of us in the clinical trials community recognize that I think clinical trials are under some stress right now, and there is a large community that has been advocating for observational approaches that, I must say, give me great trepidation.

On the other hand, we all recognize that in clinical trials, what really matters is the randomization and the double blinding. We can have a robust discussion about the adjudication, but

what ultimately matters is that we as a clinical trials community show some flexibility in what is already a much higher standard.

I think that's what I'm hearing today from the FDA, is let's recognize that randomized, double-blind, placebo-controlled trials, in this case two studies covering some overlap, is really the standard, and maybe within that construct, we can be more open-minded about whether it did or did not meet some canonical p-value. Maybe we can be more open-minded than we have in the past about what a subgroup might mean. I think this is a big difference between a random subgroup such as a zodiac sign and a non-random biologically driven subgroup such as, in this case, a lower ejection fraction.

I want to just commend the FDA and the panel today because I think what we're all talking about is how do we preserve the clinical trial structures. How do we make them less expensive? How do we enroll greater minority participants? That's come up as well. But how do we do that in

an economically viable way, at least from my perspective, to push back on this stated desire to try to do this in an observational setting where, frankly, I think these small issues that we're discussing are greatly magnified. So I think the creativity and openness to thinking about this is great, and I'm glad to see the agency moving in that direction.

DR. LEWIS: Ms. Chauhan?

MS. CHAUHAN: Thank you. Can you hear me? Hello?

DR. LEWIS: I can.

MS. CHAUHAN: Okay.

DR. LEWIS: Yes, I can hear you.

MS. CHAUHAN: Cynthia Chauhan, patient representative.

I have more general comments. I really want to thank the FDA for their deep caring and high ethical standards. I want to thank Novartis for their investment in HFpEF. It's a very needed investment. But then I want to remind you that those of us with HFpEF are a desperate population.

We are hungry for treatments. So an issue becomes rushing to judgment with anything is better than nothing attitude, and this has to be avoided because it ignores the potential and describes safety and adverse events attributable to interventions.

Because most HFpEF patients are treated or followed by community physicians, there must be an emphasis on education of those practitioners and those patients. And going forward, we must make the trial population adequately reflect the affected population. Also, I've been in many trials. I believe in trials. I really believe in double-blind trials, and I know they're expensive, but human life matters and quality of life matters. Thank you.

DR. LEWIS: Dr. O'Connor, your hand is up.

DR. O'CONNOR: I just want to remind people that, again, this was against not a placebo but a drug that probably has some active effect in this population if you look at the CHARM preserved study carefully. So while we've been saying modest

effect, that's against something that probably also has a modest effect. So I just want to make that clear. Thank you.

DR. LEWIS: Thank you.

Dr. Merz, your hand is up.

DR. BAIREY MERZ: Yes. Noel Bairey Merz. I did not weigh in earlier, but I would like to at this time. I also have not voted or found comparable the need, the clinical need, that has not shaped my thinking or decisions about this. I also would like to endorse the prior comment about using the American Society of Echocardiography normative. It is not only stratified by sex, but it is stratified by ethnicity, and it's quite comprehensive and universally available.

DR. LEWIS: Thank you, Dr. Merz.

Dr. Stockbridge, you did have your hand up. It is certainly at a point where are there any last comments from you?

DR. STOCKBRIDGE: Well, I was only going to comment earlier that I think there are two issues raised by this last topic. One is, is there some

value in adjudicators doing something instead of having site investigators do it. I think that's fundamentally different from the question of whether people should dichotomize events or give partial credit to something they think might have been a valid event.

But this has been a great conversation, a great meeting, and in many ways it has reflected the conversations we've been having internally about this topic. But there have also been a number of novel insights that we're going to have to think a little bit about.

One take away I have from this and fully endorse is the whole discussion around how we would describe this result in a label. Almost everybody avoided using the word "preserved" and I think that's exactly right. We will eventually work out a reasonable way of describing the heart failure, the spectrum, but "preserved" and "reduced" is probably not a very useful description.

So I very much appreciate everybody's input, and I hope it's a long time before we have

to discuss another failed trial. Oh, wait. I guess that's tomorrow.

(Laughter.)

DR. LEWIS: Okay. Thank you.

Yes, actually it was hard not to avoid commenting on that. I'm glad it was you doing it, Dr. Stockbridge.

Dr. Unger?

(No response.)

DR. LEWIS: Dr. Unger, your hand's up, but you're muted in the Adobe system.

DR. UNGER: Okay. Sorry about that.

Yes, I'd like to second what Dr. Stockbridge said. I know a lot of people put a lot of effort into this in terms of preparing for the meeting. The division put a lot of effort into it. The committee did. The company I think did a good job of basically lining up the issues, and I'd like to thank everybody.

The conversation was, I think, really helpful. It was wide. It was deep. The concept of this graded adjudication is something we've

talked about off and on now for a while, and it seems to have gotten a lot of support. Anyway, I would just like to thank everybody. It was enthusiastically thought through and everything was well presented, and thank you. That's all.

DR. LEWIS: Okay. Thank you, Dr. Unger.

Are there any further comments? If not, I'm going to proceed to adjourn the meeting.

(No response.)

DR. LEWIS: I don't see any hands except Dr. Unger's is still up.

Do you have a closing comment, Dr. Unger, or was that it?

DR. UNGER: That was it. Yes. Sorry.

Adjournment

DR. LEWIS: There you go. Okay. Great.

We'll now adjourn the meeting. I want to thank everybody. I echo what Dr. Unger said. I think we had a little bit of a challenging charge because it was breaking some new frontiers, and I appreciate everybody's input. And I think most of you will be back tomorrow morning, so get a good

night's rest, and we'll be back tomorrow.

(Whereupon, at 4:09 p.m., the meeting was adjourned.)